Use of Technetium-99m-MAG_3 for Renal Scintigraphy After Angiotensin-Converting Enzyme Inhibition

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Technetium-99m-mercaptoacetyltriglycine (^{99m}Tc-MAG_3) was tested in 82 hypertensive patients submitted to renal scintigraphy 1 hr after oral premedication with 50 mg of Captopril. Baseline studies were obtained only for those patients showing abnormal findings in the provocative study. All patients underwent renal arteriography. Sensitivity and specificity for the detection of renal artery stenosis (RAS) >50% were 89% and 91%, respectively. After Captopril administration, tracer parenchymal transit time increased significantly in ischemic kidneys (334 ± 93 sec in baseline conditions versus 468 ± 96 sec after Captopril, $p < 0.001$) but not in kidneys with no RAS or RAS <50% (243 ± 46 sec versus 271 ± 95 sec, p = ns). False-positive responses were mostly bilateral and associated with a marked decrease in blood pressure. Technetium-99m-MAG_3 is an effective compound for detecting RAS ≥50% with Captopril renal scintigraphy. Performing the provocative test as a first step considerably reduced the number of scintigraphic studies required.

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Renin-angiotensin system blockade has been successfully utilized in hypertensive patients to improve both scintigraphic diagnosis of renovascular hypertension (RVH) (*1–6*) and detection of renal artery stenosis (RAS) (*7*), using either technetium-99m-diethylenetriaminepentaacetic acid (DTPA), iodine-131-orthoiodohippurate (OIH), or both. While DTPA, due to its relatively low renal extraction, might result in nondiagnostic images in severely impaired kidneys (*8*), the use of radioiodinated OIH, which shows a higher extraction efficiency (*9*), is hampered by both the unfavorable physical characteristics of iodine-131 and the high cost of iodine-123. A recently proposed radiopharmaceutical, ^{99m}Tc-mercaptoacetyltriglycine (MAG_3), showed interesting properties for renal scintigraphy (*10–14*) and, in particular, some advantages were found in studying patients with impaired kidney function, not infrequently seen in renovascular disease.

To date, the preferred approach has been the execution of a baseline renal scintigraphy followed by a Captopril-enhanced study. However, due to the relatively high incidence of essential hypertension even in selected populations of hypertensive patients, this sequence entails an increase in both nuclear medicine department workload and the cost of screening procedures. Considerable reductions could be obtained from a reverse sequence by limiting the execution of baseline studies only to those cases where the provocative test was abnormal.

The purpose of our study was to investigate whether the promising results of renal scintigraphy with ^{99m}Tc-DTPA after angiotensin-converting enzyme inhibition (ACEI) in detecting RAS could be achieved by ^{99m}Tc-MAG_3. We also attempted to evaluate a study sequence involving the execution of the provocative study as the first step, followed by a baseline renal scan only for patients with abnormal findings.

MATERIALS AND METHODS

Patient Population

Eighty-two patients (44 males; 38 females), randomly selected from those referred for either evaluation of hypertension or follow-up of renal artery revascularization procedures, were submitted for Captopril-enhanced renal scintigraphy using ^{99m}Tc-MAG_3 instead of the conventional ^{99m}Tc-DTPA. Antihypertensive drugs were not discontinued, with the exception of diuretics which were suspended for at least 48 hr. When requested, the baseline study was carried out at least 24 hr later. Studies performed on patients under chronic therapy with converting-enzyme inhibiting drugs (20 cases) were considered as provocative tests. In the two cases where a baseline study had to be performed, ACEIs were withdrawn for 7 days or substituted with other antihypertensive drugs if clinical conditions did not allow therapy suspension.

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Data Acquisition

Patients, who fasted overnight and were well hydrated, were injected intravenously with 120 MBq of ^{99m}Tc-MAG$_3$ (Technescan, Mallinckrodt Diagnostica, Petten, Holland), 1 hr after oral administration of 50 mg of Captopril. Between Captopril administration and scintigraphy, the supine position was maintained and blood pressure was monitored.

Renal scans were performed by means of a large field of view gamma camera (Elscint, APEX 415) equipped with a low-energy parallel-hole all-purpose collimator. Studies were acquired in a 64 × 64 byte-mode matrix, with a frame rate of 10 sec per frame, for a total of 1120 sec.

Data Processing

Frames were grouped into 1-min images with a region of interest (ROI) drawn around each kidney identified on the 2-min image. Background ROIs, three pixels wide, were automatically placed around the lower half of each kidney, from the lower pole to the middle of the lateral contour, one pixel apart. Time-activity curves were then produced and split renal function (SRF) was calculated from the background-corrected renograms (*15*).

Additional ROIs were drawn on the left ventricle and on the kidney cortex identified on the lateral contour of each kidney from the upper to the lower pole, taking care to exclude the pelvi-calyceal system. Time-activity curves obtained from these ROIs underwent deconvolution analysis and mean parenchymal transit time (PTT) was calculated from the obtained retention function (*16*).

A parametric image of time to maximum counts (Tmax PI), depicting tracer renal transit on a pixel-by-pixel basis, was produced to visually evaluate tracer renal washout and to detect possible regional delays due to segmental RAS. This image was displayed in a continuous gray scale, where the darker levels reflected tracer transit delays.

Scintigraphic Analysis

Renal scans were inspected for kidney size and shape, relative tracer uptake, and appearance of the tracer in the pelvi-calyceal system. Renograms were inspected for shape, upslope of the second phase, downslope of the excretory phase, and graded as normal, slightly abnormal, or definitely abnormal. Split renal function was considered normal when the relative percentage uptake of each kidney was between 44%–56%. Patients with no abnormalities were discharged and RAS ≥50% was excluded. Otherwise, patients were scheduled for a second study in baseline conditions.

From a comparison with baseline results, Captopril studies were considered positive when at least two of the following conditions were satisfied: (a) SRF decrease >5% and/or its displacement outside the normal range; (b) increase of time of peaking activity >300 sec; (c) increase of PTT >20%; or (d) abnormalities in the Tmax parametric image (disruption of parenchymal-pelvic differentiation and/or segmental delays).

Renal Arteriography

Within 4 wk of the scintigraphic studies, all patients underwent renal angiography by arterial catheterization.

RESULTS

Renal Angiography

RAS was detected in 37 patients (Table 1), while 45 proved to have patent renal arteries. RAS was bilateral in 12 cases and unilateral in 25. Overall, 49 vessels were found affected by RAS. A 50% vessel diameter reduction, corresponding to a 70% arterial lumen narrowing, was considered significant. Thus, out of the 49 affected vessels, 34 were considered significantly stenosed (RAS ≥50%), while 15 were not.

Scintigraphic Results

Captopril-enhanced renal scintigraphy was normal in 30 patients and abnormal in 52 (Fig. 1). In the group of 30 patients with normal findings, RAS >50% was ruled out. Renal angiography was negative in 29/30, while RAS >50% was detected in one case.

The second group of 52 patients with abnormal scintigraphic findings after Captopril administration underwent a baseline study at least 24 hr later. In 30 cases, either an improvement or a normalization was observed in baseline conditions as compared with Captopril studies, which resulted in a diagnosis of significant RAS. Angiographic confirmation was obtained in 24/30 patients while six responses were false-positive.

Finally, significant RAS was excluded in the last 22

TABLE 1
Patient Population and Scintigraphic Results

Patients		Kidneys
82	number	162*
55	no RAS or RAS <50%	128
27	RAS >50%	34
89%†	sens	89‡
89%	spec	91%

RAS = renal artery stenosis; sens = sensitivity; and spec = specificity.

* Two patients had a single kidney.

† Identification of at least one RAS >50% in patients with bilateral disease.

‡ Identification of each ischemic kidney.

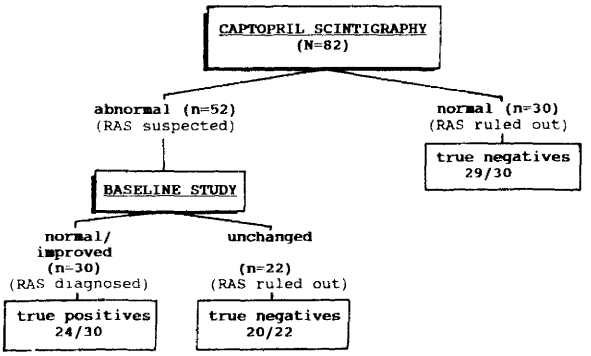

FIGURE 1
Diagnostic flow-chart of patients submitted for Captopril renal scintigraphy.

patients with abnormal Captopril findings who showed no changes in their baseline study. During renal angiography, patent renal arteries or insignificant RAS was found in 20 cases, whereas RAS >50% was detected in two patients.

Overall, evaluation of the whole scintigraphic procedure (Captopril + baseline scans) resulted in 24/27 patients correctly diagnosed as affected by RAS >50%, while the test failed in three cases. Sensitivity for patient identification was therefore 89%.

Of the 55 patients with angiographically proven patent renal arteries or RAS <50%, a negative response was obtained in 49 cases. Six patients, however, normalized their scintigraphic study in baseline conditions, thus leading to a false-positive finding. Specificity was therefore 89%. This finding is dealt with in the Discussion section.

Abnormalities induced by Captopril administration only were found in 6/27 patients (three with unilateral RAS, one with bilateral RAS, and two with segmental branch involvement). In 18 cases, Captopril administration worsened an already abnormal scintigraphic study. This behavior, specific for renin-angiotensin system activation, was of great help in overcoming one of the major constraints of renal scintigraphy in hypertensive patients, low specificity.

Table 2 summarizes results obtained by each parameter employed and their association.

A decrease of SRF from the affected side was observed in only two-thirds of the kidneys and was useful only in patients with unilateral RAS. Bilateral disease was undetectable by this parameter because of its inherent semiquantitative nature.

Captopril studies almost always showed intraparenchymal tracer trapping in kidneys supplied by stenotic arteries with a virtual absence of the third renographic phase (Fig. 2) no longer detectable in baseline conditions. This pattern was clearly distinct from uropathies, where a clear pelvi-calyceal retention was observed with

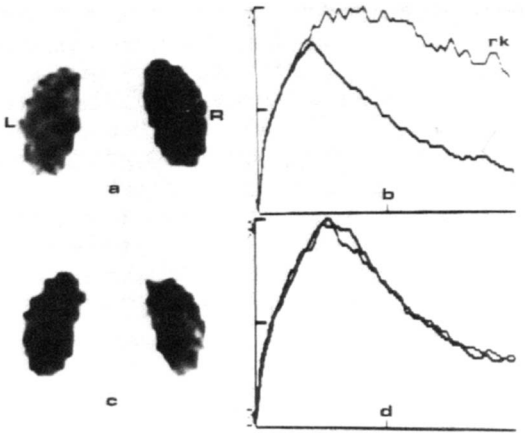

FIGURE 2
CERS results of a 59-yr-old male patient. (a and b): decreased downslope of the third phase of the right renogram. Tmax PI (a) clearly shows a marked delay of tracer transit through the right kidney (where darker colors reflect prolonged transit time). SRF: 50% both sides. PTT: 180 sec left; 320 sec right. Transit delays are no longer detectable in baseline conditions (c and d), where renal function is bilaterally normal and no delays are shown on Tmax PI (c) where both kidneys are displayed with similar color levels. SRF: 50% both sides; PTT: 185 sec left, 190 sec right.

only slight differences between baseline and Captopril studies.

After Captopril administration, PTT increased from 243 ± 46 sec to 271 ± 95 sec (p = ns) in kidneys with no RAS or RAS <50%, whereas in kidneys with RAS >50%, the increase was highly significant (334 ± 93 versus 468 ± 96, $p < 0.001$) (Table 3).

Segmental RAS was identified on Tmax parametric image as a regional delay of tracer transit, reflected by darker gray levels (Fig. 3).

Evaluation of patients with renal function impairment (five cases with plasma creatinine levels beyond 220 μmol/l), where DTPA would probably have been of little help, was accomplished with satisfying results (Fig. 4).

Overall, 134 scintigraphic studies were performed (82 Captopril studies and 52 baseline scans), which represents a significant reduction (nearly 20%) over

TABLE 2
Detection of RAS >50% (162 Renal Arteries): Sensitivity and Specificity of Each Parameter Employed and Their Association

	Sensitivity	Specificity
SRF decrease	65%	94%
Tmax delay >300 sec	68%	85%
PTT increase >20%	81%	86%
Two of the following: SRF decrease, PTT increase >20%, PI abnormalities	89%	91%

SRF = split renal function; Tmax delay = delay of time to peak counts as compared with baseline studies; PTT = parenchymal transit time; and PI = parametric image of Tmax.

TABLE 3
Parenchymal Transit Times

Renal status	BARS	CERS	Significance of difference*
Normal or RAS <50%	243 ± 46 sec	271 ± 95 sec	ns
RAS >50%	334 ± 93 sec	468 ± 96 sec	$p < 0.001$

BARS = baseline renal scintigraphy; CERS = Captopril-enhanced renal scintigraphy; and RAS = renal artery stenosis.
* Statistical significance (paired Student's t-test).

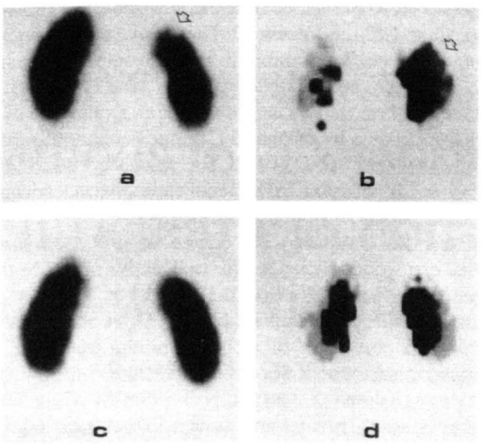

FIGURE 3
Right ureteropelvic junction stenosis and tight stenosis of the upper pole branch of the right renal artery in a 16-yr-old female. Captopril study (a and b): reduced uptake in the upper pole in the 90–150 sec image of the right kidney (a, arrow); Tmax PI (b) shows a regional delay of tracer transit on the upper half of the right kidney; tracer pelvic retention on the right side. SRF: 52% left; 48% right. PTT: 280 sec left; 370 sec right. The baseline study (c and d) confirms a marked tracer retention in the right pelvis but abnormalities on the upper half of the right kidney disappeared, both in the 90–150 sec image (c) and Tmax PI (d). SRF: 50% both sides. PTT: 270 sec left; 300 sec right.

the 164 procedures required for the opposite study sequence.

DISCUSSION

The recently proposed ^{99m}Tc-MAG$_3$, with a high renal extraction and available in kit form, has potential to overcome most of the shortcomings of other renal imaging agents and has already been successfully utilized for Captopril renography in a patient with renovascular hypertension (*17*).

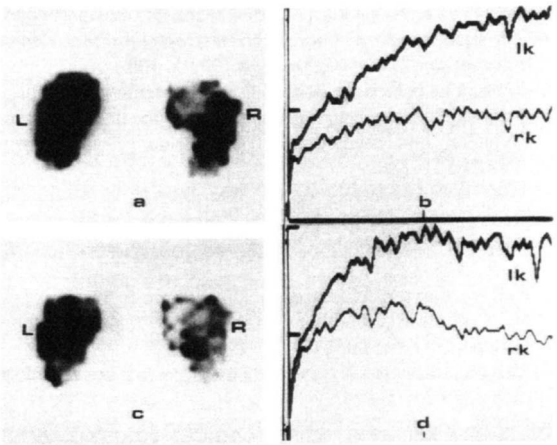

FIGURE 4
Bilateral RAS (90% left, 100% right, with collateral circulation to the right upper pole) in a 55-yr-old male. Creatininemia is 440 μmole/1. Captopril study (a and b): decreased uptake on both sides with marked PTT delay. SRF: 54% left; 46% right. PTT: 540 sec left, 490 sec right. Baseline study (c and d): increased upslope of the second phase of both renograms (d); Tmax PI (c) shows a reduction of tracer transit time through both kidneys. This behavior is diagnostic for RAS. SRF: 52% left; 48% right. PTT: 450 sec left, 370 sec right.

The effects of converting-enzyme inhibition on efferent arterioles with the consequent fall of glomerular filtration would support the use of a glomerular agent, such as ^{99m}Tc-DTPA, for Captopril renal scintigraphy. Studies on rats, however, demonstrated in normal kidneys a Captopril-induced increase in renal plasma flow, which remained virtually unchanged in ischemic kidneys (*18*). In this way, differences between the two kidneys are enhanced in unilateral RAS.

Moreover, Oei et al. (*19*) reported no differences between glomerular (DTPA) and tubular (OIH) agents for Captopril renography in a selected group of patients with unilateral disease.

In this study, we tested the use of ^{99m}Tc-MAG$_3$ for renal scintigraphy after ACEI in a large population of patients submitted to a study protocol involving a first renal scan after Captopril pretreatment, followed by baseline studies only when the provocative study proved to be abnormal.

In our experience, ^{99m}Tc-MAG$_3$ was very effective, providing a diagnostic accuracy similar to that obtained with other radiopharmaceuticals (*1–7*). In ischemic kidneys, the most frequent scintigraphic patterns after Captopril administration was an intraparenchymal tracer trapping, clearly seen on Tmax parametric image and quantitatively reflected in an increase of tracer PTT. This behavior has already been reported with OIH (*5,19*) and is consistent with renal handling of MAG$_3$, similar to that of OIH (*10,11*).

Segmental RAS was detected as a regional disruption of the parametric Tmax image. These findings support the diagnostic potential of functional imaging analysis in renovascular disease, as already reported (*20*).

Since specificity is critical for screening a low-prevalence disease such as renovascular hypertension (*21*), false-positive results deserve some consideration. In line with a previous report from our group (*7*), this study shows false-positive responses simulating bilateral disease in four patients whose diastolic blood pressure falls below 60 mmHg after Captopril administration.

Activation of the renin-angiotensin system is well known in maintaining renal function when perfusion pressure falls or in salt-depleted states (*22–24*). Inspection of scintigraphic data should therefore take into account the clinical conditions under which the test was performed. When a Captopril renal scintigraphy is bilaterally positive in a patient whose diastolic blood pressure falls below the "autoregulation limits," it might be wise to repeat the study.

For the two unilateral false-positive responses, it is worth noting that in one of these cases renal angiography showed a renal artery bifurcation close to the

ostium. In the same patient, echo-Doppler flowmetry, which is sensitive to blood flow derangements (*25*), also gave a false-positive response. Arterial blood stream impairment and a possible activation of the renin-angiotensin system as a consequence of arterial bifurcation might explain this finding. The second unilateral false-positive result was obtained contralaterally to a severely affected kidney. Since bilateral false-positive responses were also obtained in patients affected by advanced obstructive peripheral vascular disease, a possible role of intrarenal small-vessel disease might be suspected, although it still remains to be proven.

In light of our previous experience with ^{99m}Tc-DTPA (*7*) and of similarities found in the false-positive results, we feel that these results are not dependent on the radiopharmaceutical employed but rather on a renin release, which is unrelated to stenosis of the main renal artery or of one of its major branches.

In conclusion, ^{99m}Tc-MAG$_3$ proved effective for detecting RAS ≥50% in hypertensive patients or in renal artery revascularization follow-up. Sensitivity and specificity values were almost superimposable with those already reported for ^{99m}Tc-DTPA. Characteristically, affected kidneys showed a marked increase of PTTs transit times and derangements in Tmax parametric images. False-positive results obtained in some patients with a marked drop in blood pressure levels and affected by advanced peripheral obstructive vascular disease suggest caution in evaluating results obtained in similar clinical conditions.

Finally, a study sequence involving the execution of the Captopril-enhanced study as a first step, followed by a baseline renal scan only when abnormal results were found, resulted in considerable savings in department workload with no loss in diagnostic accuracy.

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