Annals of Nuclear Medicine Vol. 13, No. 2, 77–81, 1999

Prediction of response to revascularization in patients with renal artery stenosis by Tc-99m-ethylenedicysteine captopril scintigraphy

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The aim of the present study was to assess the predictive value of captopril scintigraphy with the new renal agent ^{99m}Tc-ethylenedicysteine (^{99m}Tc-EC) for post-interventional improvement in blood pressure. Twelve patients who had persistently high blood pressure with previous demonstration of various degrees of renal artery lesion on angiography were included into the study. Baseline and captopril scintigraphies were performed on the same day at 4 hour intervals after the injection of 74 and 296 MBq of ^{99m}Tc-EC, respectively. All patients had percutaneous transluminal angioplasty (PTA), and improvement in blood pressure was evaluated 3–6 months after the intervention. ^{99m}Tc-EC captopril scintigraphy successfully predicted a positive or negative outcome in 11 of 12 patients. In one patient with captopril induced renal function deterioration, scintigraphy failed to predict post-interventional response. Our preliminary findings showed that ^{99m}Tc-EC captopril scintigraphy can be used to determine patients who will benefit from revascularization.

Key words: Tc-99m-ethylenedicysteine, renovascular hypertension, renal artery stenosis, captopril scintigraphy

INTRODUCTION

The best means for the diagnosis of renal artery stenosis is arteriography but it has limitations in determining the hemodynamical significance of the stenosis and whether the detected renal anatomical lesion is the cause of the patient's hypertension. On the other hand, the standard of reference for renovascular hypertension is the cure or improvement of hypertension after revascularization. Renal scintigraphy with angiotensin converting enzyme inhibitors is recognized as a more sensitive and specific method in selecting those patients whose renin-angiotensin systems were activated secondary to renal artery stenosis and who might benefit from interventional therapy.

^{99m}Tc-ethylenedicysteine (^{99m}Tc-EC) is a new and potentially effective renal agent for evaluating kidney disorders. Besides the better physical characteristics of ^{99m}Tc labeling, easy preparation and low hepatobiliary uptake, ^{99m}Tc-EC has the potential to provide better visual and quantitative evaluation of renal function with a high renal clearance.[1] Clinical experience with this agent is limited, but initial results have shown that ^{99m}Tc-EC captopril renography is a useful test for use in the diagnosis and follow up of patients with renovascular disease.[2,3]

The aim of the present study was to assess the predictive value of ^{99m}Tc-EC captopril scintigraphy for post-interventional improvement in blood pressure.

MATERIALS AND METHODS

Patient Selection

Twelve patients who had persistently high blood pressure

Received September 25, 1998, revision accepted December 9, 1998.

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Table 1 Scintigraphic data with angiographic and revascularization correlations

Patients		Age	Sex	BUN/Creatinine (mg/d*l*)	Pre-PTA renogram grade (B/C)	Prediction	Angiography (% of stenosis)	Blood pressure (mmHg)		Revascularization response
								Before intervention	After intervention	
1	Left	22	M	35/1.1	0/4	Positive	FMD, 80–90%	180/120	130/80	PTA/cured
	Right				0/3		75%			
2	Right	26	F	15/0.7	0/1	Positive	FMD, 99% Branch stenosis	160/100	100/60	PTA/cured
3	Left	59	F	89/2.7	1/1	Negative	AS, ostial 75%	180/100	180/100	PTA/failed
	Right				1/1		50–60%			
4*		31	F	23/1.3	0/4	Positive	90% segmenter stricture	210/110	140/90	bypass + PTA/cured
5	Left	50	M	40/1.3	1/1	Negative	AS, 20% stenosis	180/110	180/110	PTA/failed
6	Left	55	F	28/1.0	4/4	Negative	AS, ostial 75%	240/160	240/160	PTA/failed
	Right				0/0		50–60%			
7	Right	41	F	26/1.2	0/3	Positive	FMD, 90%	170/110	130/80	PTA/cured
8	Left	40	F	18/0.9	0/2	Positive	FMD, 90%	220/120	220/120	PTA/failed
9	Right	35	F	16/1.0	0/3	Positive	FMD, 60%	190/120	120/80	PTA/cured
10*		22	M	42/1.8	1/1	Negative	90% string type stricture	180/110	180/110	PTA/failed
11	Left	70	M	34/1.5	1/4	Positive	AS, ostial 75%	200/120	160/100	PTA/improved
	Right				1/3		90%			
12	Left	40	M	20/1.2	0/1	Positive	FMD, 70%	190/110	130/90	PTA/cured

B/C: Baseline/Captopril, *: Transplant, FMD: Fibrous muscular dysplasia, AS: Atherosclerotic, PTA: Percutaneous transluminal angioplasty

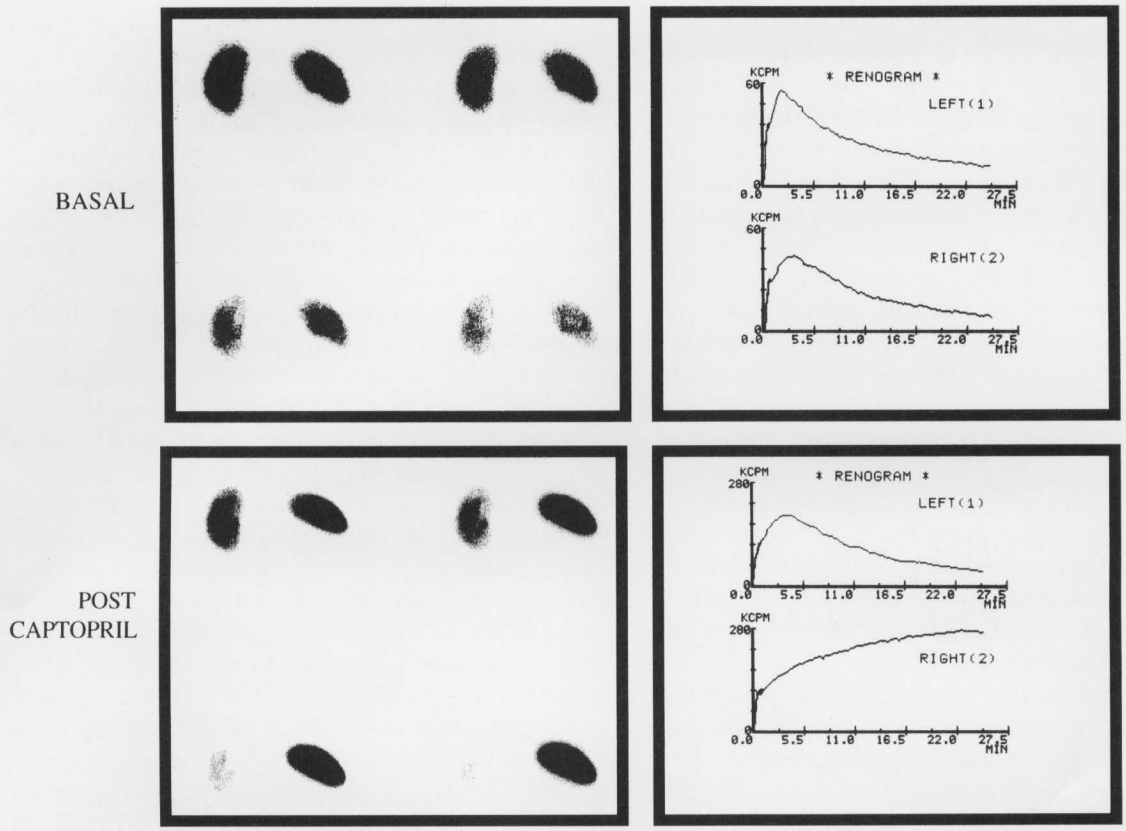
with previous demonstration of various degrees of renal artery lesion on angiography were included in the study after informed consent was obtained. Plasma creatinine and blood urea nitrogen values were determined as standard laboratory kidney function tests. Three patients had renal impairment with creatinine > 1.5 mg/d*l*. They were 5 men and 7 women with a mean age of 41 ± 15 years (4 bilateral, 5 unilateral, 1 unilateral-segmental involvement and 2 transplants with stricture at the anastomosis site). Transplant patients had their native kidneys. Angiotensin converting enzyme inhibitors and diuretics which might interfere with captopril renal scintigraphy were discontinued 1 week prior to the test.

Scintigraphy

Baseline and captopril ^{99m}Tc-EC scintigraphies were done on the same day. Basal renal scintigraphy was done after patients were hydrated with 10 m*l*/kg of water starting 1 hour before the procedure. ^{99m}Tc-EC was prepared from a commercial labeling kit (Medical University Foundation—Lodz, Poland) according to the manufacturer's instructions. Patients were placed in the sitting erect position reclining against a gamma camera equipped with an all-purpose, low energy, parallel-hole collimator. A lower-dose injection of EC (74 MBq) was given at the baseline. Dynamic images were recorded every second for 1 min and every 15 seconds for 20 min in conjunction with 2 min static images. Four hours after the baseline study captopril renal scintigraphy was performed 1 hour after the oral administration of 50 mg of captopril. The patients were injected with 296 MBq of ^{99m}Tc-EC and 40 mg of furosemide simultaneously and the data were acquired under the same conditions as the baseline scintigraphy.

Angiography and Revascularization

All the patients had transfemoral intra-arterial digital subtraction renal angiography. Renal angiograms were reevaluated by an experienced intervention radiologist who was not aware of the results of scintigraphy, with the accepted criteria.[4] Besides the degree of stenosis, lesions were also defined as fibrous muscular dysplasia (FMD) or atherosclerotic stenosis according to the criteria of Harrison and McCormack.[5] The degree of stenosis was determined by measuring the diameter of the stenosis at its greatest point compared to the diameter at a normal site and expressed as % of area stenosis. Therapeutic interventions included percutaneous transluminal angioplasty (PTA) in 11 and renal artery bypass surgery together with PTA in 1 patient. Technical failure of the intervention was excluded in these patients by showing < 50% stenosis in post-angioplasty angiography. In revascularized patients, blood pressure response to intervention was assessed 3–6 months after the therapy by applying the criteria of the cooperative study on renovascular hypertension.[6] Pre- and post-intervention blood pressures were recorded with



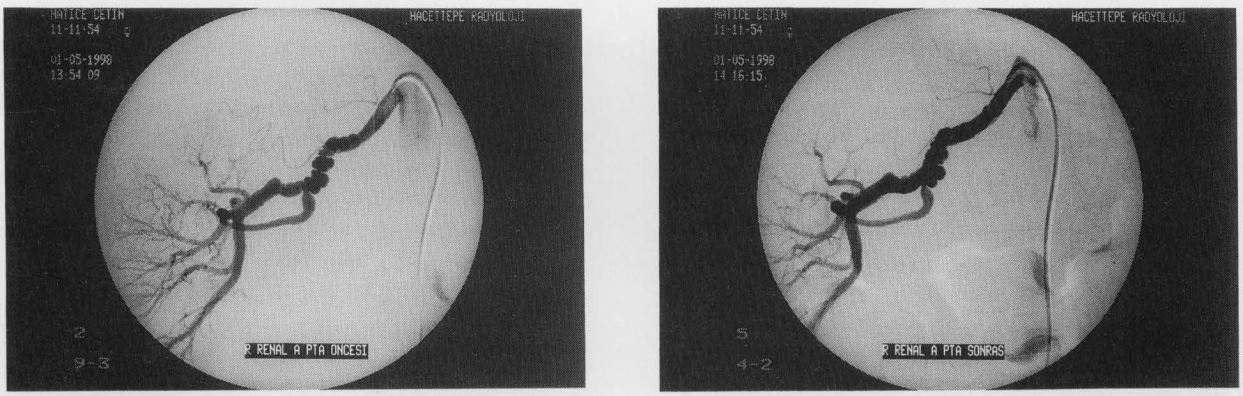


Fig. 1 Baseline and post-captopril scintigraphy in a patient with pre- and post-PTA angiographic correlation. (a) Baseline scinti-images and renogram curves showed normal findings (grade 0). After captopril there was marked parenchymal retention with an increasing type of renogram curve in the right kidney (grade 3). Scintigraphic findings predicted a positive response after revascularization. (b and c) Pre-PTA angiography showed high grade renal artery stenosis which was successfully corrected with the therapeutic intervention and post-PTA patient's blood pressure was normal.

the patients supine, after calculating the means of values obtained at least three times on different days. Cure following intervention was defined as average diastolic blood pressure ≤ 90 mmHg and at least 10 mmHg lower than pre-operative levels. Patients were considered improved, if there was a 15% decrease in average diastolic blood pressure and diastolic blood pressure > 90 mmHg. An unsatisfactory response after intervention was defined as < 15% decrease in average diastolic blood pressure or diastolic blood pressure > 110 mmHg.

Image Analysis and Interpretation of Captopril Scintigraphies

Regions of interest were drawn over the kidneys and surrounding background region corresponding to an area lateral to the kidneys. Time-activity curves of the kidneys

were obtained after background subtraction. Time to maximum activity (T_{max}) and residual cortical activity at 20 min (RCA) values were used for quantitation of renogram curves. Scintigraphies were read by two experienced nuclear physicians and consensus was reached by discussion when there was disagreement. The images were read without the knowledge of the angiography results and according to the guidelines suggested by the Radionuclides in Nephrourology group.[7] The renograms were judged by visual interpretation of the time activity curves. Patterns of renographic curves were graded from normal to an accumulation type curve (grade 0 = normal, grade 1 = minor abnormalities but T_{max} > 5 min RCA > 30%, grade 2 = markedly delayed excretion rate with a preserved washout phase, grade 3 = delayed excretion rate without a washout phase, grade 4 = renal failure pattern with measurable kidney uptake, grade 5 = renal failure pattern without measurable kidney uptake). Increases in T_{max} and RCA values were used to determine the grade of the renograms if visual classification was equivocal (to determine whether grade 0 or 1).

Captopril scintigraphies were interpreted as positive or negative outcome for the post-interventional blood pressure response according to the following criteria:

Negative outcome: 1-Normal findings in baseline and captopril scintigraphies or improvement in abnormal baseline findings (grade 1 or grade 2 renograms) after captopril intervention; 2-kidneys with reduced baseline renal function with an unchanged renogram curve predicts no improvement in blood pressure after revascularization.

Positive outcome: A change in the renogram grade ≥ 1 after captopril compared to the baseline study predicts improvement in blood pressure after revascularization.

RESULTS

Scintigraphic results with their angiographic correlation and improvement after revascularization are tabulated in Table 1.

^{99m}Tc-EC captopril scintigraphy successfully predicted a positive outcome in 7 of the 8 patients (Figure 1). On the other hand ^{99m}Tc-EC captopril test predicted all of the patients with negative outcome (4/4). There was good response to revascularization in patients with FMD (5 of 6) compared to patients with atherosclerotic stenosis (1 of 4). In one FMD patient with captopril induced renal function deterioration, scintigraphy failed to predict post-interventional response (patient No. 8). This patient had grade 2 renal function deterioration after captopril in the left kidney. There was complete resolution of scintigraphic findings in post-PTA captopril scan despite no improvement in hypertension.

DISCUSSION

Renovascular hypertension is a retrospective diagnosis defined as hypertension due to renal artery stenosis which can be cured by a revascularization procedure. Advances in PTA and surgical techniques have renewed interest in developing better screening tests for determining which patients have potentially correctable hypertension due to renovascular disease.[7] Captopril renography is accepted as one of the most cost effective among these tests for the diagnosis of renovascular hypertension.[8] The most common renal radiopharmaceuticals used to detect renovascular hypertension are ^{99m}Tc-MAG3, ^{99m}Tc-DTPA and ^{131}I- or ^{123}I-orthoiodohippurate. So far, no tracer has emerged as definitely superior and the optimal radiopharmaceutical for captopril test remains to be determined.[7,9] Recently, ^{99m}Tc-EC appeared as an alternative agent for the diagnosis of renovascular hypertension. Several authors had previously reported that a positive preoperative captopril renal scintigraphy is a strong predictor of curable hypertension by renal artery revascularization.[10,11] The remaining question is whether ^{99m}Tc-EC captopril test is any better or worse than scintigraphy with any other radiopharmaceutical. Recently, Kibar et al. compared ^{99m}Tc-EC with ^{99m}Tc-MAG3 in patients with suspected renovascular disease and concluded that ^{99m}Tc-EC has imaging properties similar to ^{99m}Tc-MAG3 and can be used safely for captopril scintigraphy.[12] The major advantage of ^{99m}Tc-EC over ^{99m}Tc-MAG3 is the easy labeling at room temperature and low hepatobiliary uptake. With the same purpose our group previously compared the performance of ^{99m}Tc-EC with ^{99m}Tc-DTPA for the diagnosis of renal artery stenosis.[13,14] We found that there is no statistically significant difference between ^{99m}Tc-EC and ^{99m}Tc-DTPA captopril scintigraphies for detecting renal artery stenosis. Nevertheless, due to its better imaging characteristics and more confident interpretation provided by the dramatic changes in the renogram grade after captopril intervention, ^{99m}Tc-EC captopril scintigraphy can be used particularly in patients with decreased renal function or branch artery stenosis.

In this study, we tested the predictive value of captopril scintigraphy with this new tracer for determining post-interventional blood pressure response. ^{99m}Tc-EC captopril scintigraphy accurately predicted a positive or negative outcome in all of the patients except one. In that patient, scintigraphy showed significant deterioration in left renal function after captopril but the patient's blood pressure did not improve despite a successful angioplasty and normal creatinine and BUN levels. Control captopril scintigraphy after 6 months gave normal findings, decreasing the possibility of restenosis. Nephrosclerosis or underlying severe essential hypertension may be the reason for the failure of revascularization to correct blood pressure. As expected there was good response to revascularization in FMD patients compared to patients

with atherosclerotic stenosis in this study. In previous reports on ^{99m}Tc-DTPA and ^{99m}Tc-MAG3, positive preoperative captopril renography has high positive predictive value for hypertension curability. On the other hand, negative captopril renography was less accurate in predicting post-operative blood pressure results.[10] Moreover, patients with atherosclerotic stenosis had a poorer response to revascularization than FMD patients. Our data were in concordance with those in the literature and, like the results obtained with other agents, captopril renography with ^{99m}Tc-EC also had a high positive predictive value (7/8). The high negative predictive value (4/4) we found with ^{99m}Tc-EC compared to studies with other agents will probably decrease as the number of patients increases.

Although these initial results should be confirmed in a broader patient population, our preliminary findings showed that captopril scintigraphy with this new renal agent can be used to determine patients who will benefit from revascularization.

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