Dynamic Renal Imaging with Technetium-99m-Sestamibi in Hypertension: Potential for Assessment of Renovascular Disorders

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The myocardial perfusion agent, ^{99m}Tc-sestamibi (MIBI), offers the potential to combine renal and myocardial imaging because of high initial renal extraction and significant renal clearance. **Methods:** Dynamic renal imaging was performed during rest MIBI injections in 3 normal subjects (NS) and 91 patients referred for cardiac assessment. Ten served as normal controls, and 81 were hypertensive. Renal activity of MIBI during the first transit, uptake and excretory phases of the study was quantified. These data were compared with the normal kinetics of ^{99m}Tc-diethylenetriaminepentaacetic acid (DTPA) in concurrent studies. **Results:** With MIBI, clear definition of the kidneys was possible on all phases in most studies; occasionally, overlap with liver or spleen provided a minor problem. Renal MIBI activity reached levels 70% greater than DTPA during first transit and remained higher throughout the study; renal/background activity ratios were also higher on the MIBI study ($p < 0.001$). During the excretory phase with MIBI, hepatic and splenic activity did not decline, and gut activity increased. In NS, 40% of the total activity was excreted in the urine in 1 hr; urinary MIBI clearances approximated creatinine clearance. Asymmetry in initial renal uptake was seen in 14 of 81 hypertensive patients (17%); renal cysts and aortic dilatation could also be identified. **Conclusion:** These data suggest that ancillary renography during rest injection of MIBI could be a useful addition to the cardiovascular assessment of selected patients.

Key Words: sestamibi; renovascular hypertension; renography

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In patients with moderate or severe hypertension, screening for a renovascular cause appears to be warranted (*1,2*). Despite the low prevalence of secondary hypertension in the hypertensive population, such an endeavor may be warranted because of the potential for cure of hypertension if detected (*3*) and the problem of deteriorating renal function should renal stenosis go untreated (*4*). Nuclear medicine techniques have recently been reestablished as a key test in screening for this condition (*1,5,6*). However, cost-effective use of this technology requires a moderately high incidence of renal artery stenosis in the target population (*7*), higher than the 1% to 2% incidence in the total hypertensive population.

Hypertensive patients referred for myocardial scintigraphy represent a population with an increased incidence of renal artery stenosis (*8–10*). These patients often have damage to target organs as a result of microvascular disease and progression of atherosclerosis; these mechanisms account for the development of anginal symptoms (*11–13*). Previous work has established the potential for ancillary thallium images obtained in relation to myocardial perfusion scintigraphy to depict renal asymmetry (*8–10,14*). In myocardial perfusion imaging, ^{99m}Tc-sestamibi (*15*) has become an attractive alternative to thallium cardiac imaging because of its high photon count. Therefore, the properties of sestamibi as a renal agent were evaluated (*16*), and images were obtained in a large series of hypertensive patients.

METHODS AND PATIENTS

Studies in Normal Volunteers

In three well-hydrated normal volunteers, renal imaging and assessment of urinary clearance of sestamibi was performed. Two studies were performed on one of the subjects (Subject 3), and one on each of the others (Subjects 1 and 2). Sestamibi was injected in a weighed syringe, and a standard was prepared. Dynamic renal imaging was obtained with rapid framing during the first 3 min followed by 30-sec frames over 15 to 30 min. Urine samples were collected hourly over the first 3 hr for measurement of radioactivity and creatinine, and blood samples were obtained every 30 min for 3 hr for measurement of plasma counts and serum creatinine. Plasma and urine samples were counted in a gamma counter. Hourly urine excretion was calculated as a percentage of the injected dose. Urinary clearances of sestamibi and creatinine were calculated for the second and third hours after injection by

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using the blood sample from the middle of each interval and the following formula:

$$\text{Clearance (ml/min)} = \frac{\text{volume (per hour)}}{60} \times \frac{\text{urine concentration}}{\text{plasma concentration}}.$$

The plasma half-life was obtained by fitting the six plasma concentration values to time on a semilogarithmic plot, similar to techniques for glomerular filtration rate (GFR) with ^{99m}Tc-diethylenetriaminepentaacetic acid (DTPA) (*17,18*).

Comparison of Sestamibi Renography with DTPA Studies

Normotensive control studies with sestamibi were obtained in 10 patients referred for rest and stress myocardial perfusion imaging. None of the patients had a history of high blood pressure or renal disease, such as nephrolithiasis or renal infection. Sequential renal imaging was obtained as described earlier during the rest injection of sestamibi. These studies were grouped with those in the normal volunteers and analyzed to show the uptake in the peak kidney. DTPA studies for comparison (*14,19*) were obtained in 13 patients who had morphologically normal DTPA renograms, normal GFR by the three-sample technique (more than 90 ml/min/1.73 m^2) and normal kidneys and renal arteries by intravenous digital subtraction angiography or intraarterial contrast angiography. The addition of frames was performed to provide data at 5-sec intervals for the first 75 sec of the study and at 30-sec intervals over the remainder of the acquisition. DTPA renal activity at each time after the injection was standardized for the injected dose and the patient's weight and compared with dynamic sestamibi studies using analysis of variance of repeated measures.

Dynamic Sestamibi Renography in Hypertensive Patients

Hypertensive patients were selected from approximately 2000 patients referred for sestamibi myocardial perfusion studies over a 5-yr period. During that interval, 81 patients were chosen for renal imaging based on significant hypertension and on camera availability at the time of the rest injection. Three of these patients had undergone revascularization procedures for renal artery stenosis (two by renal angioplasty and one by bypass grafting). Nine patients had had prior angiography, including translumbar aortograms. Eight patients had adequate visualization of the renal arteries, including a follow-up study on the patient with remote bypass surgery. Eleven patients had had ultrasound examinations for assessment of an abdominal aneurysm or renal asymmetry, and 10 had had prior renal scintigraphic studies. In the 58 remaining patients, the possibility of renal artery stenosis had not previously been investigated. Some of these patients had relatively severe hypertension, but other atherosclerotic problems, including cerebrovascular disease and cardiac disease, frequently drew attention elsewhere.

These 81 patients had rapid sequence images obtained over the first 1 to 3 min followed by 20-sec frames acquired for at least 10 min. Images were obtained on film and on computer for subsequent analysis (five studies were not available owing to an archiving problem). Differential renal uptake was measured on cumulated images at 1 to 3 min after injection and expressed as the percentage ratio of counts in the left kidney to total counts in the right and left kidneys. After nine-point smoothing, a simple region of interest (ROI) (*9,10,14*) was drawn with a computer mouse to outline each kidney; background subtraction was not used for sestamibi studies. Repeated measurements were made on each hypertensive study by each of two observers (G.A.H. and M.H.) with intervals of 1 wk between determinations, with the final value taken as the average of all measurements.

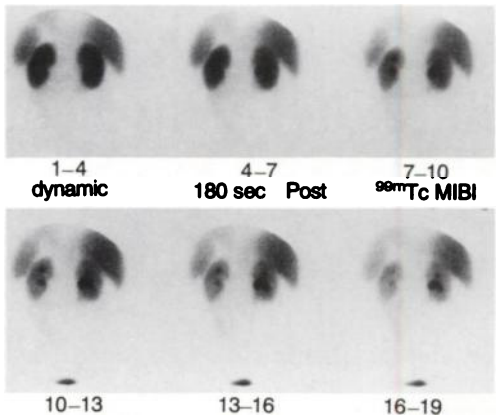

FIGURE 1. Dynamic renography with sestamibi in a normal subject. Sestamibi was injected at rest, and sequential imaging was performed over 20 min, with images obtained on film, as shown here, and on computer.

Background activity was measured by outlining regions in the liver and spleen and in a rectangular region in the lower abdomen. Renal/background ratios were calculated based on the average activity per pixel in each background region compared with that in the more intense kidney (*14*).

Poststress Static Imaging with Sestamibi

Renal imaging was also obtained after the stress injection of sestamibi in eight hypertensive patients. This was performed at 10 to 30 min after stress injection, with the intervening time for poststress electrocardiographic monitoring and transfer to a large-field-of-view camera.

RESULTS

Renal Imaging and Urine and Plasma Kinetics of Sestamibi in Normal Subjects

Figure 1 shows a renal imaging sequence obtained on film in a fashion similar to that used for dynamic renography with ^{99m}Tc-DTPA. With sestamibi, there is clear definition of the kidneys seen on the early image at 1 to 4 min after injection. Homogeneous uptake of the radiotracer is seen in the renal parenchyma, and the kidneys appear symmetric with well-defined outlines. Uptake of sestamibi can be clearly seen in the liver and spleen. Transit into the renal collecting system is seen at 4 to 7 min, and there is definite appearance in the bladder by 7 min. There is only mild reduction of the activity in spleen and liver over time. A small amount of bowel activity is visualized; it is slightly more apparent on the delayed images. On the later images, there is good clearance from the parenchyma of both kidneys.

Transit through the kidneys is reflected by urinary ex-

TABLE 1
Urinary Clearance and Plasma Half-Life of Sestamibi in Normal Subjects

Subject	Urinary excretion 0–1 hr (% dose/hr)	Urinary excretion 1–2 hr (% dose/hr)	Urinary excretion 2–3 hr (% dose/hr)	Urinary clearance* 1–2 hr (ml/min)	Urinary clearance* 2–3 hr (ml/min)	Plasma half-life 0.5–3 (hr)
1	32	6	3	280 [200]	160 [150]	1.7
2	42	6	4	130 [140]	100 [140]	2.5
3 #1	39	4	4	160 [150]	190 [220]	2.6
3 #2	50	5	3	180 [160]	130 [140]	2.8

*Creatinine clearances on corresponding samples listed in brackets.

cretion (Table 1), which ranges from 40% to 60% of the injected dose in the first 3 hr; most is excreted in the first hour. Urinary clearance of sestamibi is similar to that of creatinine over intervals from 1 to 3 hr after injection.

The plasma levels of sestamibi, expressed as percent of the injected dose per milliliter of plasma, were considerably lower than those with DTPA, representing one tenth of the levels seen in comparable studies. Plasma levels fell progressively with time, fitting a logarithmic decay model with correlation coefficients from 0.95 to 0.99 in the four studies. The plasma half-life of sestamibi determined from six plasma samples appeared longer than that of DTPA in normal studies, the latter being approximately 1 to 1.5 hr.

Sestamibi Compared with DTPA

The kinetics of sestamibi and DTPA were discerned from the activity in the peak kidney, as shown in Figure 2.

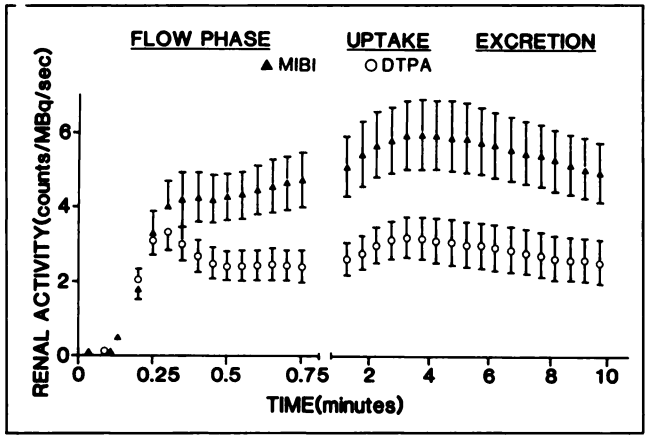

FIGURE 2. Renal activity of sestamibi compared with ^{99m}Tc-DTPA. Sestamibi data was obtained during the rest injection of 3 to 5 MBq/kg in 13 studies, including 3 normal volunteers and 10 normotensive cardiac patients. Total renal activity in the most intensely visualized kidney in each patient is shown as detected counts per MBq/sec. Error bars show 95% confidence limits for the mean. The ^{99m}Tc-DTPA data were obtained in patients referred for conventional renography, who had normal angiograms and normal renal function, as shown by DTPA clearance. Following the initial vascular phase, the activity of sestamibi in the kidneys was higher than that of DTPA when normalized for injected dose.

During the early flow phase, the renal appearance of the two radiotracers is similar. Following first transit, DTPA renal activity decreases owing to clearance of venous blood from the kidney; in contrast, the activity of sestamibi remains relatively constant during this period. During the period from 1 to 4 min, there is ongoing uptake of both radiotracers, presumably related to filtration. Following peak appearance in the kidney, there is a gradual decrease related to excretion. At all times after 20 sec, the activity of sestamibi is greater than that of DTPA ($p < 0.01$, by analysis of variance of repeated measures).

Renal definition with sestamibi is shown by the target/background ratios of this radiotracer (Table 2). The uptake of sestamibi in the kidney compared with nonorgan background was higher than that of DTPA ($p < 0.001$, by analysis of variance). Uptake in the spleen, however, was relatively higher with sestamibi ($p < 0.001$) than with DTPA. Differential renal function (left/total activity as a percent) gave somewhat different values with the two procedures. In the normotensive sestamibi studies, the range was 44% to 61%, whereas for DTPA studies in patients with normal radiometric filtration rates, the range was 44% to 57%.

Dynamic Sestamibi Renography in Hypertensive Patients

During dynamic sestamibi renography in hypertensive patients, visualization of the perfusion phase, the uptake

TABLE 2
Target-to-Background Ratios for Renal Imaging with Technetium-99m Sestamibi and Technetium-99m-DTPA; Means (s.d.) for Patients in Figure 2

Ratio	Radiotracer: Sestamibi	Radiotracer: DTPA
Kidney/Liver	1.4 (0.2)	1.4 (0.2)
Kidney/Spleen	1.2 (0.2)*	1.6 (0.2)
Kidney/Nonorgan†	6.6 (1.5)*	4.0 (0.6)

*$p < 0.001$ compared with DTPA.
†Nonorgan region = rectangle across lower abdomen.

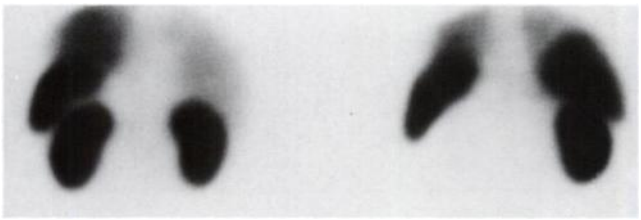

FIGURE 3. Uptake phase of sestamibi renography in patients with known renal arterial anatomy. Image on the left shows a patient who had a digital subtraction angiogram 6 yr previously with 30% stenosis of the right renal artery. All phases of the sestamibi renogram showed renal symmetry. The patient on the right had undergone angiography 1 wk prior to the sestamibi study directed at peripheral vascular disease. On an aortic contrast injection, the left renal artery and kidney were not visualized, and the right renal artery was normal. The sestamibi scan, when viewed with enhancement, showed a "ghost" kidney on the left side.

phase and the excretory phase could be obtained. In particular, the uptake phase images at 1 to 3 min provided excellent definition of renal outlines and good target-to-background ratios in most cases, allowing qualitative and quantitative assessment (Fig. 3).

Dynamic sestamibi renal imaging was successful in showing unsuspected renal asymmetry in hypertensive patients (Fig. 4). A total of seven patients had unsuspected renal asymmetry shown on the 1- to 3-min uptake images, which was confirmed by quantitation, with four showing unequivocal asymmetry and three giving borderline measurements. At the current time, only one of these patients has undergone angiography and subsequent treatment (nephrectomy) for renal artery stenosis.

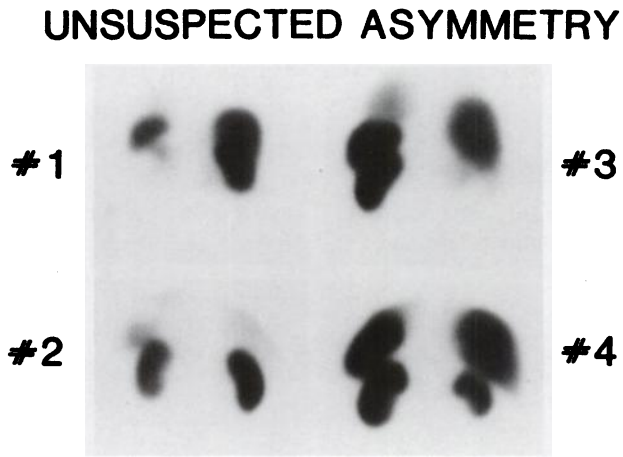

FIGURE 4. Unsuspected renal asymmetry in hypertensive patients shown by sestamibi imaging. The uptake phase (1–3 min after injection) is shown for rest sestamibi injections in four hypertensive patients. The upper left quadrant shows a patient in whom subsequent angiography demonstrated a small left kidney (11% of total renal uptake) with a severely stenotic artery; nephrectomy was performed at another center with subsequent improvement in blood pressure control. Angiography has not been performed in the other three patients, all of whom show renal asymmetry (left/total = 88%, 43% and 67% for images 2, 3 and 4, respectively).

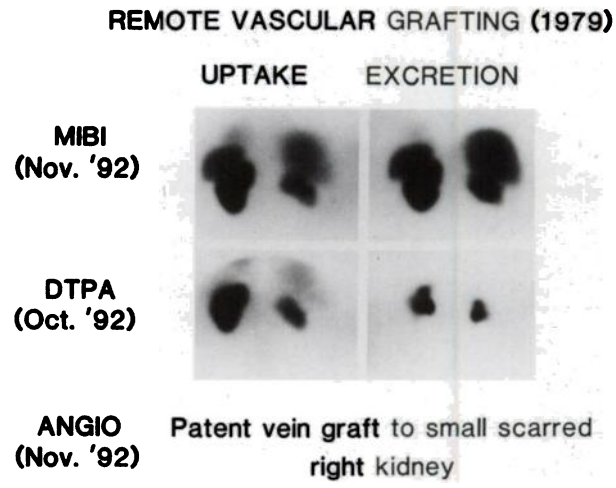

FIGURE 5. Correlation of sestamibi and DTPA imaging in a patient who was still hypertensive after renal revascularization. A vein graft had been inserted to bypass severe right renal artery stenosis in 1979. The upper images show the uptake and excretion phases of sestamibi renography performed in November 1992. The lower images show the corresponding uptake and excretion phases of a conventional DTPA renogram performed 3 wk previously. Angiography performed concurrently showed a patent vein graft to a small scarred right kidney.

Three of the patients presented more complex problems because renal artery stenosis had been previously treated by angioplasty or grafting. The patient in Figure 5 shows good correlation between sestamibi and DTPA imaging with respect to differential renal function. In this case, the smaller right kidney represents a stable situation, although revascularization had been performed 13 years previously. The current angiogram showed patency of the graft to the right kidney.

Sestamibi imaging allowed discernment of nonvascular pathologic conditions, some of which could result in asymmetry in sestamibi uptake. Renal abnormalities visualized in these hypertensive patients (Fig. 6), included renal cysts, bilaterally small kidneys and renal displacement. In patients with abdominal aneurysms, the flow phase of the sestamibi study could depict aortic tortuosity or dilatation.

Rest Versus Stress Imaging with Sestamibi

The rest dynamic renographic sequence appeared preferable to poststress imaging for anatomic evaluation of the kidneys. By the time renal imaging could be obtained after stress, activity was usually prominent in the collecting systems of the kidneys; frequently, there was increased bowel activity. When the poststress images were acquired within 20 min, they were of reasonable quality (Fig. 7). Obvious morphologic abnormalities could be seen on these images, and renal asymmetry could be ascertained, although high background activity in the liver and spleen relative to the kidneys was more problematic than on the rest imaging sequence.

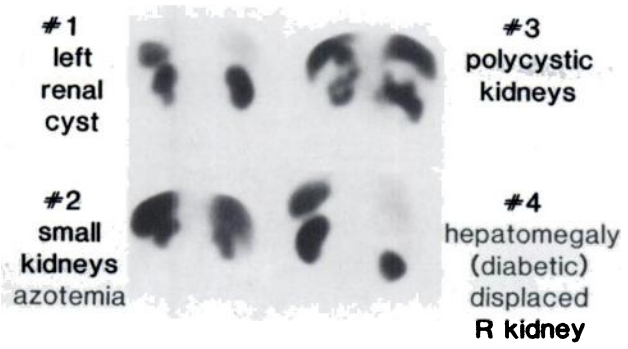

FIGURE 6. Other renal abnormalities disclosed by sestamibi imaging in four hypertensive patients. Upper left: cyst in the lower pole of the left kidney suggested by sestamibi imaging. Upper right: polycystic kidneys, as confirmed by ultrasound. Lower left: small kidneys in a hypertensive patient with moderate azotemia. Lower right: apparently smaller right kidney (38% of total renal uptake) is displaced downward in a poorly controlled diabetic patient with hepatomegaly.

DISCUSSION

Patients with significant hypertension constitute an important subgroup of patients referred for myocardial perfusion scintigraphy. In these patients, vascular damage in the coronary arterial bed may result in angina pectoris (*11–13*) and in asymptomatic myocardial ischemia (*20*). As such patients also have a propensity for atherosclerosis in other arterial sites, elucidation of a possible cause for hypertension could be of particular importance. The discovery of renal asymmetry by ancillary sestamibi renography in patients with moderate or severe hypertension could point to the need for more definitive investigation (*5,6*).

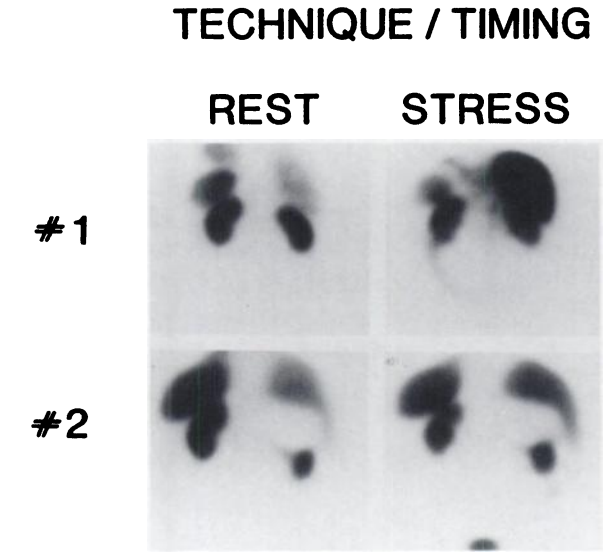

FIGURE 7. Comparison of sestamibi imaging with rest (left) and stress (right) injections. Rest images show uptake at 1 to 3 min after sestamibi injection. Following the stress injection of sestamibi, static images were acquired for 2 min at 10 to 20 min after injection. Patient shown in the upper images had symmetric kidneys and presumably has essential hypertension. Patient in the lower images with severe hypertension had a right renal cyst drained several months previously. One month following sestamibi imaging, 600 ml of fluid was again drained from the right renal cyst.

Noninvasive assessment of myocardial perfusion is frequently indicated preoperatively in patients with peripheral vascular disease, including abdominal aortic aneurysms (*21*). In such patients with significant hypertension or deteriorating renal function, evaluation of renal perfusion and function prior to projected surgery may again be of particular value (*22*). In many of these patients, renal assessment by contrast studies or ultrasonography may already have been performed at the time of referral to the nuclear medicine laboratory for myocardial perfusion assessment. Nonetheless, in a substantial portion of these patients, definition of renal perfusion and functional status concurrent with myocardial imaging could extend the clinical usefulness of the test.

The data on urinary excretion of sestamibi suggest that its net clearance by the kidney is similar to the GFR. Although initially after injection clearance by the hepatobiliary system is considerable, plasma disappearance over the interval from 0.5 to 3 hr was found to be less than that of DTPA and similar to values found in other studies (*15*). Phenomena that contribute to the complex kinetics of this substance might include delayed washout from tissues into blood (*23*) or protein binding (*24*). Nonetheless, the high initial renal uptake, coupled with major urinary excretion during the first hour after injection, support the use of sestamibi for renographic imaging.

This initial experience with ancillary sestamibi imaging in hypertensive patients suggests that relevant information could be added to the assessment of a selected group of patients referred for myocardial perfusion. The dynamic renal imaging sequence obtained with the rest study does not interfere with patient throughput or other aspects of myocardial imaging. Abnormal differential renal uptake, frequently indicating a renal perfusion abnormality, can be seen in a significant proportion of referred hypertensive patients (Fig. 8). Moreover, the quantitation of differential renal function using the initial uptake of sestamibi requires only 3 min of gamma camera time. In comparison with poststress ^{201}Tl images, which we have previously used for this purpose (*9,10,14*), there is no problem with sestamibi as a result of potential effects of stress procedures on renal function (*24–26*). Ancillary sestamibi renal acquisitions produce images of acceptable quality compared with standard renal scintigraphic agents. In selected patients, this minor investment of resources may optimize the diagnostic data derived from sestamibi imaging protocols and, therefore, appears warranted.

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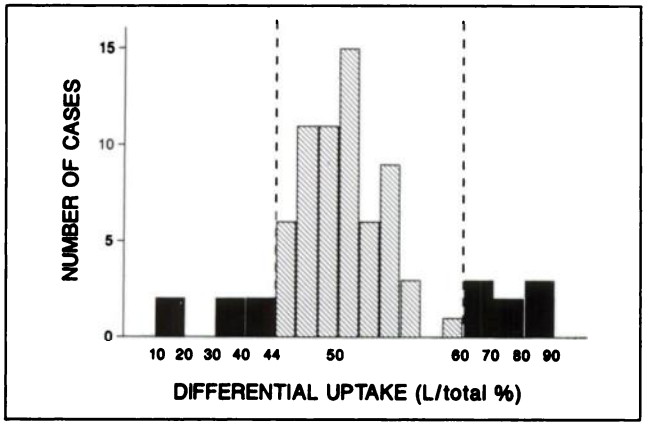

FIGURE 8. Histogram showing the incidence of renal asymmetry among the hypertensive patients. Differential renal function was measured as left/total activity as a percentage during the uptake phase, i.e., at 1 to 3 min after injection. The range for the 13 studies in normotensives was 44% to 61%. Several of the hypertensive patients with renal asymmetry had explanations for the discrepancy other than renal artery stenosis (Figs. 6 and 7); others had known or suspected renovascular hypertension (Figs. 3–5).

meeting of the Society of Nuclear Medicine in Toronto in June 1993.

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