Adenosine Technetium-99m-Methoxy Isobutyl Isonitrile Myocardial Tomography in Patients with Coronary Artery Disease: Comparison with Exercise

Alberto Cuocolo, Andrea Soricelli, Leonardo Pace, Emanuele Nicolai, Luisa Castelli, Antonio Nappi, Massimo Imbriaco, Carmine Morisco, Peter Josef Ell and Marco Salvatore

Departments of Nuclear Medicine and Internal Medicine, University Federico II and National Cancer Institute, Napoli, Italy; Institute of Nuclear Medicine, University College and Middlesex School of Medicine, London, UK

We compared the results of adenosine and bicycle exercise ^{99m}Tc-methoxy isobutyl isonitrile (MIBI) myocardial SPECT in 22 patients (18 males and 4 females, mean age 51 ± 11 yr) with angiographically documented coronary artery disease (CAD). **Methods:** All patients were submitted on separate days to three intravenous injections of ^{99m}Tc-MIBI (20 mCi); one at rest, one during exercise and one during adenosine (140 μg/kg per min for 6 min with injection of ^{99m}Tc-MIBI at 4 min). A total of 484 myocardial segments were quantitatively analyzed. **Results:** Adenosine induced a significant increase of heart rate (94 ± 16 bpm at peak versus 70 ± 13 bpm at rest, $p < 0.01$). Systolic and diastolic blood pressure were not significantly different after adenosine infusion compared to rest. In all segments, a significant relationship between exercise and adenosine ^{99m}Tc-MIBI uptake was observed ($r = 0.90$, $p < 0.0001$). Concordance between the two studies for identification of perfusion status was observed in 438 (90%) of the 484 segments (kappa value of 0.81). Agreement on localization of the perfusion defect to a specific vascular territory was 92%. **Conclusion:** Despite different hemodynamic effects, adenosine and exercise ^{99m}Tc-MIBI SPECT imaging provide similar information in the diagnosis and localization of CAD.

Key Words: myocardial perfusion; adenosine infusion; technetium-99m-methoxy isobutyl isonitrile

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Exercise ^{201}Tl scintigraphy has been widely used to assess myocardial perfusion in patients with coronary artery disease (CAD) (*1–3*). Although its value as a diagnostic and prognostic test has been well established, ^{201}Tl presents some limitations as a myocardial perfusion imaging agent. Because of its physical and biological characteristics, it is not ideal for imaging (*4*). To circumvent these limitations, ^{99m}Tc-methoxy isobutyl isonitrile (MIBI) has been proposed for cardiac imaging (*5*). Thallium-201 and ^{99m}Tc-MIBI cardiac imaging have shown excellent agreement in the detection of CAD (*6–8*). Clinical studies with ^{99m}Tc-MIBI were mainly performed using exercise testing (*5–8*) or, as recently described, dipyridamole administration (*9*) and transesophageal atrial pacing (*10*).

Maximal controlled pharmacological coronary vasodilatation with adenosine, combined with ^{201}Tl scintigraphy, appears to be a useful test for the diagnosis of CAD in patients unable to exercise (*11*). It has been recently demonstrated that adenosine and exercise ^{201}Tl myocardial perfusion imaging have high sensitivity and specificity for the detection of CAD (*12,13*). However, no data are available comparing ^{99m}Tc-MIBI adenosine and exercise tests in the same patients. Thus, the aim of this study was to directly compare the results of adenosine ^{99m}Tc-MIBI SPECT and exercise bicycle stress ^{99m}Tc-MIBI SPECT imaging in patients with angiographically documented CAD.

MATERIALS AND METHODS

Patient Population

Table 1 illustrates the clinical data of the patient population. Twenty-two consecutive patients (18 males and 4 females, mean age 51 ± 11 yr) with angiographically documented CAD were studied. At coronary angiography six patients had significant stenosis (≥50% in luminal diameter) of all three major coronary vessels; seven patients had significant stenosis of two major coronary vessels; and nine patients had significant stenosis of one major coronary vessel. Sixteen patients had previous myocardial infarction which was documented by electrocardiography (ECG). However, no patient had an acute myocardial infarction or unstable angina within 6 mo of the study. All patients required antianginal treatment, however, in all patients radionuclide studies were performed after withdrawal of all medications. Exclusion criteria for the protocol were severe hypertension, hypotension, history of asthma or severe chronic obstructive pulmonary disease, severe congestive heart failure (New York Heart Association Class III or IV) or second- or third-degree atrioventricular block. All patients gave informed consent as part of the protocol approved

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For correspondence and reprints contact: Alberto Cuocolo, MD, Via Posillipo 66, 80123 Napoli, Italy.

TABLE 1
Clinical Data of the Patient Population

Patient no.	Age (yr)	Sex	Site of previous myocardial infarction	Coronary artery stenosis (≥50%)
1	30	M	Anterior	LAD
2	32	M	Inferior	LCx, PDA
3	52	M	Anteroseptal	LAD
4	63	F	Anterior	LAD, PDA
5	49	M	None	PDA
6	50	M	None	LAD, PDA
7	53	M	None	LAD, LCx, PDA
8	63	M	Anterior, Inferior	LAD, LCx, PDA
9	39	F	None	LAD
10	61	M	Anteroseptal	LAD
11	51	M	Inferior	LCx
12	61	M	Inferolateral	LAD, LCx, PDA
13	63	F	Inferior	LAD, PDA
14	51	M	None	PDA
15	27	M	Lateral	LAD, LCx
16	40	M	Anteroseptal	LAD, LCx, PDA
17	60	F	None	LAD
18	63	M	Inferior	LAD, PDA
19	45	M	Anteroseptal	LAD, LCx, PDA
20	61	M	Anteroseptal	LAD
21	51	M	Inferior	LCx, PDA
22	56	M	Anteroseptal	LAD, LCx, PDA

LAD = Left anterior descending artery; LCx = left circumflex artery; and PDA = posterior descending artery.

by the Institutional Clinical Research Subpanel on Human Studies of our University.

Study Protocol

All patients were submitted, in random sequence, to three intravenous injections of ^{99m}Tc-MIBI (740 MBq): one under control conditions, one during bicycle exercise and one during adenosine infusion. A 3-day interval separated each of the three studies. All patients had the same preparation for each study. After an overnight fast to minimize gallbladder activity, all patients were instructed to consume a light fatty meal after ^{99m}Tc-MIBI injection and before imaging.

Exercise Protocol

All patients underwent exercise ^{99m}Tc-MIBI cardiac imaging as previously described (*10*). Briefly, a standardized multistage exercise protocol was performed with the patients seated erect on the ergometric bed with continuous monitoring of heart rate and rhythm, blood pressure and symptoms. At peak exercise (at least 85% of age-predicted heart rate, angina or severe dysfunction) ^{99m}Tc-MIBI was injected as a bolus into an intravenous line and flushed with 10 ml of NaCl 0.9% solution 2 min before the end of exercise. Tomographic images were acquired 1 hr later.

Adenosine Protocol

All patients underwent adenosine ^{99m}Tc-MIBI cardiac imaging as previously described (*12,13*). Caffeine ingestion was not allowed for at least 24 hr preceding the study. Adenosine was supplied by University College and Middlesex School of Medicine (London, UK) as a sterile isotonic aqueous solution at a concentration of 5 mg/ml (10.5-ml vials) and infused through a peripheral vein by using an infusion pump at a rate of 140 μg/kg per min for 6 min with the patients in the supine position. After 4 min, ^{99m}Tc-MIBI was injected as a bolus into an intravenous line and flushed with 10 ml of NaCl 0.9% solution into the opposite arm, and the adenosine infusion continued for additional 2 min. Heart rate and rhythm, blood pressure and symptoms were continuously monitored. Tomographic acquisition was performed in the same manner used for the exercise test; the patients were supine and acquisition was begun 1 hr after ^{99m}Tc-MIBI injection.

SPECT Acquisition and Processing

SPECT acquisition was performed using a rotating large field of view gamma camera (Elscint SP4HR, Haifa, Israel) equipped with a low-energy, all-purpose, parallel-hole collimator and connected with a dedicated computer system. Thirty-two projections (40 sec/projection) were obtained over a semicircular 180° arc, which extended from the 30° right anterior oblique to the left posterior oblique position. A 20% symmetric energy window centered on the 140-keV peak was used. All projection images were stored on magnetic disk by means of a 64 × 64 word matrix. Each projection image was corrected for nonuniformity, with a 120-million count image obtained weekly from a uniform ^{57}Co flood source. The mechanical center of rotation was determined from the projection data to align the detector data with respect to the reconstruction matrix (*6*). The raw data were initially smoothed with a nine-point weighted average algorithm. Filtered backprojection was then performed with a low-resolution Butterworth filter with a cutoff frequency of 0.5 cycles/pixel, order 5, to reconstruct a transverse axial tomogram of 6.2-mm thickness per slice, which encompassed the entire heart. Sagittal and oblique tomograms parallel to the long-axis and short-axis of the left ventricle were then extracted from the filtered transaxial tomogram by performing a coordinate transformation with the appropriate interpolation (*14*). No attenuation or scatter correction was used.

Data Analysis

In each patient, corresponding resting, exercise and adenosine ^{99m}Tc-MIBI tomographic images were evaluated for direct comparison. For each study, tomograms were divided into 22 segments (Fig. 1). Each segment was assigned to one of the major vascular territories. The anterior descending artery territory included the anterior wall (segments 1, 6, 7, 12, 13 and 18), septum (segments 5, 11 and 17), and apical wall (segments 19, 21 and 22). The right coronary artery was assigned the inferior wall (segments 3, 4, 9, 10, 15 and 16). The left circumflex artery was assigned the lateral wall (segments 2, 8 and 14). The inferoapical wall (segment 20) was assigned to the right coronary artery if the inferior wall in the apical portion of the short-axis view (segments 3 and 4) showed a perfusion defect and the anteroapical wall (segment 19) was normal.

Regional ^{99m}Tc-MIBI uptake was quantitatively analyzed. Briefly in each tomogram the myocardial region with the maximum counts was used as the normal reference region. Tracer uptake in all other myocardial segments was then expressed as a percentage of the activity measured in the reference region. Segments having <30% of the maximal uptake were categorized as Grade 0 (= threshold). Segments with an uptake between 30% and 50% were categorized as Grade 1; segments with an uptake between 50% and 70% were categorized as Grade 2; and segments with an uptake over 70% were categorized as Grade 3. Thus, each segment of the three studies (exercise, adenosine and rest) was categorized as having no uptake (0), severely reduced uptake (1), moderately reduced uptake (2) or normal uptake (3). A segment with a perfusion defect was determined to be irreversible if the assigned regional grade on exercise or adenosine tomographic

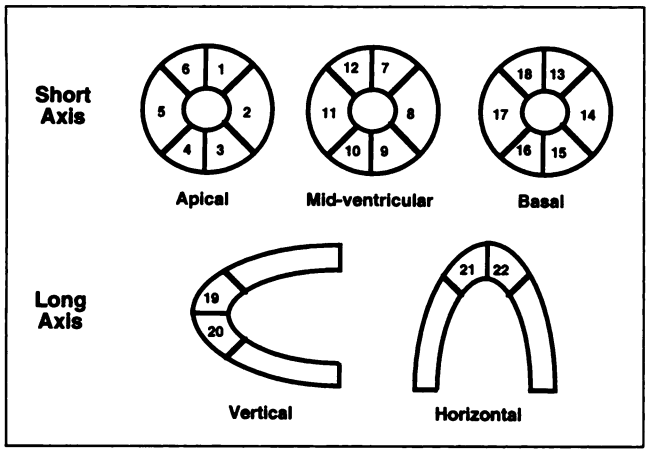

FIGURE 1. Diagram of the standard segmentation scheme used for regional quantitative analysis of exercise, adenosine and resting ^{99m}Tc-MIBI cardiac tomography.

images was abnormal and remained the same abnormal grade on resting images. Similarly, a segment with a perfusion defect was determined to be reversible if the assigned abnormal regional grade on exercise or adenosine images increased or normalized on resting images.

The anterior image in the tomographic acquisition was used to calculate heart and lung ^{99m}Tc-MIBI uptake. Heart-to-lung and heart-to-liver ratios for exercise and adenosine were computed by dividing the mean counts/pixel obtained in the regions of interest drawn over the myocardial wall (normally perfused region), left lung and upper part of the right liver lobe, as previously described (*10*).

Statistical Analysis

Data are expressed as mean ± 1 s.d. Differences in the mean values were assessed by the Student's t-test for paired data. A chi-square test was used to assess differences between proportions. Linear regression analysis was used to assess the relationship between exercise and adenosine ^{99m}Tc-MIBI uptake. Probability values <0.05 were considered significant. The kappa statistic and its standard error were used as a measure of agreement between exercise and adenosine ^{99m}Tc-MIBI tomography. A value of 1 denotes perfect agreement, and 0 indicates no agreement beyond chance (*15*). In general, kappa values of 0.6 or greater are considered indicative of good agreement.

RESULTS

Hemodynamic Parameters and ECG Changes

The hemodynamic parameters recorded under control conditions, during exercise and during adenosine ^{99m}Tc-MIBI cardiac tomography are presented in Table 2. Adenosine administration induced a statistically significant increase of heart rate and rate-pressure product (both $p < 0.001$). Systolic and diastolic blood pressure were not significantly different during adenosine compared to control conditions. Heart rate, systolic and diastolic blood pressure and rate-pressure product were significantly higher (all $p < 0.001$) during exercise than during adenosine infusion.

Mean exercise duration was 8 ± 2 min and mean percent target heart rate was 87% ± 12%. Nineteen (86%) of the 22 patients achieved 85% of their age-predicted maximal heart rate during exercise. In the remaining three patients, exercise was stopped earlier because they developed severe angina. ST segment depression indicative of myocardial ischemia occurred in seven (32%) patients during exercise and in three (14%) patients during adenosine infusion ($p < 0.01$). ECG ischemic changes during both exercise and adenosine infusion occurred in two patients.

Side Effects of Adenosine Infusion

During adenosine infusion, 8 patients (36%) did not report side effects. The remaining 14 patients (64%) experienced symptoms that were mild and transient. The most common side effects were flushing (45%), chest pain (27%), light headedness or dizziness (14%), and dyspnea (10%). However, all symptoms resolved spontaneously within 1 or 2 min after discontinuing the adenosine infusion and in no patient did side effects require premature interruption of adenosine administration or interventions.

Imaging Results

Agreement on the presence of an abnormal tomogram by adenosine and exercise was 100% by quantitative analysis (all patients had abnormal findings with both adenosine infusion and exercise). In all myocardial segments, a significant relationship between exercise and adenosine ^{99m}Tc-MIBI uptake was observed ($r = 0.90$, $p < 0.0001$).

TABLE 2
Hemodynamic Parameters Recorded Under Control Conditions and During Exercise and Adenosine ^{99m}Tc-MIBI Cardiac Tomography

	Exercise		Adenosine	
	Baseline	Peak	Baseline	Peak
Heart rate (bpm)	73 ± 13	140 ± 19*	70 ± 13	94 ± 16*†
Systolic blood pressure (mmHg)	122 ± 13	174 ± 19*	124 ± 14	120 ± 20†
Diastolic blood pressure (mmHg)	77 ± 10	101 ± 12*	80 ± 8	78 ± 12†
Rate-pressure product (bpm × mmHg)	9,015 ± 1,944	24,184 ± 4,296*	9,171 ± 2,099	12,196 ± 2,735*†
Exercise time (min)	8 ± 2		———	
Exercise workload (watts)	90 ± 20		———	

*$p < 0.001$ versus baseline.
†$p < 0.001$ versus exercise test.

The results of ^{99m}Tc-MIBI exercise and adenosine are shown in Figure 2. Segmental agreement for regional uptake scores between exercise and adenosine ^{99m}Tc-MIBI imaging is shown in Figure 3. Concordance was observed in 394 (81%) of the total 484 segments, with a kappa value of 0.65. Concordance between the two studies for identification of perfusion status in the 484 total segments analyzed is illustrated in Figure 4. Agreement was observed in 438 (90%) of the total 484 segments, with a kappa value of 0.81. Agreement on localization of the perfusion defect to a specific vascular territory was 92%. Of the total 66 vascular territories analyzed, 41 were supplied by significantly stenosed (≥50% narrowing in luminal diameter) coronary arteries. Exercise and adenosine ^{99m}Tc-MIBI cardiac tomography correctly identified 39 (95%) and 37 (90%) of these 41 vascular territories, respectively (p = ns).

Similar heart-to-lung ratios were obtained for exercise and adenosine (2.9 ± 0.7 versus 2.7 ± 0.6, respectively; p = ns). The mean heart-to-liver ratio was significantly lower in adenosine than in exercise studies (0.7 ± 0.2 versus 1.0 ± 0.3, respectively; $p < 0.001$). Significant relationships between adenosine and exercise heart-to-lung ($r = 0.64$, $p < 0.001$) and heart-to-liver ($r = 0.73$, $p < 0.001$) ratios were observed.

DISCUSSION

Maximal controlled pharmacological coronary vasodilatation with adenosine, combined with ^{201}Tl scintigraphy, appears to be a useful test for the diagnosis of CAD in patients unable to exercise (*11*). It has been previously demonstrated that adenosine and exercise ^{201}Tl myocardial perfusion imaging have high sensitivity and specificity for the detection of CAD (*12,13*). However, ^{201}Tl presents some physical limitations as a myocardial perfusion agent, and thus this tracer is not ideal for imaging purposes. Myocardial perfusion studies with ^{99m}Tc-isonitriles, particularly ^{99m}Tc-MIBI, have clear advantages over ^{201}Tl including on-site availability, shorter acquisition times and higher quality images (*4*). Most of the clinical studies with ^{99m}Tc-MIBI in patients with CAD were performed after an exercise stress test injection (*5–8,16,17*), demonstrating a good correlation between ^{99m}Tc-MIBI and ^{201}Tl in the detection of CAD. However, other cardiac stimulation techniques, such as those used with ^{201}Tl myocardial scintigraphy, can be similarly applied with ^{99m}Tc-MIBI. It has been recently dem-

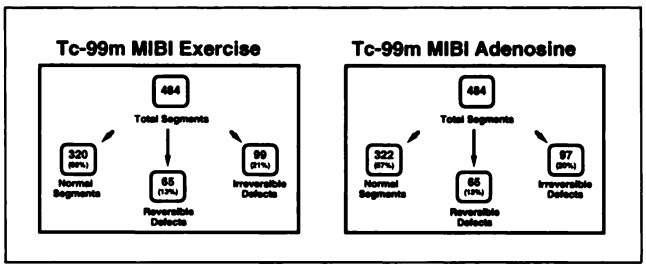

FIGURE 2. Nomogram of exercise and adenosine ^{99m}Tc-MIBI cardiac imaging findings in the 484 myocardial segments analyzed.

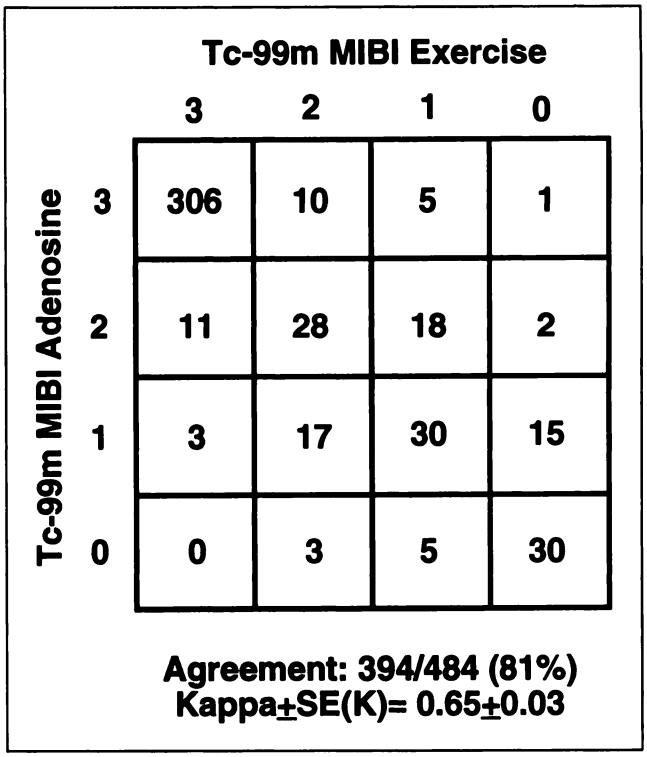

FIGURE 3. Segmental agreement for regional uptake score between exercise and adenosine ^{99m}Tc-MIBI cardiac tomography (3 = normal uptake (>70%); 2 = moderately reduced uptake (uptake between 50% and 70%); 1 = severely reduced uptake (uptake between 30% and 50%); 0 = no uptake (uptake <30%)).

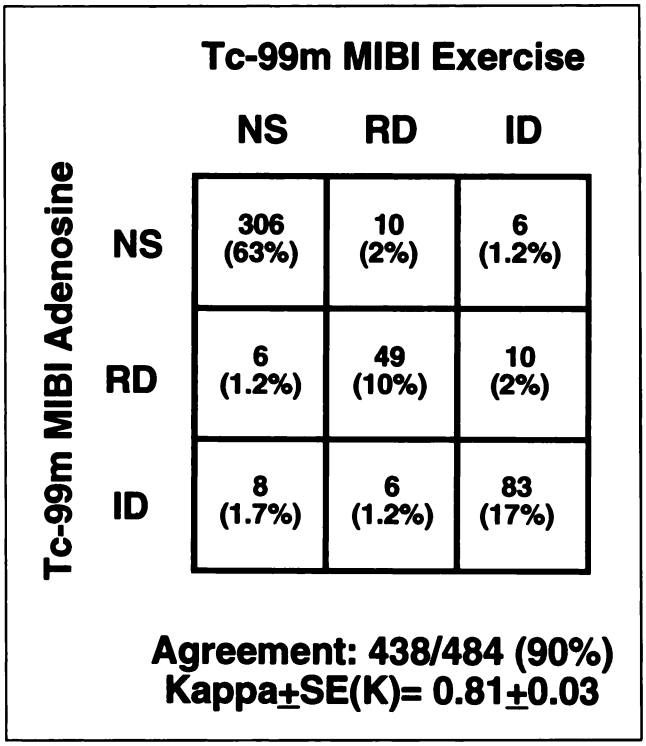

FIGURE 4. Segmental agreement for regional perfusion state between exercise and adenosine ^{99m}Tc-MIBI cardiac tomography (NS = normal segments; RD = reversible defects; ID = irreversible defects).

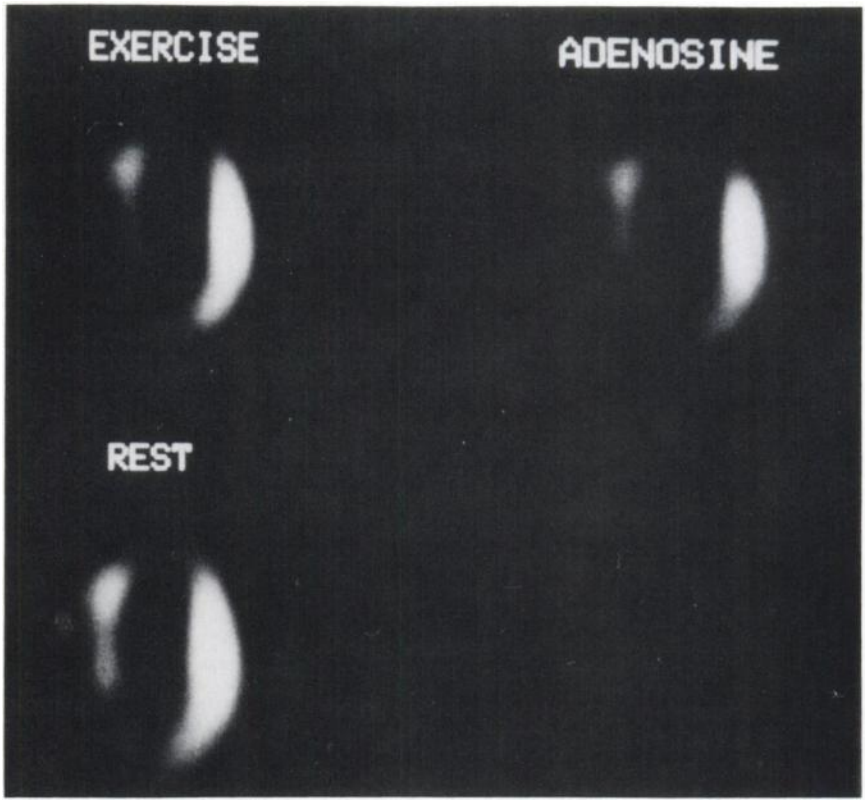

FIGURE 5. Cardiac tomography (horizontal long-axis, Patient 20) showing exercise, adenosine and resting ^{99m}Tc-MIBI images. Reversible perfusion defect of the septal wall and irreversible perfusion defect of the apical region are present on both exercise and adenosine images.

onstrated that ^{99m}Tc-MIBI same-day split injection study, with the first injection given after dipyridamole infusion, may be safely performed, giving results equivalent to those of standard exercise-redistribution ^{201}Tl studies (*9*).

In the present study, we directly compared the results of exercise and adenosine ^{99m}Tc-MIBI myocardial SPECT imaging in the evaluation of myocardial perfusion in patients with angiographically proven CAD. Our data demonstrated similar results of exercise and adenosine ^{99m}Tc-MIBI cardiac imaging in such patients. In particular, agreement on the presence of an abnormal tomogram by adenosine and exercise was 100% by quantitative analysis. One of the most important findings of this study was the similar myocardial uptake of ^{99m}Tc-MIBI with the two different types of cardiac stimulation in both normal regions and in regions with perfusion defects, as shown by the highly significant relationship between exercise and adenosine ^{99m}Tc-MIBI uptake (Fig. 5). Segmental agreement for regional uptake score between exercise and adenosine was observed in 81% of the segments, with a kappa value of 0.65 (indicating good agreement between the two tests). Adenosine and exercise ^{99m}Tc-MIBI imaging showed concordance for detecting individual coronary artery lesions.

The overall sensitivity, specificity and diagnostic accuracy for detection of stenosed vessel was comparable for adenosine. These results are similar to those reported by other investigators with adenosine and exercise ^{201}Tl SPECT imaging (*11,12*). Adenosine imaging also demonstrated excellent concordance with exercise study for differentiating between reversible and irreversible perfusion abnormalities. In particular, concordance between the two studies for identification of perfusion status was observed in 90% of the segments, with a kappa value of 0.81 (indicating excellent agreement between the two tests). However, we evaluated a relatively small number of selected patients and further similar studies in a larger series are required to confirm our results.

In our study population, the double product with adenosine was lower than that with exercise, since adenosine induced an increase in heart rate but did not significantly change blood pressure. Previous studies showed that myocardial uptake of ^{99m}Tc-MIBI increases linearly with the coronary blood flow (*18,19*). However, the uptake reaches a plateau at high flow rates. It has been demonstrated (*20*) that in normal subjects, although the double product observed during dipyridamole-induced coronary vasodilatation was lower than that observed during exercise, a similar maximal myocardial uptake of ^{99m}Tc-MIBI was obtained with these two different types of cardiac stimulation. The double product in patients with significant CAD is usually lower than in normals, and it is probable that the ^{99m}Tc-MIBI myocardial uptake will linearly correspond to the blood flow. It could be speculated that myocardial uptake of ^{99m}Tc-MIBI will be lower after adenosine than after exercise. Our results, obtained in a group of patients with angiographically proven CAD, suggest that despite different hemodynamic response, diagnostic capabilities of exercise and adenosine ^{99m}Tc-MIBI cardiac SPECT imaging are comparable. In fact, similar relative uptake of

^{99m}Tc-MIBI between exercise and adenosine in normal myocardial segments as well in regions with reversible or irreversible perfusion defects was observed.

The heart-to-lung ratio was similar in the exercise and in the adenosine studies, while the heart-to-liver ratio was higher in the exercise test. Primeau et al. (*20*) recently reported that in normal subjects, the heart-to-liver ratio was significantly higher during exercise compared to dipyridamole ^{99m}Tc-MIBI imaging. A possible explanation for the higher heart-to-liver ratio in the exercise images is a lower splanchnic and liver uptake. This different uptake could be determined by differences in the pattern of regional flow distributions between exercise and adenosine.

The results of the present study confirm that adenosine is well tolerated and safe for diagnostic myocardial perfusion imaging (*11–13*). The side effects of intravenous dipyridamole and adenosine are similar (*21–24*). The greater frequency of adverse reactions with adenosine may be related to the higher blood concentration achieved with this drug compared with that found after a standard dose of intravenous dipyridamole (*22,23*). However, in our study population all symptoms were transient and resolved spontaneously within 1 or 2 min after discontinuing the adenosine infusion. In no case did side effects require premature interruption of adenosine administration or interventions.

In conclusion, adenosine-induced maximal pharmacological coronary vasodilatation, associated with ^{99m}Tc-MIBI tomographic cardiac imaging, appears to be an accurate noninvasive technique in the diagnosis of CAD. In our group of patients with angiographically documented CAD and adequate exercise capacity, despite different hemodynamic effects, adenosine and exercise ^{99m}Tc-MIBI cardiac SPECT imaging provide similar information in the diagnosis and localization of CAD. Thus, adenosine ^{99m}Tc-MIBI myocardial scintigraphy may be particularly useful in patients unable to exercise.

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