Perfusion and Function at Rest and Treadmill Exercise Using Technetium-99m-Sestamibi: Comparison of One- and Two-Day Protocols in Normal Volunteers

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The purpose of this study was to explore the feasibility of performing rest and exercise technetium-99m-sestamibi (^{99m}Tc-sestamibi) studies on the same day. We prospectively studied 34 asymptomatic volunteers using two different protocols (17 patients studied using one-day protocol and 17 patients studied using two-day protocol). For the one-day protocol, the rest study was performed first. For the two-day protocol, the exercise study was performed first followed by a second-day rest study. Left and right ventricular ejection fractions, myocardium/lung, myocardium/liver, myocardium/spleen, and myocardium/gallbladder count ratios were similar for the one- and two-day groups. No significant difference was observed in any variable measured. These data suggest that ^{99m}Tc-sestamibi can be used for rest and treadmill exercise studies performed on the same day to provide assessment of ventricular function and perfusion similar to studies performed on separate days.

J Nucl Med 1990; 31:1128–1132

The new radiopharmaceutical Cardiolite™ (technetium-99m-methoxy isobutyl isonitrile or sestamibi) (E.I. Du Pont de Nemours and Company, Inc., N. Billerica, MA) allows assessment of ventricular function and perfusion with a single tracer injection (*1,2*). Technetium-99m-sestamibi (^{99m}Tc-sestamibi) is lipophilic, binds to a cytoplasmic protein (*3*), and has a very slow washout from the myocardium with no significant redistribution (*4*). The liver demonstrates a high uptake immediately following injection and marked clearance in about one hour with excretion into the small intestine (*4*). The possibility of using exercise treadmill testing in conjunction with first-pass radionuclide angiocardiography (RNA) followed by single-photon emission computed tomography (SPECT) or planar perfusion imaging makes this a very attractive agent for evaluating patients with coronary artery disease. A first-day exercise study followed by a second-day rest study was originally proposed due to the prolonged myocardial retention and the large amount of abdominal activity (*4*). However, the simplicity of a one-day study would be desirable for clinical application of this radiopharmaceutical. Therefore, the purpose of this study was to explore the feasibility of performing rest and exercise ^{99m}Tc-sestamibi studies on the same day using RNA and SPECT imaging in conjunction with treadmill testing.

Received Sept. 25, 1989; revision accepted Jan. 31, 1990.

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MATERIALS AND METHODS

Study Population

Thirty-four asymptomatic volunteers with less than a 5% likelihood of having significant coronary artery disease based on sex, age, and exercise treadmill results were prospectively studied (*5*). There were 27 men and 7 women with a mean age of 46 yr (range 31–76). Seventeen subjects were studied using a one-day protocol (Group I) and another 17 using a two-day protocol (Group II). Baseline and treadmill characteristics of the subjects in the two groups are listed in Table 1. The protocol was approved by the Institutional Review Board of Duke University Medical Center. Informed consent was obtained from each subject prior to the conduct of studies.

Rest and Exercise Studies

After skin preparation and local anesthesia, a sterile 20-gauge 1.25 in. intravenous catheter was placed into an external jugular or antecubital vein for injections of radiopharmaceuticals. For the one-day studies, ~10 mCi of ^{99m}Tc-sestamibi in 1 cc normal saline were flushed in as a bolus with 10–20 cc normal saline while the resting RNA was acquired with a multicrystal gamma camera (Scinticor™, Milwaukee, WI). One hour later, SPECT images were acquired. A five-minute 45° left anterior oblique (LAO) planar image was then obtained. After rest perfusion imaging, the patient had an exercise treadmill test using the Bruce protocol. When 85% of age-predicted maximal heart rate was achieved, ~30 mCi of ^{99m}Tc-sestamibi were administered in a manner similar to the rest study, and counts were recorded with the multicrystal gamma camera. Exercise was terminated 1 min after injection. Exer-

TABLE 1
Characteristics of Study Population

	Group I	Group II	p
n	17	17	ns
Age (yr)	46 ± 12	45 ± 8	ns
Exercise heart rate	173 ± 18	167 ± 12	ns
Exercise time (sec)	670 ± 206	626 ± 232	ns
METS	13 ± 5	12 ± 4	ns
% Likelihood of disease			
Pre-test	3.0 ± 2.9	2.4 ± 1.9	ns
Post-test	1.5 ± 0.9	1.4 ± 1.4	ns

cise SPECT images were acquired starting 1 hr after the second injection. The exercise planar image was then obtained for five minutes in the LAO position. The total rest and exercise evaluation did not take more than 4 hr (Fig. 1).

For the two-day studies, the exercise was performed on the first day, and the rest study was performed on the second day. The studies were performed in a fashion identical to the same-day protocol except the exercise study was obtained using only 10 mCi of tracer (Fig. 2).

RNA Studies

RNAs were acquired in the anterior projection at 20-msec intervals using a portable multicrystal gamma camera (Fig. 3). The total acquisition time was 24 sec. Each 20×20 pixel radionuclide image was stored on a high-speed magnetic disk. All the RNA data were processed using commercial software developed and validated at this institution (*6*). The histogram of counts as a function of time was used to identify end-diastolic and end-systolic frames. Beats which were at least 70% of the count activity of the maximum beat were selected for processing. Left ventricular ejection fraction (LVEF) was calculated from the background-corrected representative cycle. The left ventricular volumes were calculated by the area-length method of Sandler and Dodge (*7*). Regional wall motion was assessed using static images and a cinematic display of the entire representative cycle. Regional ejection fraction was evaluated using circle-normalized contours. The left ventricular images were divided into the anterior, apical, and inferior walls and were quantitatively analyzed using the diastolic and systolic contours.

SPECT Studies

Perfusion imaging was performed using a rotating gamma camera (Siemens Orbiter™, DesPlaines, IL) fitted with a high-

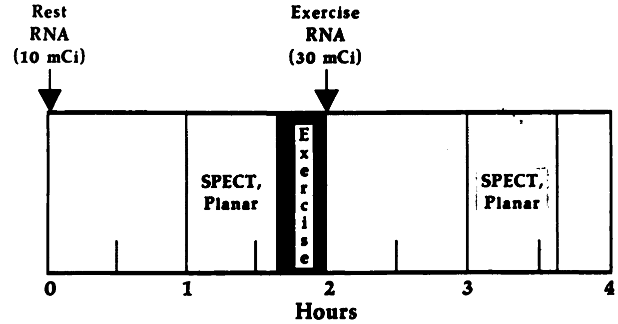

FIGURE 1
Data-acquisition protocol for a one-day ^{99m}Tc-hexamibi perfusion (SPECT) and function (RNA) study.

resolution collimator and interfaced to a computer (Medasys Paragon™, Ann Arbor, MI). SPECT acquisition was performed using a 180° arc from 45° right anterior oblique (RAO) to 45° left posterior oblique (LPO) with 64 stops imaging for 30 sec per stop. Images were recorded on a 64×64 matrix and stored on floppy disk for subsequent analysis. All images were prefiltered followed by transaxial reconstruction which employed a standard backprojection technique with a Butterworth filter (order 5% and 20% cutoff). Reconstructed tomographic slices with 6 mm thickness were reoriented in the short and vertical long axes and displayed on a color monitor for visual interpretation.

Planar Imaging

The LAO planar image was acquired to assess ratios of organ and "background" to myocardium at rest and exercise. Small regions of interest (3×3 pixels) were placed over the myocardium, lung, spleen, liver, and gallbladder. A 4×11 pixel background region was placed immediately below the inferior wall of the left ventricle (Fig. 4). Mean counts per pixel in each region were obtained to calculate the myocardium/organ ratios. The inferoapical region of the myocardium was used for the myocardium/abdominal organ and myocardium/background ratios. The posterolateral region was used to assess myocardium/lung ratios. Myocardium/spleen, myocardium/liver, and myocardium/gallbladder ratios were obtained in 17 subjects (ten Group I and seven Group II). Myocardium/lung and myocardium/background ratios were obtained in all subjects. The 45° LAO planar images were graded by two investigators blinded to the type of study (one- or two-day) to evaluate the scatter from the abdominal activity into the

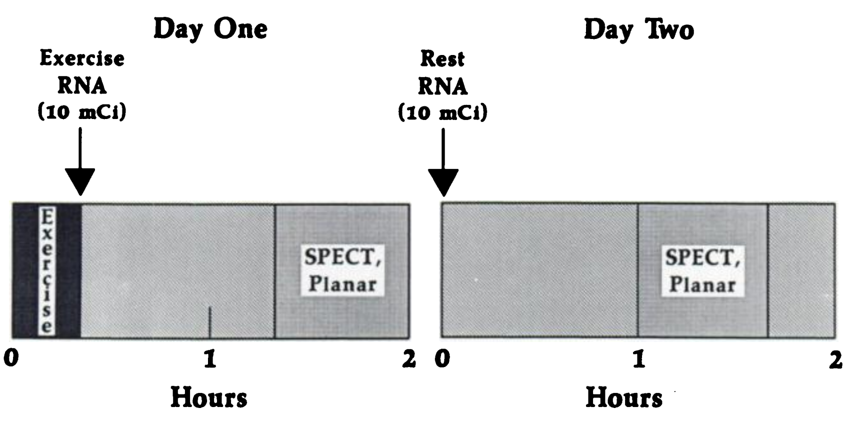

FIGURE 2
Data-acquisition protocol for a two-day ^{99m}Tc-hexamibi perfusion (SPECT) and function (RNA) studies.

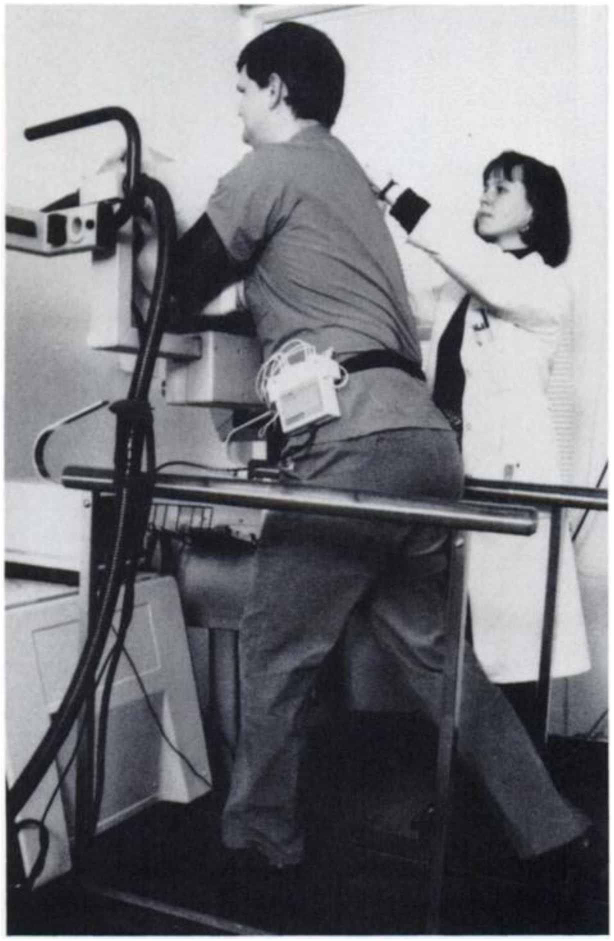

FIGURE 3
Exercise initial-transit RNA performed on a treadmill.

inferoapical wall of the left ventricle. A score of 0 was given for no scatter; a score of 1 was given for the presence of scatter above background which did not affect image interpretation; and a score of 2 was given if the scatter was similar to

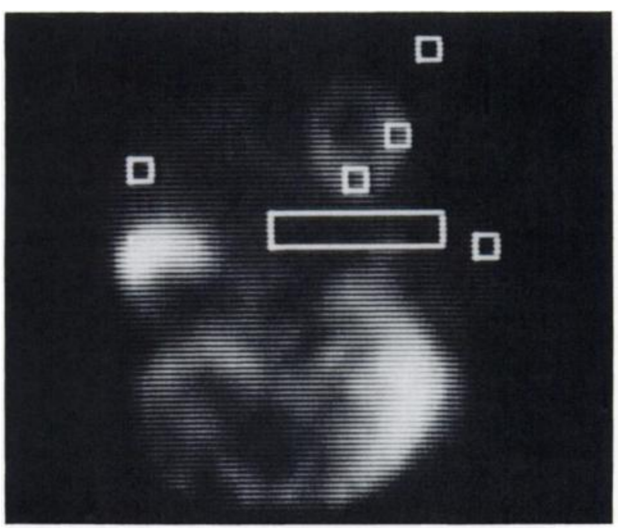

FIGURE 4
Planar image (45° LAO) with limited ROIs.

myocardial activity. Any disagreement was decided by consensus of the two readers.

Data Analysis

Baseline clinical characteristics were compared between Group I and Group II using Chi-square analysis. Exercise treadmill, ventricular function, and myocardial perfusion variables were compared between Groups I and II using the unpaired t test. Results are expressed as mean ± 1 s.d. A probability value ($p < 0.05$) was considered significant.

RESULTS

Study Population

The characteristics of the two study groups were not significantly different (Table 1). The age, treadmill results, and likelihood of disease of the two groups were similar.

Function Variables

Table 2 shows the global functional variables obtained with the RNA at rest and during exercise. The global functional parameters were not significantly different between the one-day study and the two-day study. The regional ejection fractions were also similar for the two different protocols (Fig. 5).

Perfusion Variables

Rest myocardium/organ ratios were not significantly different for the one- and two-day studies: myocardium/lung (2.6 ± 0.6 and 2.9 ± 0.4), myocardium/background (1.6 ± 0.4 and 1.4 ± 0.2), myocardium/liver (2.0 ± 0.4 and 2.0 ± 0.6), myocardium/spleen (1.6 ± 0.4 and 1.7 ± 0.6), and myocardium/gallbladder (0.8

TABLE 2
RNA Results

	Group I	Group II	p
RVEF			
Rest	52 ± 8.4	52 ± 6.8	ns
Exercise	61 ± 7.0	66 ± 10.3	ns
LVEF			
Rest	59 ± 7.4	59 ± 4.7	ns
Exercise	67 ± 6.6	66 ± 7.4	ns
LVEDV			
Rest	133 ± 29	124 ± 21	ns
Exercise	187 ± 38	181 ± 47	ns
LVESV			
Rest	54 ± 18	50 ± 11	ns
Exercise	62 ± 17	61 ± 21	ns
LV stroke volume			
Rest	74 ± 14	78 ± 16	ns
Exercise	120 ± 32	125 ± 29	ns
Cardiac output			
Rest	5.6 ± 1.4	5.3 ± 1.0	ns
Exercise	19 ± 5.6	19 ± 4.8	ns
Cardiac index			
Rest	2.9 ± 0.7	2.7 ± 0.5	ns
Exercise	10.0 ± 3.0	9.9 ± 2.6	ns

RV = right ventricular and LV = left ventricular.

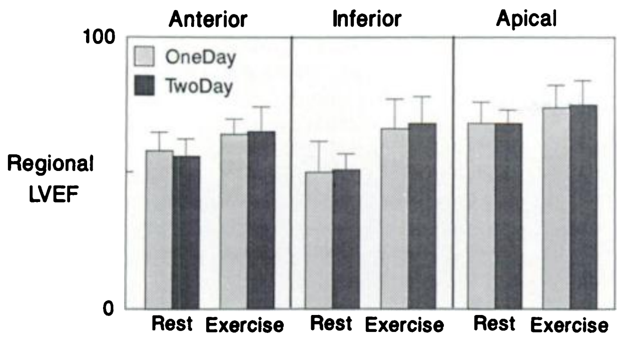

FIGURE 5
Comparison of regional LVEF for one- and two-day studies.

± 0.3 and 0.7 ± 0.6). Exercise myocardium/organ ratios were also similar for both studies: myocardium/lung (2.8 ± 0.4 and 2.9 ± 0.5), myocardium/background (2.5 ± 0.6 and 2.8 ± 0.6), myocardium/liver (2.8 ± 0.5 and 3.2 ± 0.7), myocardium/spleen (2.1 ± 0.7 and 2.7 ± 0.8), and myocardium/gallbladder (1.2 ± 1.0 and 1.2 ± 0.7) (p = ns for all variables measured).

Scatter from Abdominal Cavity

There was no significant difference for the Group I and Group II studies in scatter into the inferoapical walls on the exercise studies. Only one subject had an exercise study with scatter rated other than 0. This subject was from the same-day study protocol and had scatter to the inferoapical wall which did not interfere with interpretation. There was also no difference between the rest studies of the two protocols. Three subjects on the two-day study and two subjects on the one-day study had a scatter score of 1.

DISCUSSION

Radionuclide angiocardiography and thallium-201 (^{201}Tl) scintigraphy have been used to assess function and perfusion in patients with coronary artery disease ((*8–10*). The routine performance of these two studies on the same patient is limited by economic and practical considerations, such as two exercise tests on separate days. Moreover, two radionuclide tests using different tracers result in additional radiation exposure. Assessment of left ventricular function and perfusion using only one exercise stress session has been previously reported using gold-195m or iridium-191m in conjunction with ^{201}Tl (*11,12*). However, gold-195 and other ultrashort-lived isotopes have not become available commercially.

Planar and SPECT imaging obtained using the new radiopharmaceutical ^{99m}Tc-sestamibi have been shown to be equivalent to ^{201}Tl perfusion studies for diagnosis of coronary artery disease (*4,13*). Simultaneous assessment of ventricular function and perfusion at rest has been previously reported using ^{99m}Tc-sestamibi (*1*). Technetium-99m-sestamibi gated perfusion images have also been used for rest and exercise functional assessment of the left ventricle (*14,15*). This approach permits wall motion analysis in regions without a perfusion defect. However, measurements of LVEF are limited and measurements of right ventricular ejection fraction may be impossible with this technique.

High residual background from a first injection has been thought to preclude the performance of a second study on the same day. The large amount of radioactivity in the abdominal cavity, particularly in the liver, might obscure inferior wall perfusion defects and interfere with quantitative analysis of planar images. Our results found no difference in the ratios of myocardial/abdominal organ activity ratios between one- and two-day studies in normal volunteers. Visual analysis of the images demonstrated minimal evidence of scatter into the myocardium, and there was no difference in the number of subjects with scatter in the one- and two-day protocols. It is unlikely that perfusion defects would be missed due to scatter from abdominal activity in a one-day study but would be identified on a two-day study.

Recently, Taillefer et al. (*16,17*) reported the performance of same-day rest and exercise ^{99m}Tc-sestamibi perfusion studies. Abnormal/normal myocardium count ratios were similar for one- and two-day studies. Furthermore, when the exercise was performed before the rest study, some of the fixed perfusion defects did show reversibility on the rest/exercise study protocol (*14*). Therefore, they concluded that the same-day rest/exercise sequence would be preferable. However, cardiac function and myocardium/organ ratios were not measured and compared to a two-day protocol.

Our study clearly documents the feasibility of performing same-day rest and exercise ^{99m}Tc-sestamibi studies to assess perfusion and function in conjunction with treadmill testing. No significant difference was observed between one- and two-day studies as defined by the myocardium/organ ratios, subjective image analysis, and functional variables. Further studies combining the treadmill, RNA, and SPECT are necessary to confirm the enhancement of diagnosis and prognosis in patients with coronary artery disease.

These data demonstrated no difference for parameters of function and perfusion at rest and during treadmill exercise when ^{99m}Tc-sestamibi studies were compared, using one-day and two-day protocols in subjects with less than a 5% likelihood of coronary artery disease.

ACKNOWLEDGMENTS

This work was supported in part by NIH Grants HL17670 and CA33541 and E.I. Du Pont de Nemours and Company, Inc.

REFERENCES

1. Baillet GY, Mena IG, Kuperus JH, Robertson JM, French WJ. Simultaneous technetium-99m MIBI angiography and myocardial perfusion imaging. *J Nucl Med* 1989; 30:38–44.
2. Sporn V, Balini NP, Holman L, et al. Simultaneous measurement of ventricular function and myocardial perfusion using the technetium-99m isonitriles. *Clin Nucl Med* 1988; 13:77–81.
3. Mousa SA, Maina M, Brown BA, et al. Retention of RP-30 in the heart may be due to binding to a cytosolic protein [Abstract]. *J Nucl Med* 1987; 28:619.
4. Wackers FJ, Berman DS, and the Participating Clinical Centers in the [^{99m}Tc]sestamibi Phase I and II Studies. Technetium-99m hexakis 2-methoxyisobutyl isonitrile: human biodistribution dosimetry safety and preliminary comparison to thallium-201 for myocardial perfusion imaging. *J Nucl Med* 1989; 30:301–311.
5. Diamond BA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary artery disease. *N Engl J Med* 1979; 300:1350–1358.
6. Harpole DH, Skelton TN, Davidson CJ, Jones RH, Bashore TM. Validation of pressure-volume data obtained in patients by initial-transit radionuclide angiocardiography. *Am Heart J* 1989; 118:983–989.
7. Dodge HT, Hay RE, Sandler H. An angiographic method for directly determining left ventricular stroke volume in man. *Circ Res* 1968; 11:739.
8. Jones RH, McEwan P, Newman GE, et al. Accuracy of diagnosis of coronary artery disease by radionuclide measurement of left ventricular function during rest and exercise. *Circulation* 1981; 64:586–600.
9. Verani MS, Marcus ML, Razzak MA, Ehrhardt JC. Sensitivity and specificity of thallium-201 perfusion scintigrams under exercise in the diagnosis of coronary artery disease. *J Nucl Med* 1978; 19:773–782.
10. Borges-Neto S, Mahmanian JJ, Jain A, Roberts R, Verani MS. Quantitative thallium-201 single photon emission computed tomography after oral dipyridamole for assessing the presence, anatomical location and severity of coronary artery disease. *J Am Coll Cardiol* 1988; 11:962–969.
11. Mena I, Narahara KA, Maublant JC, et al. Simultaneous maximal exercise radionuclide angiography and thallium stress perfusion imaging. *Am J Cardiol* 1984; 53:812–817.
12. Verani MS, Lacy JL, Ball ME, et al. Simultaneous assessment of regional ventricular function and perfusion utilizing iridium-191m and thallium-201 during a single exercise test. *Am J Cardiac Imag* 1988; 2:206–213.
13. Kiat H, Maddahi J, Roy LT, Van Train K, Friedman J, Resser K, Berman DS. Comparison of technetium-99m methoxy isobutyl isonitrile and thallium-201 for evaluation of coronary artery disease by planar and tomographic methods. *Am Heart J* 1989; 117:1–11.
14. Wackers FJ, Mattera JA, Bowman L, Zaret BL. Gated Tc-99m isonitrile myocardial perfusion imaging: disparity between endo and epicardial wall motion [Abstract]. *Circulation* 1987; 76:203.
15. Corbett JR, Henderson EB, Akers MS, et al. Gated tomography with technetium-99m RP-30A in patients with myocardial infarcts: assessment of myocardial perfusion and function [Abstract] *Circulation* 1987; 76:217.
16. Taillefer R, LaFlamme L, Dupras G, Picard M, Pheneuf DC, Leveille J. Myocardial perfusion imaging with 99m-Tc-methoxy-isobutyl-isonitrile (MIBI): comparison of short and long time intervals between rest and stress injections. Preliminary results. *Eur J Nucl Med* 1987; 13:515–522.
17. Taillefer R, Gagnon A, Laflamme L, Gregoire J, Leveille J, Pheneuf DC. Same day injections of Tc-99m methoxy isobutyl isonitrile (sestamibi) for myocardial tomographic imaging: comparison between rest-stress and stress-rest injection sequences. *Eur J Nucl Med* 1989; 15:113–117.