Prognostic Value of Captopril Renal Scintigraphy in Renovascular Hypertension

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This study evaluates the prognostic value of captopril renal scintigraphy in hypertensive patients undergoing renal artery revascularization. Preoperative studies of 51 patients were correlated with blood pressure results at 6- and 12-mo follow-up. Captopril-renal scintigraphy was carried out 1 hr after oral administration of 50 mg of captopril, using either 220 MBq of ^{99m}Tc-DTPA or 74 MBq of ^{99m}Tc-MAG3, followed by a baseline study in case of abnormal results. Evidence of amelioration or normalization in relation to captopril study was considered predictive of blood pressure control following treatment. Blood pressure response was favorable in 37 patients, but failed to show any improvement in 14. The scintigraphic test was positive in 33 patients (15 cured, 17 improved, 1 failed) and negative in 18 (3 cured, 2 improved, 13 failed). Sensitivity and specificity for renovascular hypertension was 86.5% and 93%, respectively. For blood pressure cure and improvement, the test had positive and negative predictive values of 97% and 72%, respectively. A positive preoperative captopril renal scintigraphic result is a strong predictor of hypertension curability by renal artery revascularization.

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Surgical repair or transluminal angioplasty of renal arteries has long been effectively used to treat secondary forms of hypertension due to renal artery stenosis (RAS) (*1,2*).

It has been shown, however, that RAS is not necessarily related to high blood pressure, since renal artery obstructive disease has been found at autopsy in a high percentage of normotensives (*3*) and is present in almost as many normotensive as hypertensive patients (*4*). Moreover, in a consistent number of patients, it has been found that treatment of stenosis does not lead to blood pressure control (*5,6*).

Nevertheless, RAS is the most frequent remediable cause of hypertension, and a number of different techniques have been proposed to identify patients affected by renovascular hypertension (RVH) (*7*) who would benefit from renal artery revascularization. To date, however, none of these techniques has achieved widespread clinical acceptance (*8–10*).

Several groups have reported the enhanced diagnostic accuracy of renal scintigraphic studies after captopril administration in the identification of hypertension secondary to RAS (*11–17*).

The purpose of the present study was to evaluate treatment results in patients undergoing renal artery revascularization by means of surgical repair or percutaneous transluminal renal angioplasty (PTRA), with the aim of assessing predictivity of pre-intervention captopril-renal scintigraphy (CRS) for blood pressure control.

MATERIALS AND METHODS

Patient Population

The study recruited patients submitted for renal artery revascularization on the basis of clinical and angiographic criteria. After the exclusion of patients with incomplete clinical, angiographic and scintigraphic assessment before and after intervention, the study initially included 84 patients.

Because our goal was to compare blood pressure response after revascularization with preintervention scintigraphic results, patients were considered unclassifiable and therefore excluded in the following cases: (a) normotensives revascularized with the aim of improving an already deteriorated renal function; (b) technical failure of the intervention (i.e., residual stenosis >50%); (c) early recurrence of stenotic disease (within 1 mo); and (d) postoperative death. Patients with late stenosis recurrence were retained for study providing their blood pressure values had been assessed at 6 mo.

Of the 84 patients initially evaluated, 51 proved eligible for the final study sample (Table 1). Renal artery revascularization was performed by means of renal angioplasty in 24 patients, while the 27 remaining patients were submitted for surgical repair.

Pre-revascularization angiography documented a >50% RAS in all patients, except one in whom renal angioplasty was carried out in an artery with a diameter reduction of 30%. The etiology of RAS (Table 1) was assessed on the basis of arteriographic findings. Revascularization results were assessed by postintervention angiograms.

Renal impairment was found in 14 patients. Ten of whom

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TABLE 1
Patient population

	PTRA	SR	Total
Total	24	27	51
Male	14	22	36
Female	10	5	15
Age (range)	51.2 (20–72)	59.6 (18–73)	55.6 (18–73)
Revascularization			
Unilateral	21	21	42
Bilateral	3	6	9
Etiology of stenosis			
Atherosclerosis	18	23	41
Fibrodysplasia	6	4	10

Note: PTRA = percutaneous transluminal renal angioplasty and SR = surgical repair.

(20%) had plasma creatinine levels between 132 and 264 μmol/liter and 4 (8%) with levels >264 μmol/liter.

Scintigraphic Studies

All patients, who fasted overnight and were well hydrated with no change in their antihypertensive therapy, underwent scintigraphic assessment within the 4 wk before revascularization. Captopril renal scintigraphy was carried out 1 hr after oral administration of 50 mg of captopril with either 220 MBq of ^{99m}Tc-diethylene-triamine-pentaacetic acid (DTPA) (38 patients) or 74 MBq of ^{99m}Tc-mercapto-acetyl-triglycine (MAG3) (13 patients).

Details on acquisition and data processing are reported elsewhere (*18,19*). The following parameters were calculated from renographic curves of both captopril and baseline studies: split renal function; time to peak activity; parenchymal transit time. Renogram shape, kidney size and relative tracer uptake were also visually analyzed.

When no abnormalities were found in the provocative study. RVH was ruled out; otherwise patients were submitted for a conventional renal scan.

Criteria for predicting clinical success after revascularization were: (a) improvement in split renal function of at least 5% from the affected side (baseline versus captopril scan); (b) decrease of time to peak activity of at least 300 sec; and (c) reduction of parenchymal transit time of at least 20%. When these conditions were not satisfied, RVH was ruled out and poor clinical response predicted. A diagnostic flow-chart is shown in Figure 1.

Statistical Analysis

For RVH diagnosis, sensitivity was defined as the proportion of positive results in patients showing blood pressure cure/improvement after revascularization (TP/TP+FN); specificity was defined as the proportion of negative results in patients showing no amelioration (TN/TN+FP).

The positive predictive value was the probability of blood pressure cure or improvement following treatment in patients with positive CRS. Conversely, a negative predictive value was the probability of clinical failure in patients with negative captopril renography (*20*). Statistical significance was evaluated by paired Student's t-test.

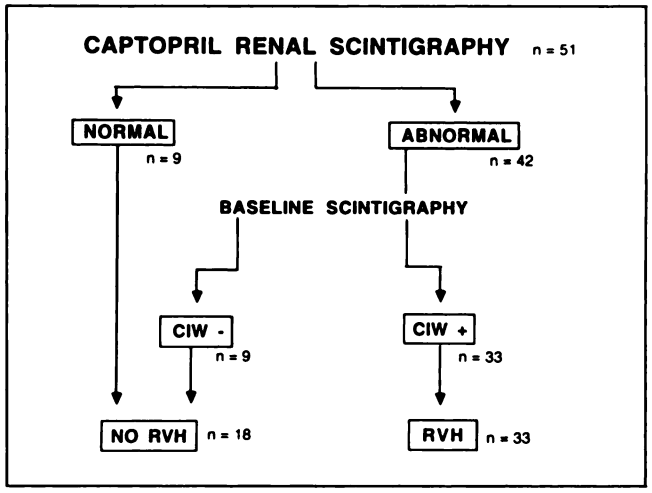

FIGURE 1. Diagnosis of renovascular hypertension (RVH) on the basis of presence or absence of captopril-induced worsening (CIW^+ and CIW^-, respectively).

RESULTS

Clinical Results

Average blood pressure values, serum creatinine and number of antihypertensive drugs for the 51 patients, assessed at 6 and 12-mo follow-up, are reported in Table 2.

Clinical outcome was evaluated on the basis of blood pressure response to revascularization. In light of studies reporting a relatively high frequency of restenosis in atherosclerotic patients (*7,21*) and nonsignificant differences between 6- and 12-mo evaluations (*22,23*), patients were

TABLE 2
Clinical Results (51 Patients)

	PTRA (n = 24)			
	Preoperatory	6 mo	12 mo	Statistical significance*
SBP	177 ± 27	153 ± 20	156 ± 23	$p < 0.01$
DBP	104 ± 11	93 ± 11	95 ± 15	$p < 0.05$
NR drugs	1.9 ± 0.8	1.5 ± 1.1	1.4 ± 1.0	$p < 0.05$
Creat	126 ± 50	119 ± 57	118 ± 46	p = ns
	SR (n = 27)			
	Preoperatory	6 mo	12 mo	Statistical significance*
SBP	176 ± 22	151 ± 20	154 ± 26	$p < 0.01$
DBP	104 ± 9	91 ± 9	92 ± 11	$p < 0.01$
NR drugs	2.0 ± 0.8	1.6 ± 0.7	1.5 ± 0.7	$p < 0.05$
Creat	167 ± 108	145 ± 118	152 ± 120	p = ns

Note: all values expressed as mean ± standard deviation.
PTRA = percutaneous transluminal renal angioplasty; SR = surgical repair; SBP = systolic blood pressure; DBP = diastolic blood pressure; NR drugs = number of assumed antihypertensive drugs; Creat = creatininemia in μmol/liter.
* Preoperatory vs. 12 mo.

classified as benefiting or not benefiting from treatment on the basis of clinical assessment at 6 mo.

By applying the Cooperative Study on Renovascular Hypertension criteria (*24*), clinical results were therefore classified as: (a) cured, when average diastolic blood pressure was 90 mmHg or less and at least 10 mmHg lower than preoperative levels; (b) improved, in the event of a 15% decrease in average diastolic blood pressure and diastolic blood pressure >90 mmHg but <110 mmHg; (c) failed, a <15% decrease in average diastolic blood pressure and diastolic blood pressure >90 mmHg or diastolic blood pressure >110 mmHg.

Blood pressure was recorded with the patients supine, after calculating the mean of values obtained at least three times on different days. Eighteen patients were classified as cured, 19 improved and 14 failed. Table 3 summarizes blood pressure response to revascularization.

Patients benefiting from treatment had a preintervention diastolic blood pressure of 173 ± 23 mmHg (mean ± s.d.), systolic blood pressure of 104 ± 10 and creatininemia of 119 ± 49 μmol/liter. The mean number of assumed antihypertensive drugs was 1.9 ± 0.7.

Patients failing to respond to treatment had a preintervention diastolic blood pressure of 178 ± 30 mmHg, systolic blood pressure of 103 ± 11 and creatininemia of 175 ± 110 μmol/liter. The number of assumed antihypertensive drugs was 2.0 ± 0.8. These differences between the two subgroups were not statistically significant except in the case of creatininemia ($p < 0.05$).

Of the 10 patients with fibromuscular dysplasia, 9 responded positively and only 1 failed to show any benefit; in the atherosclerotic group, 9 were cured, 19 improved and 13 showed no benefit.

Scintigraphic Results

On the whole, scintigraphic studies were positive in 33 cases and negative in 18. Test positivity, suggesting renin-angiotensin system activation and a potential benefit from treatment, occurred in 15/18 cured, in 17/19 improved and in only 1/14 failed patients (Fig. 2).

For patients benefiting from revascularization (cure + improvement), the captopril renography positive predictive value was 97%. The negative predictive value (absence of blood pressure control) was 72%.

By considering renovascular hypertensives as those patients in whom renal artery surgery or renal angioplasty led to amelioration of blood pressure, sensitivity and specificity of CRS in detecting RVH was 86.5% and 93%, respectively.

TABLE 3
Blood Pressure Outcome

	Cured	Improved	Failed
PTRA	7 (29.2%)	9 (37.5%)	8 (33.3%)
SR	11 (40.7%)	10 (37.0%)	6 (22.2%)

Note: PTRA = percutaneous transluminal renal angioplasty and SR = surgical repair.

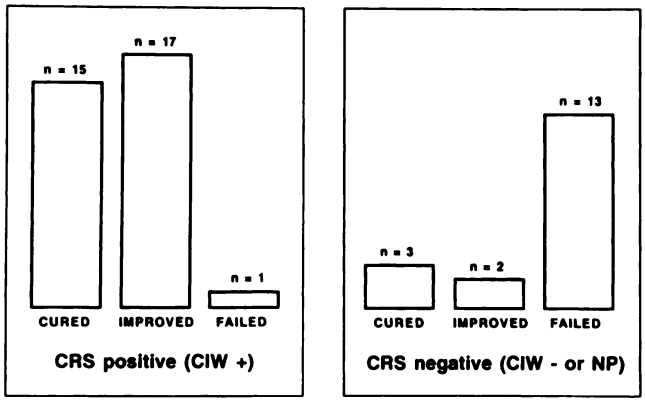

FIGURE 2. Subdivision of clinical results for cure, improvement or failure (see text for definitions) according to presence (CIW^+) or absence (CIW^-) of captopril-induced worsening (CIW).

DISCUSSION

Hypertension and RAS are two distinct conditions from both a physiopathologic and diagnostic point of view. Indeed, unlike RAS, which is identified by techniques based on morphological assessment of renal artery anatomy, such as angiography (*25,26*) and echo-Doppler flowmetry (*27*), RVH is a retrospective diagnosis. It can be inferred only from results of functional studies capable of detecting or unmasking renin activation due to RAS.

Tests such as renal vein renin ratio and captopril stimulation have proved, however, to be insufficiently accurate (*8–10,28,29*) in the detection of patients affected by RVH.

Promising results using revascularization techniques, especially renal angioplasty, have led to their widespread use on larger groups of patients. Indeed, in many centers, hypertensives with RAS >50% are submitted for renal artery revascularization, a procedure which is not risk-free and which may cause complications in at least 10% of treated patients (*5,30*). Furthermore, studies dealing with long-term follow-up report 10%–40% of patients in whom treatment failed to show any beneficial effect on blood pressure (*5,6,30*).

Patients undergoing renal revascularization could therefore benefit from a noninvasive test that can predict their blood pressure response.

Since the main mechanism involved in RVH is activation of the renin-angiotensin cascade, it might be assumed that a test capable of unmasking renin activation could reliably predict clinical outcome following treatment.

Captopril-renal scintigraphy may potentially be regarded as a test of this kind, although its role has not been fully defined. In many studies, it has been employed for RAS identification (*11,12,18,19,31*), while in others it has

been used to detect RVH, albeit in small groups of patients (*13–17*).

In the present study, renal angioplasty and surgical repair effects on blood pressure in a relatively large population were correlated to captopril-induced scintigraphic abnormalities in preintervention studies.

Renal angioplasty and surgery results in our study compare well with other reports (*5,6*) with regards to clinical outcome (29% cured, 37% improved, 33% failed for renal angioplasty and 41% cured, 38% improved and 22% failed for surgery).

Thus, in comparison with literature data, there are no differences in our results that could adversely affect our conclusions regarding the use of CRS.

We found a high correspondence between scintigraphic diagnosis and pressure control. In 45/51 patients (88%), captopril renography correctly predicted blood pressure outcome. In particular, cure or improvement in hypertension was achieved in 32/33 patients whose preintervention CRS detected signs of renin-angiotensin system activation (97% positive predictive value). The only case of clinical failure in the presence of positive captopril renography occurred in a patient with already compromised renal function (serum creatinine = 546 μmol/liter, the highest value in the population studied). The inefficacy of revascularization in patients affected by severe renal impairment has already been documented (*32*).

Negative CRS, on the other hand, was less accurate in predicting blood pressure results: 5/18 patients with negative CRS benefited from intervention (3 cured; 2 improved), for a negative predictive value of 72%. In this respect, one of the cured patients presented with multiple renal arteries, one of which was affected by stenosis and subsequently dilated. The parametric images, reported elsewhere as effective in detecting segmentary perfusion abnormalities (*19*), failed in this case to identify the patient in question. Furthermore, it is worth noting that in the remaining two cured patients, the lesion etiology was fibromuscular dysplasia, which has a very high cure rate (*5,6*).

As regards RAS severity, stenoses reduced vessel diameter by >50% in all patients, with the one remarkable exception of a 30% stenosis presenting clinical features of possible renovascular origin. This patient, who had a strongly positive CRS, underwent renal angioplasty and completely recovered. This patient confirms that stenosis severity is not necessarily related to its hemodynamic significance, which can be effectively detected by captopril renography.

The present study reports a lower sensitivity for RAS detection (33/51, 65%) than our earlier works (*18,19*). This may be accounted for by the population profile, which includes all those subjects from the two preceding reports who had subsequently undergone renal angioplasty or surgical repair, except those falling under exclusion criteria previously reported. For fortuitous reasons, all cases rated as false-negatives in those studies are represented here, thus artificially increasing the relative incidence of nonresponders to captopril administration.

Since they failed to show any improvement after treatment, these nonresponders were classified here as true-negatives for prediction of cure/improvement of blood pressure. This finding confirms the technique's high specificity for unmasking renin-angiotensin activation.

In conclusion, our study demonstrates that CRS is a strong predictor of blood pressure control in patients suspected of having RVH. While the predictivity of a negative test is fairly accurate (although further investigation is required), a positive CRS almost certainly predicts blood pressure cure or improvement. This is particularly relevant for clinical decision-making in patients at high surgical risk.

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(continued from page 2035)

SELF-STUDY TEST
Skeletal Nuclear Medicine
ANSWERS

diagnosed in the second and third decades of life. Chondroblastoma might be considered in this patient because this tumor typically involves an epiphysis or apophysis of a long tubular bone. However, by the time a chondroblastoma is symptomatic, the plain radiographs should show a radiolucent lesion. Additionally, these lesions generally show intensely increased activity on bone scintigraphy and would not be expected to give a photon-deficient lesion without marked destruction evident on the radiograph.

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ITEMS 17–21: Focal Renal Uptake of ^{99m}Tc MDP

ANSWERS: 17, T; 18, T; 19, F; 20, F; 21, T

Figure 4 demonstrates asymmetric renal activity at 3 hours and local retention of ^{99m}Tc MDP in the upper pole of the left kidney at 24 hours. Asymmetric renal activity is a common finding on bone scintigraphy and is most often due to slower clearance of the tracer from the more capacious collecting system of the kidney with greater activity. It is of potential clinical importance because it may be confused with or mask an osseous lesion in the 12th rib. Usually, by repeat imaging with the patient erect, this activity will disappear secondary to gravitational drainage or will change in position (as the kidney descends) such that its true nature will be apparent. Occasionally, repeat imaging at 24 hours or after administration of furosemide is necessary to resolve the problem. Even then, however, if there is focal calyceal obstruction by stone, tumor, or an inflammatory process, activity might persist in the affected calyces to 24 hours.

Most renal masses, including nearly all renal cell carcinomas, will appear on bone scintigraphy as focal areas of decreased activity by comparison with the normal renal parenchymal activity. One unusual exception is osteosarcoma metastatic to the kidney, in which there is accumulation of ^{99m}Tc MDP in the bone produced by the tumor. This is the actual cause of the abnormality seen in this patient.

Radiation therapy also has been reported to cause focal retention of ^{99m}Tc MDP within the irradiated volume of the kidney. This may reflect the reduced blood flow and prolonged tracer transit time in the irradiated renal tissue or accumulation in injured tissue.

In patients with sickle cell anemia, bone scintigraphy typically shows diffusely increased renal parenchymal activity in enlarged kidneys; locally increased activity is not seen. The increased activity in the upper pole of the left kidney of this patient should not be confused with the splenic uptake often seen in patients with sickle cell disease.

[Test Figure 4 reprinted with permission from Gilbert LA, Weiss MA, Hawkins HH, Nishiyama H, Aron BS. Detection of renal metastasis of osteosarcoma by bone scan. *Clin Nucl Med* 1983;8:325.]

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For further in-depth information, refer to the syllabus pages in Nuclear Medicine Self-Study I.