Comparison of Same-Day Protocols Using Technetium-99m-Sestamibi Myocardial Imaging

Jaekyeong Heo, Jeffrey Kegel, Abdulmassih S. Iskandrian, Virginia Cave, and Basil B. Iskandrian

Philadelphia Heart Institute, Presbyterian Medical Center of Philadelphia, Philadelphia, Pennsylvania

Two same-day protocols (rest/exercise [Protocol 1] and exercise/rest [Protocol 2]) with sestamibi (hexakis 2-methoxy-2-isobutyl-isonitrile) were performed within 2 to 14 days of each other after randomization. The initial study in each protocol was done using a dose of 185–296 MBq of ^{99m}Tc-sestamibi. The second study in each protocol used a dose of 555–925 MBq. SPECT imaging was started 30 to 60 min after injection using a 180° anterior arc. Segmental analysis was interpreted as normal, scar or ischemia (20 segments/patient). Among the protocols, there was concordance in 93% of the segments (593/640 segments). In the 11 patients with coronary artery disease and no prior myocardial infarction who had ischemic abnormality, count densities from abnormal and normal zones were compared between the two protocols. Protocol 1 showed greater count differences between abnormal and normal zones on exercise images with better normalization of abnormality on rest images than Protocol 2 ($p < 0.05$). Technetium-99m-sestamibi provides high quality images using either of the two same-day protocols. However, the rest/exercise protocol provides better image contrast and ability to detect reversibility of perfusion defects, and is the preferred same-day protocol.

J Nucl Med 1992; 33:186–191

Since its introduction into clinical use in 1973, ^{201}Tl imaging has been widely used in the diagnosis of coronary artery disease, risk stratification, and in the assessment of viability and results of therapeutic interventions (*1,2*). Recently two ^{99m}Tc-labeled perfusion imaging agents have been approved for clinical use by the Food and Drug Administration: sestamibi (hexakis 2-methoxy-2-isobutyl-isonitrile) and teboroxime (bis[1,2-cyclohexanedione dioximato(1-) - O]-[1,2-cyclohexanedione-dioximato(2) - O]-methylborato(2-) - N,N′,N″,N‴,N⁗,N′′′′′] - chlorotechnetium, Cardiotec®, Squibb Diagnostics) (*3*). Sestamibi (Cardiolite®, E. I. DuPont DeNemours) does not redistribute significantly; thus, separate injections are required at rest and during stress, usually performed on separate days. Previous studies found a good correlation between the results of thallium imaging and sestamibi imaging using the separate-day protocol (*4–7*). In clinical practice, however, a same-day protocol is preferred, at least in some patients, because of convenience, scheduling logistics, and early availability of results to expedite the decision-making process. The feasibility of completing both rest and stress sestamibi studies on the same day was investigated in this study. There are two same-day protocols; in the first, the rest study is done initially followed by the exercise study. In the second, the sequence is reversed. Additional experience is necessary for deciding which of the two sequences is preferable. This report compares the two protocols in image quality and the ability to detect reversibility of the perfusion defects.

Received May 29, 1991; revision accepted Aug. 30, 1991.

For reprints contact: Jaekyeong Heo, MD, Associate Director, Nuclear Cardiology Lab, Philadelphia Heart Institute, Presbyterian Medical Center, 39th and Market Streets, Philadelphia, PA 19104.

MATERIALS AND METHODS

Study Population

A total of 32 patients were enrolled in the same-day protocol study. There were 19 patients with coronary artery disease (CAD) by coronary arteriograms and 13 subjects with either normal coronary artery angiograms (n = 5) or normal volunteers (n = 8) with low pretest probability of CAD on the basis of risk factors and previous exercise study. The pertinent demographic data are summarized in Table 1. All subjects agreed to participate in the study and signed a consent form approved by the Institutional Review Board of the hospital. This report also presents quantitative data on 11 of 19 patients with CAD who had no prior myocardial infarction but abnormal stress images.

Study Design

Patients were randomized as to which protocol to start first. The two protocols (rest/exercise [Protocol 1] and exercise/rest [Protocol 2]) were performed within 2 to 14 days of each other (Fig. 1). Medications were not withheld for the study and remained unchanged between the two study days. None of the patients had prior coronary artery bypass grafting or percutaneous transluminal coronary angioplasty.

Coronary arteriography was performed using standard techniques in multiple views. The results were interpreted by two angiographers without prior knowledge of scintigraphic results. Significant coronary artery disease was defined as ≥50% diameter stenosis in one or more of the major coronary arteries or their major branches.

Exercise Testing

All patients underwent symptom-limited exercise testing in the fasting state using the Bruce protocol. The end points during

TABLE 1
Patient Demographics

Sex (male/female)	21/11
Age (yr)	53 ± 16
History of hypertension	14 (44)
History of diabetes mellitus	1 (3)
ECG Q-wave MI	5 (16)
Medications	
Nitrates	9 (28)
β-blockers	9 (28)
Calcium antagonists	11 (34)
Coronary anatomy	
0 VD	5 (16)
1 VD	6 (19)
2 VD	10 (31)
3 VD	3 (9)
Normal volunteers	8 (25)

ECG = electrocardiogram; MI = myocardial infarct; VD = vessel diseased.
Numbers within parentheses represent percentages.

the first exercise study were angina of at least moderate severity, excessive fatigue, weakness, shortness of breath, ≥2 mm ST-segment depression, hypotension (≥20 mmHg drop), or dizziness. The second exercise study was terminated at a workload, heart rate and double product comparable to those achieved during the first study in each patient. The results of the exercise electrocardiograms were interpreted as positive, negative, or nondiagnostic as previously described (*8*).

SPECT Imaging

The initial study in either protocol was done using a dose of 185–296 MBq (5–8 mCi) of ^{99m}Tc-sestamibi; the second study in each protocol was performed with a dose of 555–925 MBq (15–25 mCi). Imaging was started 30 to 60 min after injection of the tracer. Stress and rest imaging was completed within 4 hr of each other. SPECT acquisition was performed on a GE 400AT rotating gamma camera/Starcam computer system (GE Medical Systems, Milwaukee, WI). Thirty-two images were obtained over an anterior 180° arc starting from the 45° right anterior oblique to the 45° left posterior oblique. Each image was obtained for 30 sec for the first study and 20 sec for the second study using a 64 × 64 matrix.

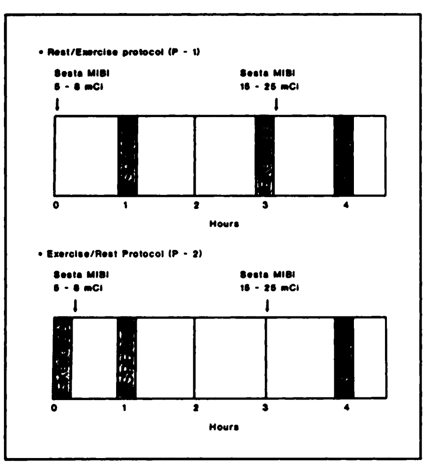

FIGURE 1. Schematic diagram of the study design using the two one-day protocols.

Image Processing

Standard filtered backprojection techniques were used to generate transaxial tomograms using a ramp-Hanning filter with a cutoff frequency of 0.83 cycle/cm. Transaxial tomograms were reoriented to yield oblique angled tomograms, i.e., the short-axis, vertical long-axis, and horizontal long-axis tomograms with each slice of one pixel thickness.

Qualitative Analysis

Qualitative analysis was performed using 20 segments per study (Fig. 2); three short-axis slices at the apical, mid- and basal levels and one vertical long-axis slice. Each short-axis slice was divided into six segments; one anterior, one inferior, two septal, and two lateral segments. In addition, from the vertical long-axis slice at the mid-ventricular level, two segments were analyzed, antero-apical and infero-apical. The sestamibi images were interpreted by two experienced observers without prior knowledge of results of other studies. By definition, an ischemic abnormality was present when a perfusion abnormality was observed in the stress images, but not present or smaller in the corresponding rest images.

Quantitative Analysis

In the 11 patients with CAD and no prior infarction who had ischemic abnormality, count densities from abnormal and normal zones were compared between the two protocols by one experienced observer (*9*). From representative short-axis tomograms, regions of interest (ROIs) were drawn manually in the territories of normal and diseased arteries. The midventricular short-axis tomogram of stress and rest images from the two protocols were displayed using appropriate display window for identical ROIs. Count densities from each ROI were used to derive count ratios of abnormal to normal regions of four tomograms (Fig. 3). The intraovserver variability in measuring count densities was small (r = 0.95, $p < 0.001$).

Statistical Analysis

The results were expressed as mean ± standard deviation. The paired and nonpaired Student's t-test, chi-square test and McNemar's test of symmetry were used when indicated (*10*). A p value of ≤0.05 was considered statistically significant.

RESULTS

Coronary angiography revealed that six patients had one-vessel disease, ten patients had two-vessel disease, and three patients had three-vessel disease.

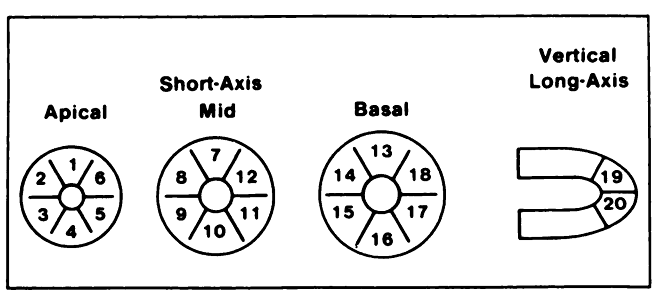

FIGURE 2. Schematic presentation of 20 segments per study (see text).

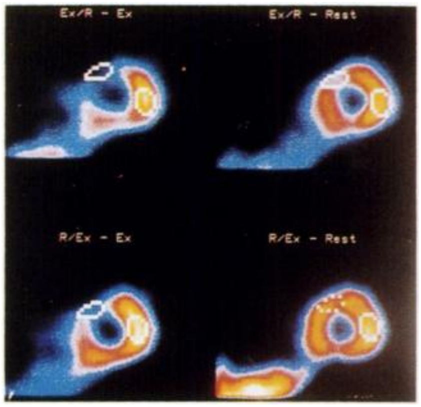

FIGURE 3. ROI placement in four representative short-axis tomograms at stress and rest from the two protocols. The top row represents the exercise/rest protocol, stress image on the left and rest image on the right. The bottom row represents the rest/exercise protocol, stress image on the left and rest image on the right.

Exercise Testing

The results of exercise testing are shown in Table 2. As expected, there were no significant differences between the two exercise tests in peak heart rate, systolic blood pressure, workload, and exercise time. Twelve patients during Protocol 1 and 14 patients during Protocol 2 had positive exercise electrocardiographic responses (p = ns).

SPECT Imaging

The image quality of sestamibi SPECT was good in both of the two one-day protocols. Representative examples of both protocols in the same patient are shown in Figure 4. The results of sestamibi SPECT images using the two protocols by qualitative analysis are summarized in Table 3. Sensitivity and specificity of both protocols were identical. The nature of the perfusion pattern (ischemia, scar, or normal) was concordant in 93% of the segments (597/640 segments, $p < 0.005$; Fig. 5).

Image Contrast and Viability

The count densities in normal and abnormal areas are shown in Figure 6. As expected, the second study in each protocol had a much higher count density (because of higher dose) than the initial study. The abnormal-to-normal count ratios at rest and during exercise are shown in Figure 7. In Protocol 1, the difference between the abnormal and normal area was smaller at rest and greater during exercise than in Protocol 2. The change in count ratios from exercise to rest in both protocols is shown in Figure 8. This change was higher in Protocol 1 ($p < 0.05$). Thus, the diagnostic certainty of presence and nature of perfusion abnormality was better in Protocol 1 than Protocol 2.

TABLE 2
Results of Exercise Testing

	Protocol 1	Protocol 2
Exercise heart rate (bpm)	149 ± 25	149 ± 29
Exercise SBP (mmHg)	180 ± 25	177 ± 25
Exercise time (min)	8.0 ± 3.7	7.9 ± 3.2
Exercise workload (METS)	10 ± 4	10 ± 4
Exercise ECG response		
Positive (%)	14 (44)	12 (38)
Negative (%)	15 (47)	14 (44)
Inconclusive (%)	3 (9)	6 (19)
Angina during exercise (%)	1 (3)	2 (6)

ECG = electrocardiograms and SBP = systolic blood pressure.
None of the above differences was statistically significant.

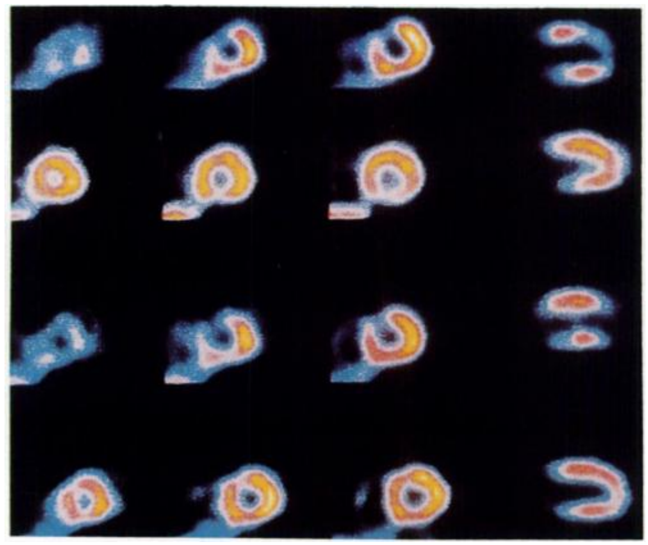

FIGURE 4. Stress and rest sestamibi images of both protocols. The top two rows represent stress images (top row) and rest images (second row) of Protocol 1 (rest/exercise). The bottom 2 rows show stress images (third row) and rest images (bottom row) of Protocol 2.

DISCUSSION

Despite the wide acceptance of thallium myocardial perfusion imaging, the physical characteristics of ^{201}Tl are less than ideal. Its low photon energies (69–83 keV) results in considerable attenuation and scatter (*3*); its long physical half-life of 73 hr makes it difficult to repeat serial imaging in a short time period. Also, patient dosimetry is unfavorable, limited to a 111–148-MBq dose. Finally, its cyclotron production requires daily delivery to the nuclear imaging laboratories from the radiopharmacy. On the other hand, ^{99m}Tc is generator-produced, readily available 24 hr/day, and inexpensive with superior imaging characteristics. It has a short half-life of 6 hr and optimal photon energies of 140 keV. Recently, two groups of ^{99m}Tc-labeled myocardial perfusion imaging agents have been investigated clinically: isonitrile complex and boronic acid adducts of technetium dioxime (BATO) compounds.

TABLE 3
Results of Sestamibi Imaging

	Protocol 1	Protocol 2
Sensitivity (%)	89 (17/19)	89 (17/19)
Specificity (%)	100 (13/13)	100 (13/13)
Predictive accuracy (%)	94 (30/32)	94 (30/32)
Detection of ischemia	16	16

Protocol II \ Protocol I	Normal	Ischemia	Scar
Normal	527	6	4
Ischemia	24	62	5
Scar	1	3	8

Segment agreement: 597/640 (93%)
Kappa statistics: 0.74 ± 0.04, p<0.005

FIGURE 5. The nature of perfusion abnormalities between the two one-day protocols.

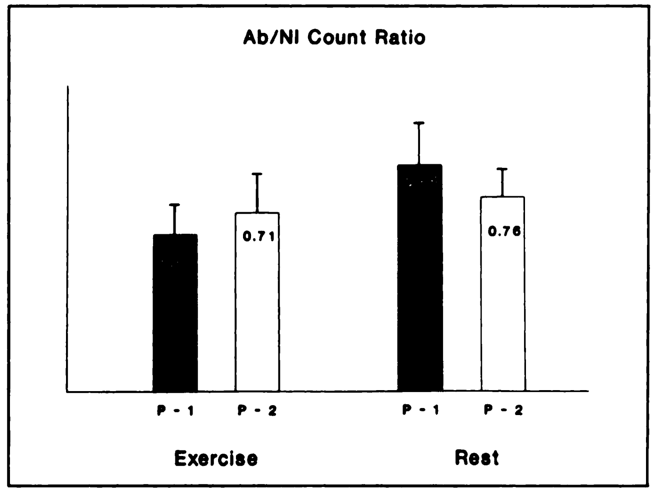

FIGURE 7. The abnormal-to-normal count ratios on rest and postexercise images of the two protocols (p = ns). Abbreviations: Ab = abnormal; Nl = normal; P-1 = Protocol 1; and P-2 = Protocol 2.

Sestamibi

Of the family of isonitrile complexes, sestamibi is the most promising agent. It is a lipophilic cationic complex and is taken up by viable myocardium in relation to regional blood flow. Sestamibi binds with high affinity to a low molecular weight cytosolic protein. Unlike its precursors, i.e., tertiary butyl isonitrile (TBI) or carbo-methoxy isopropyl isonitrile (CPI), myocardial uptake of sestamibi is adequate with minimal lung uptake and transient liver uptake with the excretion into the biliary system (*11–13*). Animal studies have shown that myocardial uptake of sestamibi is proportional to coronary blood flow similar to ^{201}Tl (*14–16*). However, like other diffusible cations, there is a relative increase in extraction of sestamibi in low flow regions and a decreased extraction at high flow rates. The first-pass extraction fraction for sestamibi is less than that of ^{201}Tl at any given flow (*17*), although the net retention fraction is higher than thallium because of lower clearance. Due to lack of redistribution, two separate injections of sestamibi are required: one at rest, and another during stress (either exercise or pharmacological stress testing). Previous studies show excellent correlation between thallium imaging and sestamibi imaging with stress and rest studies performed on two separate days using either planar or SPECT techniques (*4–7*). In general, the image quality with sestamibi is better than that with ^{201}Tl due to high count statistics and less attenuation and scatter problems. The short half-life of ^{99m}Tc allows high dose administration (up to 1110 MBq); bolus injection also allows acquisition of first-pass radionuclide angiograms with a multi-crystal camera or a digital single-crystal camera (*5,18*). Thus, simultaneous evaluation of myocardial perfusion and left ventricular function is feasible. Encouraging results have been reported using gated planar or SPECT sestamibi imaging for evaluation of wall thickening and wall motion abnormality (*19,20*).

Planar Versus SPECT Imaging

SPECT thallium imaging has proven to be superior to planar techniques in relation to better image contrast, lack of superimposition of normal and abnormal areas, and a three-dimensional presentation of the site and extent of perfusion abnormality (*21*). However, ^{201}Tl may not be ideally suited for tomographic imaging due to its low photon energy and the phenomenon of redistribution during image acquisition. Unlike ^{201}Tl, sestamibi shows minimal redistribution over time and has a suitable photon

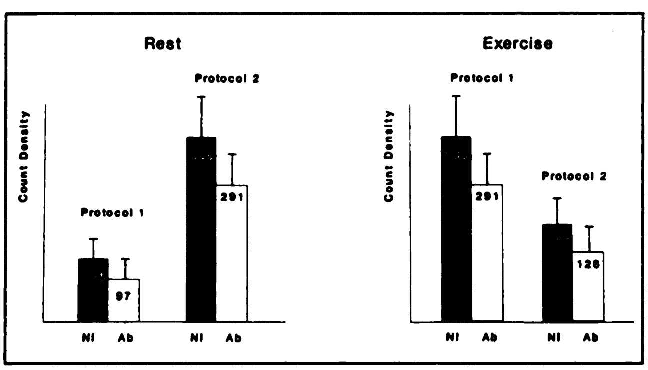

FIGURE 6. The count densities in normal and abnormal areas (p = ns). Abbreviations: Ab = abnormal; Nl = normal

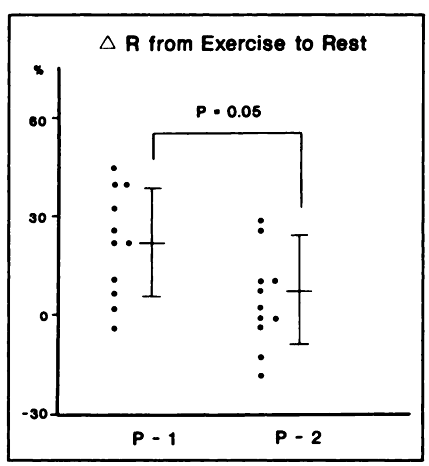

FIGURE 8. The change in count ratio from exercise to rest. Abbreviations: ΔR: change in count ratio; P-1 = Protocol 1; P-2 = Protocol 2. Bars represent mean ± s.d.

energy, providing ideal conditions for tomographic imaging. In fact, planar images of sestamibi tended to underestimate perfusion abnormality due to overlap of abnormal and normal areas (*7*). For SPECT thallium imaging, 180° image acquisition has been the routine practice over 360° acquisition. Maublant et. al. compared 180° acquisition (32 views, 30 sec each) to 360° acquisition (64 views, 15 sec each) using ^{99m}Tc-sestamibi in 12 patients with single-vessel disease (*22*). Their results showed that the best balance between sensitivity and specificity was achieved with the 180° acquisition.

Current Study

Although the two-day protocol is preferable from a physics standpoint, in clinical practice, a same-day protocol is preferred in some patients because of convenience and scheduling logistics. The results of the current study showed that the same-day protocol is feasible. To overcome the residual background activity from the first study, the second study is performed with a dose that is roughly three times larger than the initial dose. The two same-day protocols are comparable in determining the presence or absence and nature of perfusion abnormalities; however, quantitative and qualitative analysis confirm that the ischemic abnormality is better appreciated using rest/exercise sequence. Using rest/exercise sequence, rest images represent true resting perfusion. With an exercise/rest sequence, resting injection will provide a similar increase in counts in both abnormal and normal areas; thus, it may be difficult to "fill-in" the abnormal area completely, resulting in incomplete normalization and apparent partial redistribution. Using a higher dose during exercise also allows better visualization of the stress-induced perfusion abnormality. Finally, if the first-pass technique is used to measure exercise left ventricular ejection fraction, the higher dose results in more reliable information due to high count statistics. The rest/exercise sequence, however, is not a traditionally accepted method when compared to thallium imaging (exercise/4-hr redistribution) as a standard for comparison; it may also mean that some exercise studies are done later in the day than early morning. These logistics, however, are not difficult to overcome. Our results are similar to those of Taillefer et al. who studied 18 patients with same-day protocols (*23*). The nature of the perfusion abnormality was analyzed as normal, ischemic, or scar in 16 segments per study. There was agreement in 283 of 324 (87%) segments between the two protocols. However, 24 segments (7%) were judged ischemic in the rest/stress protocol but were considered scar on stress/rest protocol. In one patient, ischemia was better appreciated on stress/rest sequence. Our results also showed 93% segmental agreement between the two protocols. However, there was no significant difference between the two protocols in reference to the nature of perfusion abnormality.

An issue to consider is that if the initial exercise images are normal with exercise/rest sequence protocol, then there is no need to perform the rest images. This may, in fact, be an acceptable alternative in patients with a low likelihood of CAD. The important point to note is that both protocols are comparable in their sensitivity and specificity. The differences are subtle in terms of image quality and viability assessment (extent of reversible abnormality versus scar), which may be important in patients with previous myocardial infarction.

In summary, ^{99m}Tc-sestamibi provides high quality images using either of the two same-day protocols. However, the rest/exercise protocol provides better image quality of exercise images and the ability to detect reversibility of perfusion abnormality.

ACKNOWLEDGMENTS

The authors would like to thank Susan Kelchner for her expert secretarial assistance in the preparation of this manuscript. This study was presented in part at the Annual Meeting of the American College of Cardiology, Atlanta, GA, March 3-7, 1991.

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