Captopril Renal Scintigraphy in Patients with Hypertension and Chronic Renal Failure

Ioannis E. Datseris, Jamshed B. Bomanji, Edwina A. Brown, Kuldip S. Nijran, Ajit K. Padhy, Qaisar H. Siraj and Keith E. Britton

Department of Nuclear Medicine, St. Bartholomew's Hospital; and Department of Nuclear Medicine and Nephrology, Charing Cross Hospital, London, England

The aim of this prospective study was to determine the ability of the captopril renogram to reveal the presence of angiotensin II-dependent renovascular disorder in hypertensive patients with chronic renal failure and to assess the possibility of predicting beneficial effect of angiotensin-converting enzyme (ACE) inhibitors on renal function. **Methods:** Forty-one patients were evaluated. Baseline renal scintigraphy was performed with 80 MBq of ^{99m}Tc-mercaptoacetyltriglycine (MAG3) injected intravenously. Scintigraphy was repeated within a week with 25 mg of oral captopril given 60 min prior to the test. Using the measurements outlined by the Working Party on Diagnostic Criteria of Renovascular Hypertension with Captopril Renography, the patients were categorized into high (7 patients), indeterminate (19 patients) and low (15 patients) probability for renal artery stenosis (RAS). **Results:** In five of the seven patients with high probability, the presence of RAS was confirmed angiographically and corrective surgical procedure performed in two. In patients with GFR of 10 ml/min/1.73 m^2 and/or split renal function of 10% or less, all qualitative and semiquantitative scintigraphic parameters were nonspecific. Mean parenchymal transit time of tracer was a useful parameter to predict the beneficial effect of ACE inhibition therapy in 23 patients (14 low and 9 indeterminate probability of RAS). **Conclusion:** In hypertensive patients with renal failure, captopril renal scintigraphy can be utilized to identify the presence of angiotensin II-dependent renal dysfunction and possibly help to predict the beneficial effect of ACE inhibitor therapy.

Key Words: renal scintigraphy; captopril renal scintigraphy; hypertension; chronic renal failure

J Nucl Med 1994; 35:251–254

Angiotensin-converting-enzyme (ACE) inhibitors are now being increasingly used in patients with hypertension and renal failure since there is some evidence that they may be renoprotective (*1,2*). However, in clinical situations where the renin-angiotensin-aldosterone mechanism is active (e.g., renal artery stenosis), ACE inhibitors can have a detrimental effect on renal function (*3,4*). In this context, a noninvasive test that could detect functionally significant renal artery stenosis and identify beneficial or detrimental renal effect of ACE inhibitors in kidney failure would be very useful.

Numerous methods have been utilized for detecting renovascular disease (*5*). The benchmark diagnostic procedure is arteriography. However, with this investigation, the risk of acute renal failure in patients with moderate to severe impairment of kidney function is high (*6*). Furthermore, arteriography reveals only structural information with no indication whether any stenosis is of functional significance. An investigation that has become popular is captopril renal scintigraphy (*7*). This technique utilizes the pharmacologic effects of ACE inhibitors to unmask angiotensin II-dependent renovascular hypertension. However, experience with this technique in patients with chronic renal failure is limited (*8,9*).

The aim of this study was to demonstrate the presence of angiotensin II-dependent renovascular dysfunction with captopril-enhanced renal scintigraphy and to assess the possibility of predicting beneficial or detrimental effects of ACE inhibitors on renal function in hypertensive patients with chronic renal failure.

MATERIAL AND METHODS

Patient Selection

Forty-one patients (22 males, 19 females) ages 24–78 yr (mean = 59 yr), with hypertension and chronic renal failure were evaluated prospectively. There were 14 patients with diabetic nephropathy (insulin dependent 5; noninsulin dependent 9), six with intrinsic renal parenchymal disease documented histologically (glomerulonephritis 3; vasculitis 1; interstitial nephritis 1; scleroderma nephropathy 1) and 21 with severe uncontrolled hypertension. At presentation, seven patients were in heart failure (severe hypertension 6, diabetic 1). A comprehensive clinical and biochemical examination was undertaken prior to the referral. In each case obstructive uropathy was excluded with planar x-rays and ultrasonography. Glomerular filtration rate (GFR) was measured with ^{51}Cr EDTA and values were expressed in ml/min/1.73 m^2 body surface area (*10*). Only patients with clinical evidence of chronic renal failure (GFR of 50% or less than predicted normal value) and hypertension (systolic BP >140 mmHg and diastolic BP >95 mmHg) were included in this study. The duration of hypertension varied between 1 and 17 yr.

Received Aug. 17, 1993; revision accepted Oct. 11, 1993.

For correspondence or reprints contact: Dr. J. Bomanji, Dept. of Nuclear Medicine, St. Bartholomew's Hospital, West Smithfield, London EC1A 7BE, U.K.

TABLE 1
Grading System for the Renogram According to the Working Party on Diagnostic Criteria of Renovascular Hypertension with Captopril Renography (*11*)

Grade 0	Normal
Grade 1	Mild delay in upslope, maximal activity, T_{max} ($6 \leq T_{max} \leq 11$), or excretory phase.
Grade 2	A. Delay in upslope and T_{max} with evidence of an excretory phase. B. Delay in upslope and T_{max} without evidence of an excretory phase.
Grade 3	Marked reduction or absence of uptake.

Renal Scintigraphy

A standard imaging protocol was followed for all patients. ACE inhibitors, if prescribed, were stopped 7 days prior to scintigraphic study. Other medication was continued during performance of the test. A large field of view gamma camera (GE 400 AT and Scintronix 480) with a general purpose, parallel-hole, low-energy collimator with an on-line computer (Micas V) was used. The patient sat in a reclining position with the camera positioned posteriorly, angled at approximately 10°–20° back from vertical. The camera field of view included the left ventricle and the kidneys. Data was acquired immediately after a bolus injection of 80 MBq ^{99m}Tc-mercaptoacetyltriglycine (MAG3). The data were collected in 10-sec frames with a 64 × 64 pixel matrix for 120 frames.

Renal scintigraphy was repeated within a week with 25 mg of oral captopril administered 60 min prior to injection. Blood pressure was monitored before captopril and at 15-min intervals for 2 hr.

The studies were classified according to the criteria outlined by the Working Party on Diagnostic Criteria of Renovascular Hypertension with Captopril Renography (*11*). Briefly, the scintigraphic images and computer-generated time-activity curves were evaluated and the following parameters were calculated: upslope, maximal activity and third phase of each time-activity curve; and time to maximal activity (T_{max}). Based on these parameters, the renograms were graded from 0–3 (Table 1). Deterioration of grade following captopril administration was deemed as high probability of renal artery stenosis, no change in grade (except grade 0) as indeterminate and improvement in grade as low probability of renal artery stenosis (*11*).

In addition to the above criteria, split renal function (percentage of total uptake in the left and right kidneys) was calculated. Furthermore, the possibility of using mean parenchymal transit time (MPTT) of the tracer as another parameter was also evaluated. MPTT was calculated as described previously and a value of less than 240 sec was considered within the normal range (*12*). A change of greater than 30 sec in MPTT after captopril was considered significant. A significant fall in MPTT was considered as a beneficial effect and a rise in MPTT as a detrimental effect of a single dose of captopril. The physiological basis of these parameters obtained for a nonreabsorbable solute such as ^{99m}Tc-MAG3 are discussed elsewhere (*7,13*).

In each case, blood pressure and renal function were monitored for a minimum of 6 mo after captopril renal scintigraphy. Renal angiography was only performed when the patient was young or where blood pressure control was poor after 4 wk of treatment and where clinical risks of complications were considered to be minimal. Angiography was not considered as a mandatory gold standard for this study.

RESULTS

Seven patients were classified as having a high, 15 patients had a low and 19 patients had an indeterminate probability of renal artery stenosis (Table 2). No side effects were noted in response to 25 mg of oral captopril in this study. The maximum observed fall in systolic BP was 25 mmHg and diastolic BP was 25 mmHg. There was no correlation between probability of finding renal artery stenosis on scintigraphic criteria and the degree of fall in the blood pressure.

In the seven patients with a high probability of renal artery stenosis, all scintigraphic parameters after captopril intervention, including MPTT, were abnormal. In five of these cases, the diagnosis was confirmed by renal arteriography. Of the five patients, two underwent angioplasty with subsequent improvement in blood pressure (although not to the normal range) and renal function. In the other three patients, intervention was considered unwise because of technical difficulties and risk of complications. In two cases, renal arteriography was not performed as it was thought that this investigation would have carried a high risk of complication. One of the two patients had a low GFR (18 ml/min) and was put on dialysis. The second patient had received a heart transplant and was on a high dose of cyclosporin at the time of captopril scintigraphy.

In the indeterminate probability group, the MPTT showed no change in seven, a bilateral significant fall in five (MPTT range 45–174 sec) and a unilateral fall in four (MPTT range 35–158 sec) with no significant change in the contralateral kidney. In the remaining three cases, bilateral significant prolongation of MPTT (range 54–312 sec) was observed in two cases, and in the third patient, prolongation of MPTT in the left kidney and a decrease in the contralateral kidney was noted.

In 15 patients with a low probability of renal artery stenosis, the MPTT showed a bilateral significant fall in seven, a unilateral significant fall in seven (contralateral kidney had MPTT within normal range) and no change in one.

The GFR ranged from 10–53 ml/min/1.73 m^2 body surface area (mean = 37 ml/min). In six patients classified in the indeterminate category, with GFR of 10 ml/min (three

TABLE 2
Patients with Renal Failure and Hypertension Classified According to the Working Party on Diagnostic Criteria of Renovascular Hypertension with Captopril Renography

	High	Indeterminate	Low
Diabetic nephropathy	2	6	6
Severe uncontrolled hypertension	5	9	7
Intrinsic renal parenchymal disease	0	4	2

TABLE 3
Glomerular Filteration Measurements in Patients on and off ACE Inhibition Therapy During the Study

Total no. of patients	MPTT	GFR (expressed in ml/min/1.73 m²) Time of imaging	GFR (expressed in ml/min/1.73 m²) Follow-up (~6 mo)
23 (on ACE)	decrease	15–53 (mean = 36)	15–56 (mean = 38.3)
8 (off ACE)	increase or no change	11–46 (mean = 24.5)	12–44 (mean = 23.6)
3 (off ACE)	IM	10	on dialysis

on ACE = ACE inhibition therapy was initiated or continued; off ACE = ACE inhibition therapy was discontinued; IM = imprecise; MPTT = mean parenchymal transit time.

patients) and/or where the split renal function was less than 10% (three patients), all qualitative and semiquantitative scintigraphic parameters were thought to be imprecise due to poor count statistics.

In 23 patients (indeterminate probability of RAS 9 and low 14) where MPTT was significantly reduced on post-captopril scintigraphy, ACE inhibition therapy was initiated or continued. In these patients, GFR, measured approximately 6 mo postscintigraphy, showed improvement (but not statistically significant) or remained stable (rate of GFR decline <0.2 ml/min/mo) (Table 3). In 11 patients (indeterminate probability of RAS 10 and low 1) where MPTT was significantly prolonged or showed no change, ACE inhibition therapy was not initiated or was discontinued and other antihypertensive medication was started. Of these 11 patients, three went on dialysis during the follow-up period, while the remaining eight showed no significant change (rate of GFR decline <0.2 ml/min/mo).

DISCUSSION

In this study we have demonstrated that ^{99m}Tc-MAG3 captopril scintigraphy could be used to identify the presence of angiotensin II-dependent renovascular dysfunction in a subset of patients with hypertension and chronic renal failure.

In moderate to severe renal failure, some of the qualitative and semiquantitative parameters used to assess captopril renal studies can produce erroneous results depending on the degree of renal impairment. The logical question which still needs to be answered is what degree of renal impairment invalidates the semiquantitative scintigraphic parameters of a captopril study mentioned previously? The tentative answer obtained from our data suggests that a total GFR of approximately 10 ml/min, or a kidney with split function of 10% (GFR less than 5 ml/min) or less, the semiquantitative parameters obtained with ^{99m}Tc-MAG3 captopril renal scintigraphy should be viewed with caution. We have observed similar results in nonhypertensive patients with chronic renal failure (unpublished data).

The comparison of split renal function before and after captopril has been the simplest and most commonly used semiquantitative parameter to assess the changes in renal function. This measure is quite sensitive in patients with unilateral functionally significant renal artery stenosis (*14,15*). However, in renal failure and bilateral renovascular disorder, it may not accurately reflect the change in renal function. Furthermore, bilateral or unilateral improvement in function after captopril is difficult to assess on the basis of split renal function.

The T_{max} of the renogram curve and MPTT are useful measures in mild failure. However, as the failure progresses to moderate and severe stages, time-activity curves show very prolonged upslope without evidence of a third phase or marked reduction of uptake and absence of T_{max}. In these cases it is difficult to utilize T_{max} as an index to assess captopril-induced changes. MPTT, however, does not suffer from this problem, especially if calculated by the deconvolution method (*12*). This advantage of MPTT over T_{max} was observed in patients categorized as indeterminate, where a reduction in MPTT after captopril was shown in nine cases, indirectly predicting a beneficial effect of ACE inhibition therapy.

It was interesting to note that in patients where MPTT was significantly reduced after captopril (9 indeterminate and 14 low probability of RAS) and where ACE inhibition therapy was initiated or continued, the renal function showed improvement or no change on follow-up. This further reinforces the predictive value of this test. However, where MPTT was further prolonged after captopril or showed no change, ACE inhibition therapy was not initiated. This essentially was the limitation of our study since the detrimental predictive value of this test in indeterminate probability of RAS could not be evaluated. It would have been interesting to know if the hemodynamic changes would have been different in these patients if long term ACE inhibition therapy had been administered.

In this study, it was also observed that a high probability captopril renal study does not always imply the presence of renal artery stenosis; rather it confirms the presence of intrarenal renin-angiotensin-aldosterone mechanism activation. Patients with scleroderma nephropathy and cyclosporin toxicity are examples of pathologic states in which it is known that the renin-angiotensin-aldosterone mechanism may be active (*16,17*). In this study, the patient with scleroderma nephropathy was labeled as indeterminate probability and the patient with cyclosporin toxicity as high probability for renal artery stenosis. In both cases, MPTT was significantly prolonged after captopril. In the case of cyclosporin toxicity, the captopril study was repeated after 3 wk on a comparatively low dose of cyclosporin and the second study was classified as low probability of renal artery stenosis. However, the second scintigraphic investigation was not included in this series for analysis. Further work is required to evaluate the efficacy of captopril renal scintig-

raphy in conditions other than renal artery stenosis where the renin-angiotensin-aldosterone mechanism is active.

In conclusion, we feel that a ^{99m}Tc-MAG3 captopril renal study with MPTT measurements should be performed in high-risk patients with hypertension and chronic renal failure who have a total GFR of greater than 10 ml/min and split renal function of greater than 10%. If abnormal, the result would be consistent with angiotensin II-dependent renovascular dysfunction. If normal, it may indicate a beneficial effect of ACE inhibition on renal function.

REFERENCES

1. Williams GH. Converting-enzyme inhibitors in the treatment of hypertension. *N Engl J Med* 1988;319:1517–1525.
2. Keane WF, Anderson S, Aurell M, Zeeuw D de, Narins RG, Povar G. Angiotensin converting enzyme inhibitors and progressive renal insufficiency. *Ann Intern Med* 1989;111:503–516.
3. Hricik DE, Browning PJ, Kopelman R, Goorno WE, Madias NE, Dzau VJ. Captopril-induced functional renal insufficiency in patients with bilateral renal artery stenoses or renal artery stenosis in a solitary kidney. *N Engl J Med* 1983;308:373–376.
4. Rimmer JM, Gennari FJ. Atherosclerotic renovascular disease and progressive renal failure. *Ann Intern Med* 1993;118:712–719.
5. Mann SJ, Pickering TG. Detection of renovascular hypertension. State of the art: 1992. *Ann Intern Med* 1992;117:845–853.
6. Berns JS, Rudnick MR. Radiocontrast media associated nephrotoxicity. *Kidney* 1992;24:1–5.
7. Nally JV, Black HR. State-of-the-art review: captopril renography-pathophysiological considerations and clinical observations. *Semin Nucl Med* 1992;22:85–97.
8. Scoble JE, Mclean A, Stansby G, Hamilton G, Sweny P, Hilson AJW. The use of captopril-DTPA scanning in the diagnosis of atherosclerotic renal artery stenosis in patients with impaired renal function. *Am J Hypertens* 1991;4:721S–723S.
9. Setaro JF, Chen CC, Hoffer PB, et al. Captopril renography in the diagnosis of renal artery stenosis and the prediction of improvement with renovascularization: the Yale Vascular Center experience. *Am J Hypertens* 1991;4:698S–705S.
10. Nimmon CC, McAlister JM, Hickson B, Cattell WR. Study of the post-equilibrium slope approximation in the calculation of glomerular filteration rate using the Cr-51 EDTA single injection technique. In: *Dynamic studies with radioisotopes in medicine*, Vol. I. Vienna: IAEA; 1974:249–256.
11. Nally JV, Chen C, Fine E, et al. Diagnostic criteria of renovascular hypertension with captopril renography: a consensus statement. *Am J Hypertens* 1991;4:749S–752S.
12. Al-Nahas A, Marcus A, Bomanji J, et al. Validity of mean parenchymal transit time as a screening test for the detection of functional renal artery stenosis in hypertensive patients. *Nucl Med Commun* 1989;10:807–815.
13. Britton KE, Maisey MN, Hilson AJW. Renal radionuclide studies. In: Maisey MN, Britton KE, Gilday DL, eds. *Clinical nuclear medicine*, 2nd ed. London: Chapman & Hall Medical; 1991:91–130.
14. Sfakianakis GN, Bourgoignie JJ, Jaffe D, et al. Single dose captopril scintigraphy in the diagnosis of renovascular hypertension. *J Nucl Med* 1987; 9:1983–1992.
15. Sadler MC, Black HR. Captopril renal scintigraphy: a clinician's perspective. In: Hoffer PB, ed. *The year book of nuclear medicine 1990*. Chicago: Year Book Medical Publications, Inc.; 1990:13–34.
16. Zawada ET, Blements PJ, Furst DA, et al. Clinical course of patients with scleroderma renal crisis treated with captopril. *Nephron* 1981;27:74–78.
17. Dubovsky EV, Russell CD. Diagnosis of renovascular hypertension after renal transplantation. *Am J Hypertens* 1991;4:724S–730S.

EDITORIAL

Should the Role of Captopril Renography Extend to the Evaluation of Chronic Renal Disease?

The article by Datseris et al. in this issue of the *Journal* (*1*) addresses an important question in the differential diagnosis of renovascular hypertension. It also suggests another potential use for captopril scintigraphy in patients with hypertension and renal disease.

Numerous studies have been reported which evaluate the sensitivity and specificity of captopril renography in renovascular hypertension (*2*). Changes induced in the renogram of a patient with unilateral renovascular disease may be quite dramatic. An otherwise normal-appearing kidney curve may become abnormal after blockade of the renin-angiotensin system by captopril or some other converting enzyme inhibitor. As the baseline renogram curve becomes increasingly abnormal with declining renal function, the changes induced by converting enzyme inhibitors become increasingly unreliable and difficult to interpret (*3*). Among patients with severely reduced renal function, the administration of converting enzyme inhibitors may be of no value at all in the differential diagnosis of essential from renovascular hypertension. This is a significant problem since a large number of patients with renovascular hypertension suffer from a reduction in renal function, either as a consequence of bilateral disease or as a result of long-standing severe hypertension and associated nephrosclerosis. Even in the presence of severe unilateral renal artery stenosis, the captopril renogram may be difficult to interpret.

Hypertension is an invariable consequence of the loss of renal function in patients with chronic renal failure. Therefore, the nephrologist or nuclear medicine physician is faced with two groups of patients who may appear quite similar on the basis of clinical findings, but whose disease has very different etiologies. The problem is further compounded by the high prevalence of secondary renal artery stenosis in hypertensive individuals (*4*). Thus, the patient with significantly impaired renal function and secondary hypertension is not easily differentiated from the patient with primary renovascular disease and secondary impairment of renal function.

A further dilemma is the occurrence of compromised renal function after therapeutic administration of angiotensin-converting enzyme inhibitors to patients with bilateral renal artery stenosis or renal artery stenosis in a solitary kidney. Acute renal failure may occur in these patients because a vital compensatory mechanism to maintain renal function is pharmacologically

Received Nov. 2, 1993; accepted Nov. 12, 1993.
For correspondence or reprints contact: M. Donald Blaufox, MD, Albert Einstein School of Medicine, 1300 Morris Park Ave., Bronx, NY, 10461.