False-Positive Captopril Renography in Patients Taking Calcium Antagonists

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Captopril-enhanced renography is the noninvasive test of choice for the diagnosis of renovascular hypertension. Previous studies have shown that bilateral symmetrical changes are associated with many renal conditions. However, patients with normal renal angiography occurred in our institutions despite this scintigraphic pattern, and no known conditions could explain these results. The purpose of this study was to evaluate the diagnostic implications of bilateral symmetrical renal function deterioration on captopril renography. **Methods:** Eighty-six captopril renal scintigraphies performed at two centers to exclude renovascular hypertension (50 consecutive patients after the observation of a bilateral symmetrical renal function deterioration despite a normal angiogram at one institution and 36 patients with both captopril renography and renal angiography at the other institution) were retrospectively reviewed. Baseline and captopril-enhanced renograms were obtained with ^{99m}Tc-mercaptoacetyltriglycine and a 1-day protocol in 50 patients; 36 patients were studied using ^{99m}Tc-diethylenetriamine pentaacetic acid and a 2-day protocol. Bilateral symmetrical renal function deterioration was detected. **Results:** Ten patients presented with bilateral symmetrical renal function deterioration on their captopril renograms; 9 of them were taking calcium antagonists ($p = 0.015$). Control studies performed in 5 patients without these medications demonstrated normal captopril renograms in 4 and persistant renal dysfunction in 1. No explanation was found for the patient who was not taking any medication. Angiograms performed in 5 patients showed normal renal arteries. An 11th patient who was taking a calcium antagonist showed dysfunction of his one kidney on the captopril renogram but no artery stenosis on the renal angiogram. **Conclusion:** Calcium antagonists can cause false-positive captopril renograms. These medications should be stopped before captopril renography, and physicians should be aware of this possible drug interaction if bilateral symmetrical renal function deterioration is seen on a patient's captopril renogram.

Key Words: angiotensin-converting enzyme inhibitor; renography; renovascular hypertension

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Hypertension is a major cardiovascular risk factor. On the other hand, renovascular hypertension is the most frequent cause of curable hypertension, and captopril renal scintigraphy is still the noninvasive test of choice for diagnosing renovascular hypertension (*1*).

It is well known that renovascular hypertension depends on the high production of renin by the juxtaglomerular apparatus of the kidney(s) perfused through a stenotic artery. The captopril renogram exploits the blocking effect of an angiotensin-converting enzyme (ACE) inhibitor on the hyperproduction of angiotensin II that is found in these patients. After the decrease of the production of angiotensin II, the postglomerular arterioles resistance falls and this causes a secondary reduction in glomerular filtration pressure, which results in a decrease of the function of the affected kidney(s). This reduction in renal function can be detected when a baseline study is compared to captopril-enhanced renography. Therefore, bilateral renal function deterioration is expected in patients with renovascular hypertension caused by bilateral artery stenosis.

However, the occurrence of a patient who had normal renal angiography despite bilateral symmetrical renal function deterioration prompted us to evaluate the significance of symmetrical renal dysfunction on captopril renograms. We report the clinical effects of calcium antagonists on captopril renography.

MATERIALS AND METHODS

Patient Population and Preparation

The files of 86 patients who underwent captopril renography were reviewed retrospectively. These patients were investigated in two institutions with two different protocols and had been referred for possible renovascular hypertension.

Patients in Group A were studied at the Complexe Hospitalier de la Sagamie from October 1995 to January 1996. Fifty patients who underwent captopril renography to exclude renavascular hypertension were chosen at random and included in a control study after normal renal angiography despite bilateral symmetrical renal function deterioration on captopril renography.

Patients in Group B were studied at the Hôtel-Dieu de Montréal Hospital from January 1993 to December 1995. All patients who underwent a baseline and a captopril study on separate days followed by renal angiography were included in this study.

Fifty patients (Group A: 28 women, 22 men; mean age 63 ± 12 yr) underwent captopril renography with ^{99m}Tc-mercaptoacetyltriglycine (MAG3) and a same-day protocol. Thirty-six patients (Group B: 27 women, 9 men; mean age 61 ± 12 yr) underwent captopril renography with ^{99m}Tc-diethylenetriamine pentaacetic acid (DTPA) and a 2-day protocol. All ACE inhibitors were withheld 48–72 hr before imaging at both institutions. Patients in Group A were instructed to drink only water and to fast at night, whereas patients in Group B were instructed to eat a light breakfast without drinking coffee or tea before the test.

Baseline Study

Group A. Two hundred ninety-six MBq (8 mCi) ^{99m}Tc-MAG3 were injected in a forearm vein, and images were obtained with the patient in a supine position. The gamma detector was fitted with a low-energy, all-purpose, parallel-hole collimator and positioned under the imaging table. The photopeak was centered at 140 keV with a 20% energy window. Both analog and sequential digital images were acquired to obtain serial renal scintigraphy (20 frames × 60 sec). Automated lateral regions of interest (ROIs) were used to estimate the background activity, and background-corrected time-activity curves were executed with ROIs drawn over cortical activity and the whole kidney.

Group B. The renogram and sequential images were obtained after injecting 370 MBq (10 mCi) ^{99m}Tc-DTPA in a forearm vein

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with the patient in a supine position. The analog images included a dynamic study (16 frames × 3 sec) and sequential renal images (9 frames × 60 sec followed by 9 frames × 120 sec). Digital data also were recorded each second for the first 60 sec (flow study) and with a 15-sec frame rate afterward for 30 min. ROIs were drawn around the whole kidney, cortex and pelvis. Semilunar background ROIs were drawn also. Cortical time to peak and residual cortical activity at 30 min were obtained from the background-corrected time-activity curves. The differential glomerular filtration rate (GFR) percentage was derived from the background-corrected whole-kidney counts that were integrated between 1 and 3 min postinjection. Finally, the GFR was calculated from the ^{99m}Tc-DTPA plasmatic curve using three blood samples and a monoexponential model.

Captopril Study

Group A. After the baseline study, 25 mg captopril were administered, and the patient had to drink 800 ml water. After a waiting period of 1 hr, renography was repeated with 555 MBq (15 mCi) ^{99m}Tc-MAG3. Both analog and digital images were acquired to obtain a flow study (20 frames × 3 sec) and serial renal scintigraphy (20 frames × 60 sec). Background-corrected time-activity curves also were executed with ROIs drawn over cortical activity and the whole kidney. Blood pressure was recorded before and after the administration of captopril.

Group B. The captopril ^{99m}Tc-DTPA study was done on a separate day. This study was performed 1 hr after administration of 25 mg captopril. Blood pressure was monitored both before and at 15-min intervals for the next hour after the captopril administration. Patients had to drink 500–800 ml water during this same period, and both analog and digital studies were repeated using the same acquisition protocol as for the baseline study.

Data Analysis

Group A. Scintigraphic images were analyzed visually, and the renograms were interpreted on the basis of a grading system derived from the Working Party on Diagnostic Criteria of Renovascular Hypertension with Captopril Renography criteria (*2,3*). The grading system was as follows: Grade 0, normal; Grade 1, mild delay in the time to maximal activity (Tmax) with 6 min ≤ Tmax ≤ 11 min or mild delay in excretory phase; Grade 2A, delay in Tmax ≤ 11 min with evidence of an excretory phase; Grade 2B, delay in Tmax without evidence of an excretory phase; and Grade 3, marked reduction or absence of uptake. The renogram was interpreted as a high probability of renovascular hypertension when a higher grade was observed on the captopril-enhanced renogram. The renogram was judged as an intermediate probability of renovascular hypertension when the baseline study and captopril-enhanced renogram showed the same grade except for Grade 0, in which case a low probability of renovascular hypertension was reported. A captopril renogram with a lower grade than the baseline study was interpreted as a low probability of renovascular hypertension except when a Grade 3 captopril renogram was associated with a Grade 2B baseline study, in which case an intermediate probability of renovascular hypertension was reported. Patients with symmetrical renal function deterioration were identified, and their renal angiography results were recovered.

Group B. The diagnosis of renovascular hypertension was made if two of three criteria were observed when comparing the captopril study with the baseline ^{99m}Tc-DTPA study. The criteria were: (a) time to peak increased ≥ 1 min; (b) residual cortical activity at 30 min increased ≥ 10%; and (c) GFR of the affected kidney decreased ≥ 10%. Patients with bilateral symmetrical renal function deterioration were identified, and their renal angiography results were recovered.

TABLE 1
Medication Taken by Patients Who Had Bilateral Symmetrical Renal Function Deterioration on Captopril Renography

Patient no.	Medication (mg/day)
Group A	
1	Amlodipine besylate (10), indapamide (2.5)
2	Amlodipine besylate (10), metoprolol (200), ASA (650)
3	Amlodipine besylate (10)
4	Verapamil (240), indapamide (2.5)
5	Nifedipine (60)
6	None
Group B	
7	Diltiazem-long action (240)
8	Nifedipine-long action (60), clonidine (0.1), triamterene-hydrochlorothiazide
9	Diltiazem (180), acebutolol (100), diclofenac (as needed)
10	Hydrochlorothiazide (12.5), atenolol (50)
11*	Nifedipine-long action (40), indapamide (2.5), atenolol (50)

*Patient with one kidney.

Statistical Analysis

The chi-square test was used to investigate a possible difference in the rate of bilateral symmetrical renal function deterioration between patients taking calcium antagonists and those who did not. We considered it statistically significant if $p \leq 0.05$.

RESULTS

Forty-nine (57%) of the 86 patients who underwent captopril renography were taking calcium antagonists before their test. Ten (20%) had bilateral symmetrical renal function deterioration on their renograms. Only 1 of the 37 patients (2.7%) who did not take calcium antagonists presented with bilateral symmetrical renal dysfunction on renography. The difference between the two groups was statistically significant ($\chi^2 = 5.92$, $p = 0.015$).

Ten patients (6 in Group A and 4 in Group B) showed bilateral symmetrical renal function deterioration on captopril renography. An 11th patient in Group B showed functional deterioration of a single kidney. All baseline studies were normal (Grade 0) in these patients. In Group A, the grade of the captopril renogram was 1 in 3 patients and 2B in the other 3 patients. In Group B, the captopril renograms corresponded to Grade 1. Renal angiography was performed in 6 patients (1 in Group A and 5 in Group B, including the patient with one kidney) and showed normal renal arteries.

After the angiographic results of the patient in Group A, a drug interaction was suspected as the cause of the bilateral symmetrical renal function deterioration. Ten of these patients (including the patient with one kidney) were taking calcium antagonists (Table 1). Three patients were taking amlodipine besylate, 5 were taking nifedipine, 1 was taking diltiazem and 1 was taking verapamil. The last patient did not take any medication, and no explanation was found for the renal function deterioration observed on this patient's captopril renogram.

Among the patients in Group A, a control study performed 3 days after the cessation of calcium antagonists (without stopping other medications) demonstrated normal results in 4 patients (Fig. 1) and persistent renal function deterioration in 1 (Fig. 2). Overall, 18 patients (36%) in Group A and 31 patients (86%) in Group B were taking calcium antagonists at the time of their captopril scan. In Group A, 3 patients who were taking diltiazem at the time of the study had normal captopril renography results. No patient had hypotension after the administration of captopril (Table 2), and no patient had pelvic retention.

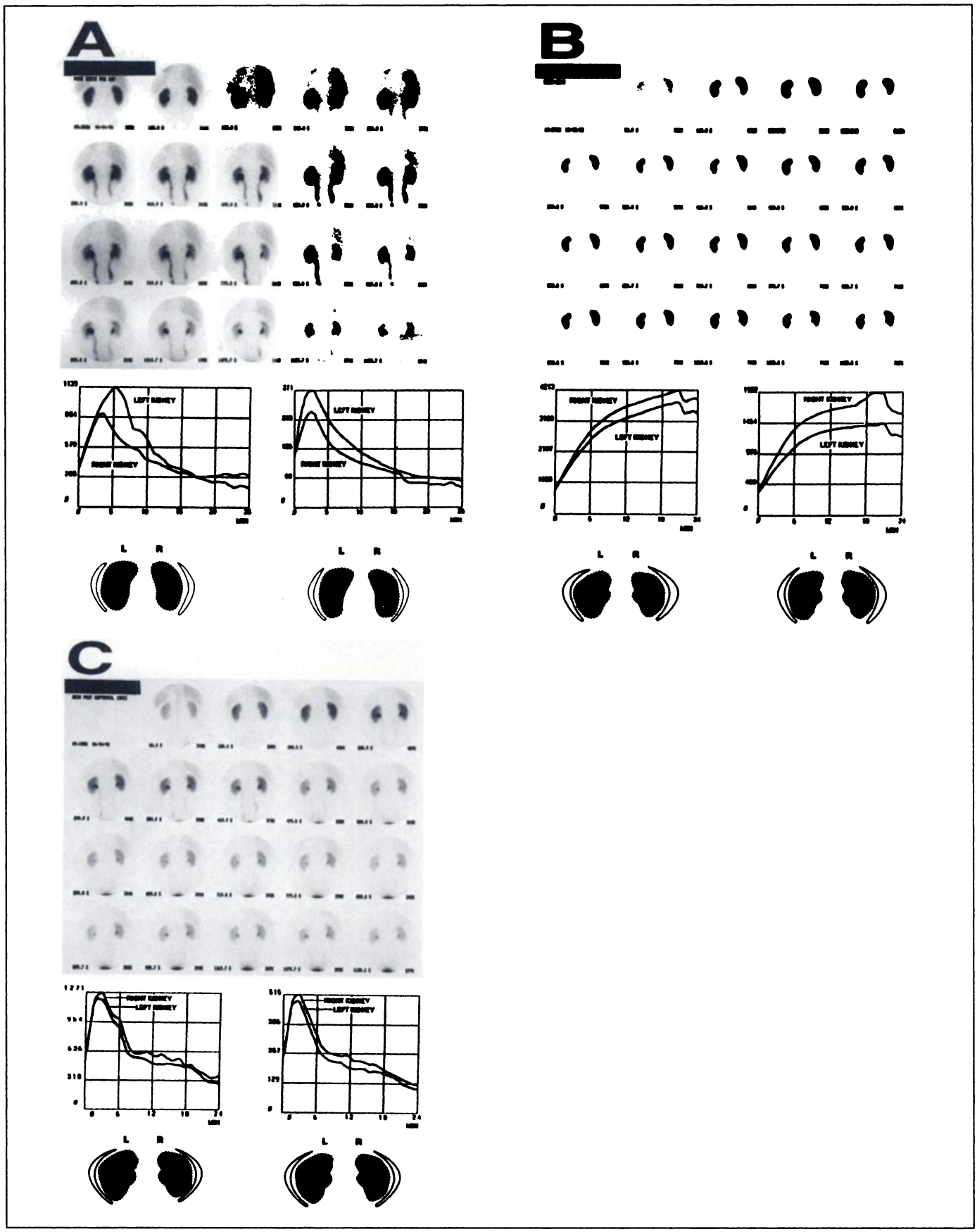

FIGURE 1. Example of bilateral symmetrical renal function deterioration observed on ^{99m}Tc-MAG3 captopril renogram. This 63-yr-old man was referred for hypertension de novo and was taking amlodipine besylate. He was not taking any other medication. Upper half: Serial renal scintigrams (20 min). Lower half: Total and cortical renograms (time-activity curves = 25 min) with regions of interest over kidneys (dotted lines) and background (solid lines). (A) Normal baseline renography and renograms. (B) Bilateral symmetrical renal dysfunction on captopril renography and renograms. (C) Normal captopril renography and renograms after cessation of calcium antagonist.

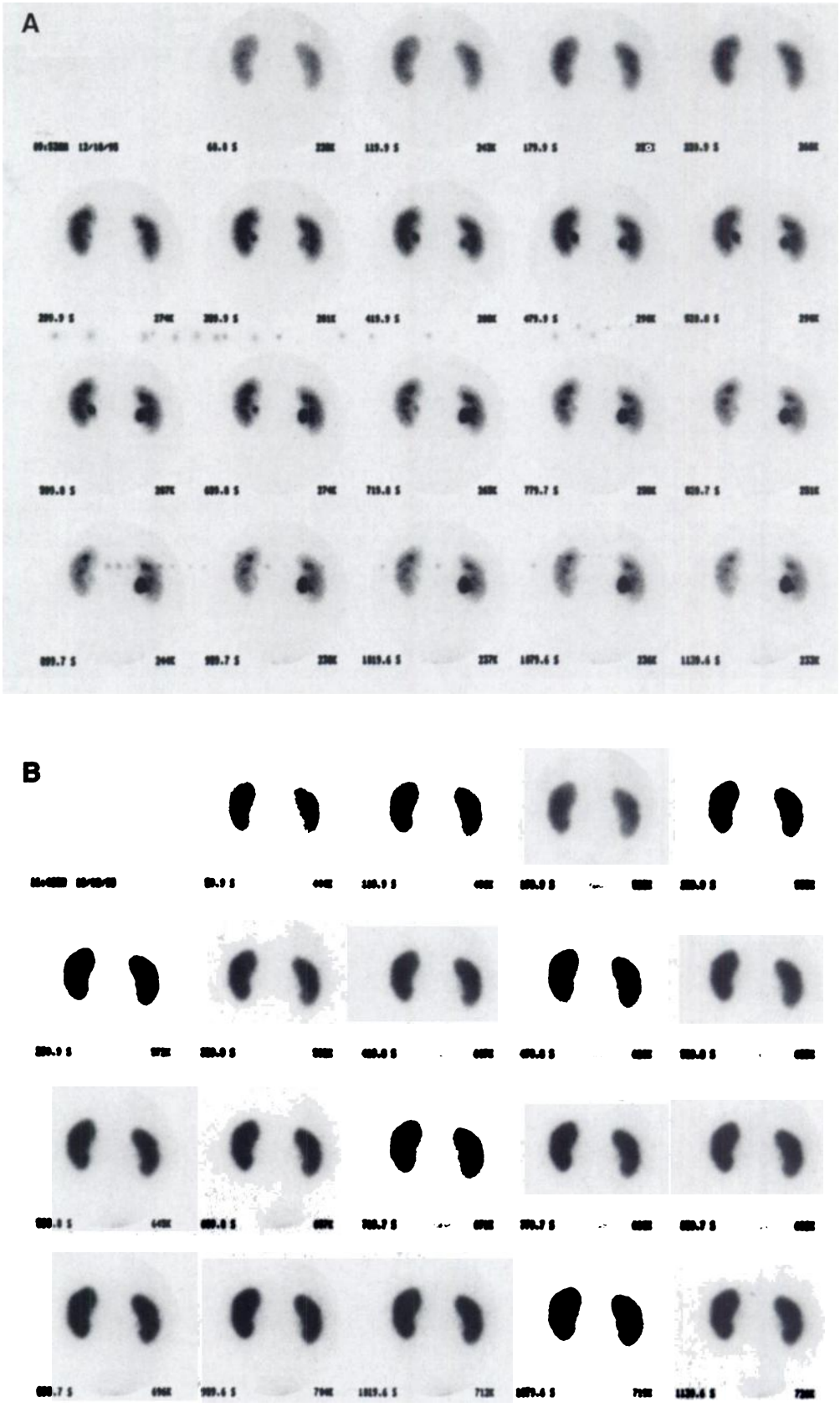

FIGURE 2. Serial baseline and captopril renograms of patient who presented with bilateral symmetrical renal dysfunction on captopril scan. This 45-yr-old man was referred for hypertension de novo. He was not taking any medication at time of study. (A) Baseline serial ^{99m}Tc-MAG3 renal scintigrams (20 min). (B) Serial ^{99m}Tc-MAG3 renal scintigrams 1 hr after 25 mg captopril. There was bilateral cortical stasis of radiotracer without pelvic retention.

DISCUSSION

Captopril renography is still the noninvasive screening test of choice for the diagnosis of renovascular hypertension. When performed in patients with moderate or high clinical suspicion of renovascular hypertension, sensitivity of 93% and specificity of 95% can be attained (*1*). The blockade of the renin-angiotensin cascade with an ACE inhibitor markedly reduces the production of angiotensin II. This effect represents the physiopathological basis for this nuclear medicine test, the topics of which have been reviewed by Nally and Black (*2*).

TABLE 2
Blood Pressures of Patients with Bilateral Renal Dysfunction on Captopril Renography (mm Hg)

	With calcium antagonist		Without calcium antagonist	
Patient no.	Basline	Postcaptopril*	Baseline	Postcaptopril*
Group A				
1	140/90	135/85	140/95	130/85
2	150/90	140/90	140/95	140/90
3	140/80	130/80	140/90	130/85
4	150/100	150/95	170/100	165/95
5	150/100	140/95	160/100	150/90
6	140/80	150/90	180/100	170/100
Group B				
7	190/105	160/90	—	—
8	150/100	140/100	—	—
9	184/100	180/95	—	—
10	140/90	120/75	—	—
11	130/80	110/70	—	—

*One hr after 25 mg captopril by mouth.

The occurrence of a patient who had normal renal angiography despite bilateral symmetrical renal function deterioration prompted us to evaluate the significance of these results. It was observed that calcium antagonists can interfere with captopril renography and cause false-positive results (i.e., bilateral symmetrical functional deterioration not associated with renovascular hypertension). This bilateral symmetrical renal function deterioration has been observed with both ^{99m}Tc-MAG3 and ^{99m}Tc-DTPA using 1-day and 2-day protocols, respectively. The exact mechanism responsible for this effect in human beings is not known, but experimental studies suggest some explanations (*4*). Using kidneys isolated from a normotensive rat and perfused with Tyrode's solution, Cooper et al. (*5*) observed that angiotensin II increases the influx of Ca^{++}, probably consequent to its interaction with a specific receptor. Experimental studies (*4–7*) also have demonstrated that angiotensin II requires extracellular Ca^{++} to produce renal vasoconstriction and that the rise in perfusion pressure produced by angiotensin II is attenuated significantly by extracellular calcium antagonists. Furthermore, dantrolene sodium, ryanodine, or TMB-8-, agents that inhibit release of Ca^{++} from intracellular sites (*8–10*), failed to alter angiotension II-induced renal vasoconstriction in the presence of extracellular Ca^{++}. In fact, their results suggest that intracellular Ca^{++} may have only a small contribution in the vasoconstriction elicited by angiotgensin II. Therefore, we can hypothesize that an acute dose of captopril and the long-term effects of the extracellular calcium antagonist interact at the level of postglomerular arterioles to provoke an excessive vasodilation that is causing a fall in the glomerular filtration pressure (leading to the deterioration of the renograms in 9 patients who were taking nifedipine, amlodipine besylate, verepamil or diltiazem in our study). One patient in Group A still had bilateral renal function deterioration despite the cessation of his calcium antagonist. We cannot explain the bilateral renal function deterioration of the other patient in Group A who was not taking any medication. A consensus report on ACE-inhibitor renography for detecting renovascular hypertension (*11*) indicated that bilateral symmetrical changes in the renogram curve after ACE inhibition have been associated with salt depletion, hypotension during the study, insufficient hydration and a distended bladder (*12,13*), and it is well established that bilateral renal dysfunction is frequently associated with false-positive results.

Three patients in Group A who were taking diltiazem at the time of the study did not have any renal function deterioration on their ^{99m}Tc-MAG3 renograms. One patient in Group B had bilateral symmetrical renal function deterioration associated with diltiazem despite normal renal angiography. Fleming et al. (*14*) observed that the renal microvascular actions of nitrendipine and diltiazem were similar in their study (preferential preglomerular dilation) but that their actions on the preglomerular vessels were different; diltiazem evoked a more uniform dilatation of the various preglomerular vessels than did nitrendipine at all bath concentrations of their split hydronephrotic kidney preparation. In doing so, the more pronounced preglomerular dilatation provoked by diltiazem could, theoretically, counterbalance the vasodilatatory effect of diltiazem and captopril at the level of the postglomerular arterioles.

Not all patients taking calcium antagonists had bilateral (or any) renal function deterioration in this study. Theoretically, differences among patients could explain this observation, such as a different drug concentration, a different degree of preexisting arteriolar tonus or a varying degree of renin-angiotensin-aldosterone system activation. Even if only bilateral symmetrical renal function deterioration was observed as bilateral false-positive results in patients taking calcium antagonists, we should be aware that calcium antagonists also could interfere with captopril renography in patients with an abnormal baseline study (unilateral renal dysfunction or bilateral asymmetrical renal dysfunction) and thus create false-positive asymmetrical renal function deterioration.

Calcium antagonists ideally must be stopped before captopril renography to avoid false-positive bilateral results. Moreover, bilateral symmetrical renal function deterioration on captopril ^{99m}Tc-MAG3 renography or ^{99m}Tc-DTPA renography should alert the reporting physician of a higher risk of drug interaction instead of bilateral renovascular hypertension, and we must remember that such a scintigraphic pattern frequently is associated with a false-positive result.

CONCLUSION

Calcium antagonists may cause false-positive captopril renograms, i.e., false-positive bilateral symmetrical renal function deterioration not associated with renovascular hypertension. It is suggested that these drugs be stopped before captopril-stimulated renography, and physicians should be aware of a possible drug interaction or other causes of false-positives if bilateral renal function deterioration occurs on a patient's captopril renogram.

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Comparative Study of Technetium-99m-Sestamibi and Thallium-201 SPECT in Predicting Chemotherapeutic Response in Small Cell Lung Cancer

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The purpose of this study was to evaluate the relationship between ^{99m}Tc-sestamibi (MIBI) accumulation by tumor and response to chemotherapy in small cell lung cancer patients compared with ^{201}Tl-chloride. **Methods:** There were 19 patients with small cell lung cancer just before chemotherapy initiation. The patients were classified by a follow-up CT into complete remission, partial remission and no change groups. All patients underwent dual-isotope imaging with ^{201}Tl-chloride and ^{99m}Tc-MIBI. Regions of interest were placed over the tumors and contralateral normal lung tissue on one coronal view with a clearly defined lesion, and the tumor-to-normal (T/N) ratio and retention index were calculated. **Results:** Early and delayed T/N ratios for ^{99m}Tc-MIBI in complete remission and partial remission groups were significantly higher ($p < 0.05$) than in the no change group. There was no significant correlation between T/N ratio and tumor response using ^{201}Tl-chloride. There were no significant differences in the retention index with respect to the tumor response in both ^{201}Tl-chloride and ^{99m}Tc-MIBI SPECT images. **Conclusion:** Technetium-99m-MIBI SPECT may be more effective than ^{201}Tl-chloride SPECT for evaluating response to chemotherapy in patients with small cell lung cancer.

Key Words: technetium-99m-sestamibi; thallium-201-chloride; small cell lung cancer; dual-isotope imaging; chemotherapy

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Use of ^{201}Tl-chloride SPECT is now attracting attention for detection of lung cancer (*1,2*). In recent years, however, several ^{99m}Tc-labeled imaging agents have also been under investigation. Labeling with ^{99m}Tc has several advantages over using ^{201}Tl. Noncardiac uses of ^{99m}Tc-sestamibi (MIBI; hexakis 2-methoxyisobutylisonitrile), such as visualization of lung cancer, have also been investigated. Morphologic imaging techniques such as CT, ultrasonography and MRI cause problems in the evaluation of treatment response and in establishing whether a residual mass is due to a residual tumor or local recurrence. Nuclear medicine imaging techniques may be applicable to the evaluation of therapeutic efficacy and the prediction of therapeutic response in cancer. The primary therapeutic modality for small cell lung cancer is chemotherapy. Resistance of malignant tumors to chemotherapeutic agents is a major cause of treatment failure. In this study, we evaluated the prediction of chemotherapeutic effect using ^{99m}Tc-MIBI SPECT in small cell lung cancer patients in comparison with ^{201}Tl-chloride SPECT.

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MATERIALS AND METHODS

Patients

There were 19 patients (15 men, 4 women; age range 39–86 yr) with small cell lung cancer who were investigated before chemotherapy. Diagnosis was made by cytologic or histopathologic analysis of sputum, CT-guided needle biopsy or endoscopic samples. The lung lesions were staged according to the tumor-node-metastasis classification. The smallest tumor was 3 cm, and the largest was 8 cm by CT scan. All patients underwent simultaneous dual-isotope SPECT of the chest with ^{201}Tl-chloride and ^{99m}Tc-MIBI just before chemotherapy initiation. After the imaging study, all patients received multidrug chemotherapy regimens consisting of cyclophosphamide, doxorubicin, vincristine, etoposide, cisplatin, mitomycin-C and vindesine. The patients were classified by a follow-up CT examination within 4 wk after last chemotherapy into the following groups: complete remission (CR), when there was no evidence of disease; partial remission (PR), when there was ≥50% decrease in the sum of the product of the maximum perpendicular diameters of all measurable lesions; and no change (NC), when there was <50% decrease in the sum of the product of the maximum perpendicular diameters of all measurable lesions.

Simultaneous Dual-Isotope Imaging

Dual-isotope imaging was performed with a large field-of-view gamma camera, with high resolution and a parallel-hole collimator (Picker Prism 2000; Picker International, Cleveland, OH). This camera was interfaced to a dedicated computer (ODYSSEY; Picker International). Doses of 111 MBq ^{201}Tl-chloride and 600 MBq ^{99m}Tc-MIBI were injected intravenously. Early SPECT acquisition was performed 15 min after the injection of each radioisotope, whereas delayed SPECT images were acquired 2 hr after injection. For SPECT images of chest, 72 projections were obtained using a 64 × 64 matrix for 45 sec/view in a step-and-shoot mode. Using a