Simultaneous Assessment of Left Ventricular Wall Motion and Myocardial Perfusion with Technetium-99m-Methoxy Isobutyl Isonitrile at Stress and Rest in Patients with Angina: Comparison with Thallium-201 SPECT

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The newly developed technetium-99m (^{99m}Tc) isonitriles can be used for the simultaneous evaluation of ventricular function and myocardial perfusion. We compared technetium-99m hexakis-2-methoxy isobutyl isonitrile ([^{99m}Tc]MIBI) derived first-pass left ventricular wall motion at stress and rest with simultaneous myocardial perfusion defined by [^{99m}Tc]MIBI SPECT. These results were then compared with ^{201}Tl SPECT. We examined 28 patients with coronary artery disease; 25 had a previous myocardial infarction. We found concordance between segmental wall motion and myocardial perfusion imaging in defining normal, ischemic, and infarcted myocardium in 68% and 69% of segments using [^{99m}Tc]MIBI and ^{201}Tl respectively. The best agreement between wall motion and myocardial perfusion was seen in the inferior wall, while most of the discrepancies were found at the apex. Agreement between [^{99m}Tc]MIBI and ^{201}Tl SPECT myocardial perfusion was seen in 93% of segments. Technetium-99m-MIBI appears to be an ideal radiopharmaceutical for the simultaneous evaluation of ventricular function and myocardial perfusion during stress and at rest.

J Nucl Med 1990; 31:457–463

Myocardial perfusion scintigraphy with thallium-201 (^{201}Tl) is the current noninvasive procedure of choice for the diagnosis and evaluation of coronary artery disease (CAD) (*1–4*). Thallium-201 single-photon-emission-computed tomographic (SPECT) or planar imaging can determine the location and extent of ischemia and/or infarction. First-pass radionuclide ventriculography (FPRNA) can assess ventricular function by detecting abnormalities of wall motion and ejection fraction (EF) at stress or at rest (*5–8*). Left ventricular wall motion and EF can be influenced by factors other than myocardial perfusion, including changes in loading conditions as well as valvular integrity. Thus, FPRNA performed alone evaluates only the hemodynamic status of the left ventricle while ^{201}Tl imaging assesses only perfusion.

Ideally, a comprehensive cardiac evaluation would combine myocardial perfusion imaging as well as an assessment of left ventricular function. We (*9,10*) and others (*11*) have previously described such a combined test by injecting the ultra-short-lived radionuclide, ^{195m}Au, at rest and during stress in combination with ^{201}Tl (*10*).

Recently, two categories of technetium-99m-labeled compounds have been developed for myocardial imaging. They are the isonitriles and the boronic acid technetium dioximes (also known as BATO compounds). The BATO compounds have been used in clinical trials (*12*), and their high extraction fractions represent a potential advantage for myocardial imaging (*12–14*). The disadvantage of the BATO compound currently under investigation (SQ-30217) is its fast clearance from the myocardium ($t_{1/2}$ = 10–15 min) which limits image acquisition. Technetium-99m 2-methoxy isobutyl isonitrile ([^{99m}Tc]MIBI) belongs to the family of technetium hexakis isonitrile compounds, which have a myocardial distribution proportional to coronary blood flow. The potential advantages of [^{99m}Tc]MIBI as compared to ^{201}Tl have been reported extensively (*15–22*). The availability of [^{99m}Tc]MIBI allows for the simultaneous evaluation of ventricular function and myocardial perfusion with a single injection of isotope (*15,16*).

We investigated the use of [^{99m}Tc]MIBI in the eval-

Received May 16, 1989; revision accepted Oct. 31, 1989.

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uation of patients with CAD using resting and stress FPRNA and ^{99m}Tc SPECT imaging. The results of the [^{99m}Tc]MIBI imaging were compared with ^{201}Tl SPECT studies performed during exercise and after redistribution. Left ventricular wall motion was compared with both [^{99m}Tc]MIBI SPECT and ^{201}Tl SPECT myocardial perfusion. Finally, the relationship between [^{99m}Tc]MIBI and ^{201}Tl myocardial perfusion imaging in patients with CAD was evaluated.

MATERIALS AND METHODS

Patient population

Twenty patients were given [^{99m}Tc]MIBI in a previous report from this laboratory (*15*). For this study, 28 additional patients were evaluated. All patients gave their informed consent to a protocol approved by the Harbor-UCLA Medical Center Human Subjects Committee. All patients were in a cardiac rehabilitation program and were presumed to have CAD. Patients with severe concomitant disease were excluded from this protocol. Twenty-five of the 28 patients had a previous myocardial infarction (MI). Based on clinical history and EKG, the infarcts were located in the right coronary artery distribution in 11, in the left anterior descending artery territory in 14, and in the circumflex artery distribution in 2. Two patients had more than one MI. Three patients had a non-Q-wave infarction without definite localization. Coronary artery disease was documented by cardiac catheterization in 17/28, 6 patients had previous percutaneous transluminal coronary angioplasty, and 3 had prior coronary artery bypass grafting. Nine patients were taking beta blockers, 12 patients were taking calcium channel blockers, and 6 patients were receiving both beta and calcium channel blockers. Other medications including diuretics, antihypertensives, and nitrates were continued during the examination period. Nineteen patients had bicycle stress testing and 9 underwent treadmill stress testing.

Group 1: Rest/Exercise First-Pass and Myocardial Perfusion Imaging. The patients were subjected to two stress tests at identical levels of exercise (n = 19). During the first exercise test, a stress and redistribution ^{201}Tl SPECT study was performed. During the second stress test, exercise, [^{99m}Tc]MIBI FPRNA and SPECT imaging were obtained. Patients visited the nuclear medicine department a third time for resting [^{99m}Tc]MIBI FPRNA and SPECT studies. The order of the three studies was random, and they were performed within a mean of 17 ± 17 days of each other. With one exception, the patients had: no significant change in their clinical condition, no changes in medications, and no surgical interventions between studies. One patient had an infarct after completing his [^{99m}Tc]MIBI studies but before the ^{201}Tl SPECT could be obtained. This patient's data was not compared to ^{201}Tl SPECT. The mean age of the group was 51 ± 8 yr; 13 patients were men and 6 were women. Seventeen of 19 patients (89%) had a previous MI. One patient had typical exertional angina without evidence of previous MI. Based on clinical and stress electrocardiographic results, he had a high probability (>98%) of having CAD (*23*), and angiography showed a 70% mid left anterior descending stenosis. One patient, a 45-yr-old woman, with atypical angina and 2-mm ST segment depression during exercise had a pre-^{201}Tl SPECT probability of 39% for having CAD.

Group II: Rest/Exercise Myocardial Perfusion. Comprised of nine patients who had characteristics similar to the group described previously (patients with CAD in a cardiac rehabilitation program), these patients had two treadmill stress tests of identical duration. Thus, only SPECT [^{99m}Tc]MIBI and ^{201}Tl imaging without FPRNA was performed. As in the previous group, resting [^{99m}Tc]MIBI SPECT images were recorded on a separate day. Seven men and 2 women with a mean age of 55 ± 5 yr were in this group. Eight of nine patients had a previous infarction.

Stress Testing

All 28 patients had stress studies which were matched for time and workload. The duration of the first exercise test determined the duration for the second. In group I (rest/exercise FPRNA and myocardial perfusion), two identical graded upright bicycle exercise tests were performed on the 19 patients. The exercise began at 25 watts and was increased 25 watts every 3 min until the exercise end point was reached. In group II (exercise/rest or redistribution myocardial perfusion), nine patients had two treadmill studies of equal duration using a Bruce protocol. The reason for terminating exercise was fatigue in 27 of 28 patients; one patient developed exertional angina and 2-mm ST segment depression. Twelve lead electrocardiograms and blood pressure measurements were obtained at baseline, at each exercise level, and during successive minutes of recovery.

Isotope Preparation and Dosimetry: [^{99m}Tc]MIBI and ^{201}Tl

Technetium-99m hexakis 2-methoxy isobutyl isonitrile ([^{99m}Tc]MIBI) was prepared by reconstituting the lyophilized kit with 60–70 mCi of [^{99m}Tc]O_4. The dose of 25–30 mCi was injected intravenously within 3 hr after preparation, although the compound is known to be stable for more than 6 hr after reconstitution.

The radiation exposure from the 30-mCi study dose of [^{99m}Tc]MIBI is as follows: upper large intestine (4.7–4.8 rads), lower large intestine (3.2–3.3 rads), the gallbladder (2.4–2.9 rads), and the small intestine (2.8–2.9 rads) (*17*). The target organ for ^{201}Tl is the renal medulla, which receives 3.6 rads from a 3-mCi dose (*24–26*).

Data Acquisition, Processing and Display

During the stress evaluations, both ^{201}Tl and [^{99m}Tc]MIBI were injected near maximal stress, and exercise was continued for ~60 sec thereafter. After the injection of [^{99m}Tc]MIBI followed by a saline flush, a 25-sec first-pass radionuclide angiogram was acquired in a 30-degree right anterior oblique (RAO) projection in list mode (*27*). Thallium-201 was injected intravenously without a flush. Stress ^{201}Tl SPECT acquisition was begun within 10 min of the tracer injection. The redistribution study was obtained 180 min after the injection. SPECT acquisition commenced 120 min after the injection of [^{99m}Tc]MIBI for both the stress and resting studies to allow for liver clearance of the tracer. The same gamma camera, collimator, acquisition, processing, and display protocol were used for [^{99m}Tc]MIBI and ^{201}Tl SPECT. Only the energy setting of the gamma camera was modified. Details of the SPECT acquisition, reconstruction and display were reported previously (*15*).

The FPRNA processing has been described in detail elsewhere (*27*).

Interpretation of FPRNA and of Myocardial Perfusion Imaging

To correlate SPECT studies with FPRNA wall motion (WM), four segments were analyzed: the anterior, apical, inferior, and inferoposterior walls. The septal and lateral walls were not analyzed, as they were not imaged in a FPRNA gathered in the 30-degree RAO projection. The segments were graded as normal = 2, hypokinesis = 1, akinesis or dyskinesis = 0 (*15*). A transient WM abnormality present only during stress was interpreted as ischemia, while a fixed WM abnormality present at rest and stress was considered to be infarction. A total of 76 segments were compared in the 19 patients who had both [^{99m}Tc]MIBI SPECT studies and a FPRNA examination. Seventy-two segments were analyzed in patients who had ^{201}Tl SPECT imaging and a FPRNA.

Thallium-201 and [^{99m}Tc]MIBI SPECT images in the short axis, long axis, and vertical long axis were analyzed. Abnormal myocardial perfusion was defined as areas with <60% of the maximal image counts in any myocardial slice. Six segments were scored in each study, anterior, apical, inferior, inferoposterior, lateral and septal. In interpreting stress and resting studies, each segment was graded as: normal = 2, ischemic = 1, infarcted = 0. Both focal decreased activity at rest and stress and absent uptake at rest and at stress were considered to be infarction. The same format was used for both ^{201}Tl and [^{99m}Tc]MIBI SPECT images. Figure 1 depicts selected short axis slices. The total number of segments compared in the 27 patients was 162 segments.

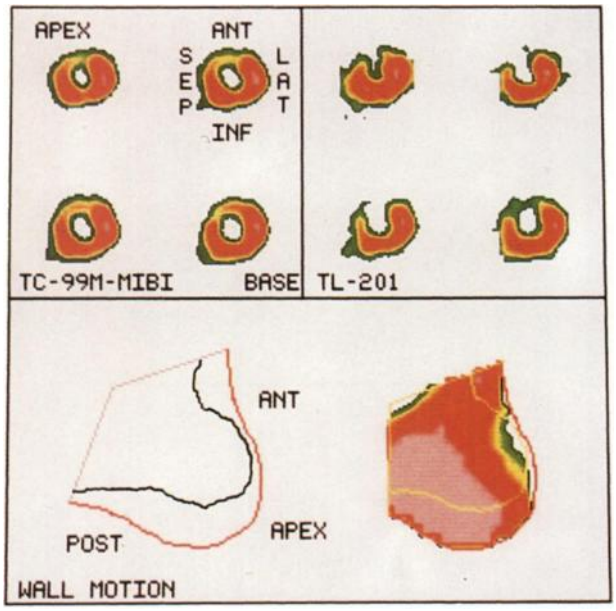

FIGURE 1
Short axis slices of stress [^{99m}Tc]MIBI and ^{201} Tl SPECT show anterior wall hypoperfusion. Left ventricular wall motion gathered with [^{99m}Tc]MIBI at stress in the RAO projection demonstrates hypokinesis of the anterior wall. The end-systolic and end-diastolic contours as well as the ejection fraction image is presented.

Statistical Analysis

Comparisons were made using the Student's t-test. Results are expressed as the mean ± s.d. A probability value of $p < 0.05$ was considered significant.

RESULTS

Two exercise tests of equal duration were performed by each patient. During the exercise test where [^{99m}Tc]MIBI was used, the double product, maximal heart rate, and systolic blood pressure were slightly higher than in the ^{201}Tl SPECT studies, but there was no statistical difference (Table 1). The mean time for completing the three imaging studies at stress and rest was 17 ± 17 days. Only 15% of the patients in our series achieved >85% of their predicted heart rate, which is consistent with their beta blocker and/or calcium-channel blocker therapy. None had a serious arrhythmia during testing.

Figure 1 shows selected short-axis slices of a patient with stress-induced anterior wall hypoperfusion and hypokinesis. The abnormality is well represented with the three imaging modalities. The resting studies are normal. An interpretation of each myocardial segment using the three imaging modalities is presented in Table 2.

The segmental left ventricular WM at stress and rest was graded and compared with the corresponding segments of the ^{201}Tl SPECT and the [^{99m}Tc]MIBI SPECT images (Figs. 2 and 3). Agreement between WM analysis and [^{99m}Tc]MIBI SPECT perfusion was found in 68% of segments and in 69% of the myocardial segments with ^{201}Tl SPECT. Table 3 shows that the highest concordance between left ventricular WM and myocardial perfusion was seen in the inferior wall with a 74% agreement for [^{99m}Tc]MIBI SPECT and 83% for ^{201}Tl SPECT. However, most of the disagreements between WM and [^{99m}Tc]MIBI SPECT and ^{201}Tl were seen in the apex, with only 62% and 55% agreement, respectively.

Each ^{201}Tl and [^{99m}Tc]MIBI SPECT imaging pair were compared segment by segment, and the results are presented in Figure 4. The results show complete agreement in 93% of the segments. Disagreement by 1 level

TABLE 1
Exercise Test Results (28 Patients)

	^{201}Tl	[^{99m}Tc]MIBI	p
Maximal HR	114 ± 19	125 ± 26	0.08
% of target HR	68 ± 11	73 ± 11	0.10
Systolic BP, mmHg	162 ± 25	168 ± 30	0.42
Duration, min	8.2 ± 3.3	8.2 ± 3.3	1.00
Double product/100	184 ± 40	206 ± 49	0.07
Days between studies	17 ± 17		

HR = heart rate in beats per minute; BP = blood pressure; and Double product = systolic BP × maximal HR/100. Results are expressed as mean ± s.d.

TABLE 2
Characteristics of Six Myocardial Segments Imaged with [^{99m}Tc]MIBI, ^{201}Tl SPECT, and [^{99m}Tc]MIBI FPRNA in 28 Patients

Location	[^{99m}Tc]MIBI SPECT (n = 28)	^{201}Tl SPECT (n = 27)	[^{99m}Tc]MIBI FPRNA (n = 19)
Anterior			
normal	15 (53)	14 (52)	10 (53)
ischemia	5 (18)	6 (22)	5 (26)
infarct	8 (29)	7 (26)	4 (21)
Apex			
normal	16 (57)	16 (59)	12 (63)
ischemia	4 (14)	2 (7)	5 (26)
infarct	8 (29)	9 (33)	2 (11)
Inferior			
normal	12 (43)	11 (41)	7 (37)
ischemia	8 (29)	7 (26)	5 (26)
infarct	8 (29)	9 (33)	7 (37)
Infero-post			
normal	16 (57)	16 (59)	10 (53)
ischemia	4 (14)	3 (11)	1 (5)
infarct	8 (29)	8 (30)	8 (42)
Lateral			
normal	27 (96)	26 (96)	—
ischemia	1 (3)	1 (3)	—
infarct	0	0	—
Septal			
normal	21 (75)	20 (74)	—
ischemia	3 (11)	4 (15)	—
infarct	4 (14)	3 (11)	—

Results expressed in number of segments and as % of each location in parentheses.

was defined as a segment that was judged to be infarcted by one imaging agent and ischemic by the other, or ischemic by one isotope study and normal by the other. This situation was seen in 7% of the segments (11 segments in 8 patients). The location of the discordant segments were in the anterior wall (n = 3), apex (n = 2), inferior (n = 1), and inferoposterior (n = 2) walls. The most common disagreement (n = 3) was a segment that was interpreted as infarcted on the ^{201}Tl SPECT study and as ischemic on the [^{99m}Tc]MIBI SPECT evaluation. Greater disagreements were not observed. Four patients had completely normal studies by both [^{99m}Tc]MIBI SPECT and ^{201}Tl SPECT perfusion scanning.

The number of infarcted and ischemic segments for each imaging technique are presented in Table 4 as the mean ± s.d.

DISCUSSION

In this study, we evaluated left ventricular WM and myocardial perfusion simultaneously at rest and during stress in patients with coronary disease. Technetium-99m-MIBI, a cation with blood flow-related distribution (*28–32*), was compared with ^{201}Tl.

We used the same SPECT reconstruction algorithm

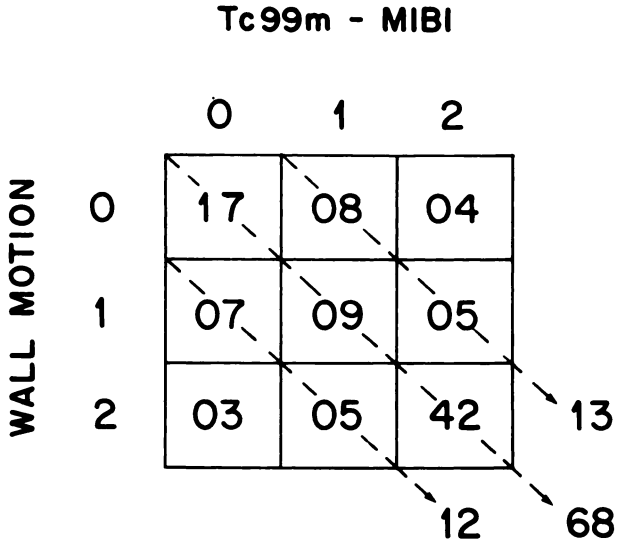

FIGURE 2
Segment by segment relationship between [^{99m}Tc]MIBI SPECT and left ventricular wall motion. In 28 patients, 76 segments were scored as follows: 2 = normal, 1 = ischemia, 0 = infarct. Results are expressed as percent.

for both studies, although it may be appropriate to use different reconstruction filters, specific for the higher-energy photons of [^{99m}Tc]MIBI and for the lower-energy ^{201}Tl. We selected a threshold to define abnormally perfused myocardium that we have previously found to be useful for ^{201}Tl SPECT and [^{99m}Tc]MIBI SPECT (*15*).

In CAD, the left ventricle may manifest WM abnormalities during stress (*5–8*). Both ventricular function and myocardial perfusion are often concordant, showing abnormalities in the same vascular territories. We demonstrated complete agreement between left ventric-

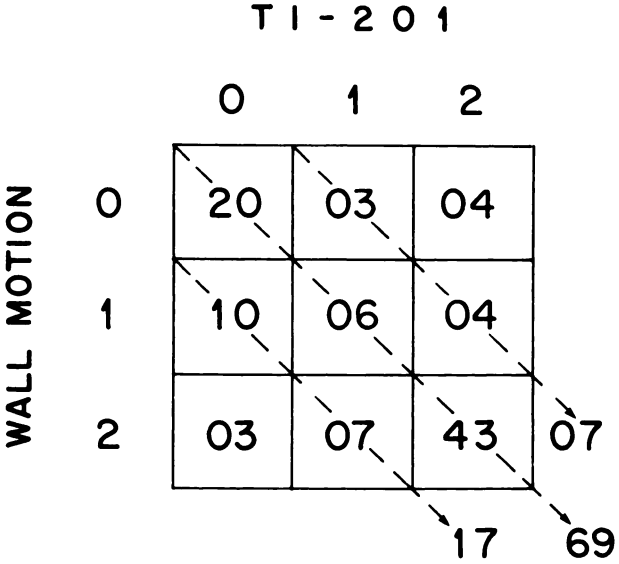

FIGURE 3
Segment by segment relationship between ^{201}Tl SPECT and left ventricular wall motion. In 27 patients, 72 segments were scored. Results are expressed in percent.

TABLE 3
Agreement Between Imaging Modalities for Each Myocardial Segment

	Ant	Apex	Inf	Infero-post	Sept	Lat
[^{99m}Tc]MIBI and ^{201}Tl	85%	96%	89%	89%	93%	96%
[^{99m}Tc] and WM	66%	62%	74%	68%	—	—
^{201}Tl and WM	67%	55%	83%	72%	—	—

% complete agreement.
Anterior, apical, inferior, infero-posterior, septal, and lateral left ventricular walls were evaluated independently.
[^{99m}Tc]MIBI = isonitrile myocardial perfusion.
^{201}Tl = thallium myocardial perfusion.
WM = left ventricular wall motion.

TABLE 4
Mean (± s.d.) of Normal, Ischemic and Infarcted Segments

	Normal segments	Ischemic segments	Infarcted segments
[^{99m}Tc]MIBI	3.8 ± 1.6	0.9 ± 1.1	1.3 ± 1.4
^{201}Tl	3.7 ± 1.6	1.0 ± 1.0	1.3 ± 1.4
Wall Motion	2.0 ± 1.4	0.8 ± 0.9	1.2 ± 1.1

Myocardial perfusion was scored in 6 segments, and wall motion was scored in 4 segments.

ular WM and myocardial perfusion imaging in 68% of the myocardial segments in this investigation with [^{99m}Tc]MIBI SPECT and in 69% with ^{201}Tl SPECT. Segmental WM analysis showed the best correlation with inferior wall myocardial perfusion while the most frequent disagreement was found in the apex (Table 3). The determinants of left ventricular function are multiple: contractility and loading conditions, previous MI, the presence of coronary stenosis(es) and their hemodynamic severity, effect of collateral circulation, and the location of the coronary artery stenosis. The value of the WM evaluation lies in the determination of the functional significance of a perfusion defect.

Our patient population was a selected group, all patients had presumed CAD, and 25 of 28 had a previous MI. Therefore, the results presented will probably not reflect the sensitivity of the test when performed for the detection of CAD in the general population. The majority of the segments analyzed were either normal or infarcted, with fewer ischemic segments (Figures 2–4). The frequency of infarction provided a greater opportunity to evaluate resting WM abnormalities and perfusion defects.

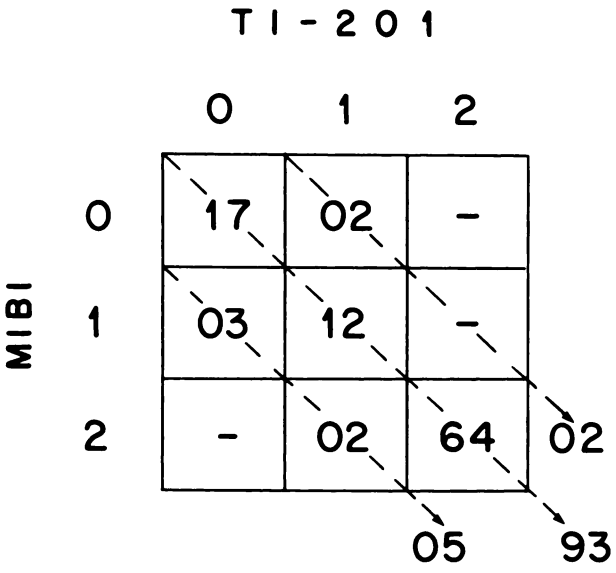

FIGURE 4
Segment by segment relationship between [^{99m}Tc]MIBI and ^{201}Tl SPECT at stress and rest. In 27 patients, a total of 162 segments were scored. The results are expressed as percent.

We found good correlations in myocardial perfusion imaging at stress and rest between ^{201}Tl SPECT and [^{99m}Tc]MIBI SPECT imaging. The segment-by-segment analysis demonstrated complete agreement in 93% of the segments (Fig. 4). The most common disagreement was a segment considered infarcted by ^{201}Tl and ischemic by [^{99m}Tc]MIBI (3%). However, no major disagreements were seen. The extent of disease as assessed by the number of abnormal segments were similar with both [^{99m}Tc]MIBI and ^{201}Tl SPECT imaging (Table 4). Nevertheless, perfusion defined by [^{99m}Tc]MIBI and ^{201}Tl were not identical (Table 2 and Fig. 4), and may represent differences in the uptake of the two tracers. It is known that ^{201}Tl fails to redistribute at 4 hr in some areas perfused by an artery with high-grade stenosis but with viable myocardium (*32,33*). Twenty-four hour views or a resting study with reinjection of ^{201}Tl are possible solutions to overcome this problem. Differences in myocardial kinetics of [^{99m}Tc]MIBI and ^{201}Tl have been reported (*34–36*). Hence, the precise role of [^{99m}Tc]MIBI in the evaluation of ischemia is difficult to evaluate in the absence of a gold standard.

Almost all the patients we studied had prior MIs which would tend to improve the correlations between resting WM and myocardial perfusion. However, our results are concordant with literature reports describing the similarity of both myocardial perfusion agents. Using planar imaging in a series of 48 patients, Taillefer described complete agreement between [^{99m}Tc]MIBI and ^{201}Tl in 89% of myocardial segments (*19,37*). Kiat reported sensitivities of 93% and 80% for [^{99m}Tc]MIBI and ^{201}Tl, respectively, and specificities of 75% for both modalities in the diagnosis of CAD (*15*). Maublant described sensitivities of 94% for [^{99m}Tc]MIBI SPECT and 76% for ^{201}Tl SPECT in detecting LAD stenosis with specificities of 85% for both techniques (*20*).

In conclusion, we found that ventricular function and myocardial perfusion can be evaluated simultaneously with [^{99m}Tc]MIBI SPECT and FPRNA at rest and during stress. By assessing left ventricular function with [^{99m}Tc]MIBI FPRNA, information regarding the functional significance of myocardial perfusion abnormali-

ties can be assessed. Thallium-201 and [^{99m}Tc]MIBI SPECT provide equivalent information regarding myocardial perfusion. Technetium-99m-MIBI when compared to ^{201}Tl has the advantage of higher counting rates, which results in higher quality images. Logistic advantages of [^{99m}Tc]MIBI are important, as 24 hr availability is feasibile and stress SPECT imaging can be performed at a time remote from the injection of the isotope. Technetium-99m-MIBI may become the agent of choice for the simultaneous evaluation of myocardial perfusion and ventricular function.

ACKNOWLEDGMENTS

MIBI was supplied by DuPont Medical Products, North Billerica, MA. The authors appreciate the support of Mr. Leopoldo Camin and Mr. David Smith from DuPont Medical Products.

The authors acknowledge Marianne Brizendine, RN and Hazel Kawasaki, RN for performing the stress tests and coordinating the patients' studies. We are thankful for the technical support of Arnulfo Pleyto, CNMT, Lee Pham, CNMT, Sheldon Chelsy, and the secretarial assistance of Linda Blakely and Debra Carroll.

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