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Exercise-Rest Same-Day SPECT Sestamibi Imaging to Detect Coronary Artery Disease

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This study examined the results of exercise-rest same-day SPECT protocol in 193 patients, of whom 132 had coronary artery disease (CAD) by angiography ($\geq 50\%$ diameter stenosis), and 61 had a low pretest probability of CAD. **Methods:** The rest study was combined with first-pass radionuclide angiography using the multicrystal gamma camera in 72 patients. **Results:** The sensitivity of SPECT was 76% (25/33 patients) in patients with one-vessel, 84% in patients with two-vessel (38/45) and 98% in patients with three-vessel CAD (53/54) ($P = 0.01$ versus one- or two-vessel CAD). The sensitivity of SPECT in patients with CAD was higher than ST depression (88% versus 28%, $P = 0.001$). The exercise was submaximal in 53 patients (40%). The perfusion defects were reversible (complete or partial) in 80 patients and fixed in 36 patients. The left ventricular ejection fraction was $50 \pm 12\%$ in patients with reversible defects ($n = 44$) and $39 \pm 9\%$ in patients with fixed defects ($n:19$) ($P = 0.0004$). The normalcy rate in subjects with a low pretest probability of CAD was 95% (53 of 61 subjects). **Conclusion:** The exercise-rest same-day sestamibi protocol provides high diagnostic accuracy for CAD detection. The protocol may eliminate the need for rest studies in patients with normal exercise images, help improve laboratory throughput and lower costs.

Key Words: coronary artery disease; sestamibi; single-photon emission computed tomography

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Currently in the U.S. approximately 30%-40% of perfusion studies are performed with ^{99m}Tc-sestamibi using one of several protocols: two-day protocol, same-day stress-rest and same-day rest-stress protocol (1-7). Each of these protocols has advantages and limitations. The two-day or, more precisely, separate-

day protocol is used primarily in overweight patients because of the need for higher doses of sestamibi (20-30 mCi or 740-1110 MBq) for each of the stress and rest studies. For the same-day protocol the rest-stress sequence is more commonly used than stress-rest. One advantage of rest-stress is that the higher dose (30 mCi) is used with the stress study. A high dose is necessary to obtain high-quality images and gating. It also has been suggested, based on limited experience, that the rest-stress protocol is better than the stress-rest protocol for detecting reversible defects (2,3). The main disadvantage of the rest-stress protocol is the requirement to perform the rest study on every patient, the need to perform the stress studies later in the day and the contamination of the stress images by the tracer activity from the rest study. This study describes our experience with the same-day exercise-rest protocol in detecting CAD.

MATERIALS AND METHODS

Patients

We studied 670 patients in our laboratory between July 1993 and August 1994. Of those, 132 patients had CAD by coronary angiography within 3 mo of the exercise study and 61 patients had low pretest probability of CAD on the basis of clinical presentations and coronary risk factors (8). The demographics of patients with and without CAD are listed in Table 1. Coronary angiography was performed in multiple projections using standard techniques. Significant CAD was defined as $\geq 50\%$ diameter stenosis in any one of the major coronary arteries or their branches. The degree of stenosis was assessed by two angiographers unaware of the scintigraphic findings.

Exercise Testing

All patients underwent symptom-limited exercise testing using the Bruce protocol. The endpoints of exercise were: angina of at least moderate severity, excessive fatigue, weakness, shortness of

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TABLE 1
Demographics of Study Population

	CAD (n = 132)	Low pretest (n = 61)
Gender (male/female)	111/21	19/42
Age (yr)	60 ± 11	46 ± 12
Weight (lb)	180 ± 27	177 ± 44
Height (in)	68 ± 3	66 ± 4
Hypertension	60 (45)	25 (41)
Diabetes mellitus	22 (17)	3 (5)
Q-Myocardial infarction	21 (17)	0 (0)
Nitrates	58 (44)	4 (7)
β-blockers	63 (48)	9 (15)
Calcium-antagonists	74 (56)	9 (15)

breath, ≥2 mm ST segment depression, hypotension or dizziness. At peak exercise, 10 mCi ^{99m}Tc-sestamibi were injected intravenously, and the patient was asked to continue exercising for additional 1–2 min. Imaging was started 30 min after injection of the tracer (3).

Rest Imaging

For rest imaging, a 30-mCi dose of ^{99m}Tc-sestamibi was injected 4 hr after the stress study. Imaging was started approximately 60 min after the injection. SPECT imaging was performed on a GE 400 AT gamma camera/Starcam computer system (GE Medical Systems, Milwaukee, WI) with the acquisition of 64 images over an anterior 180° arc starting from the 45° right anterior oblique projection and ending at the 45° left posterior oblique projection (7). Each image was obtained for 25 sec (64 views) for the stress study and 20 sec (64 views) for the rest study using a 64 × 64 matrix. Standard filtered backprojection techniques were used to generate original transaxial tomograms using a Butterworth filter with a cutoff frequency of 0.4 and order of 10 for stress, and a cutoff frequency of 0.5 and an order of 5 for rest studies. Oblique-angled tomograms were generated on the basis of the long-axis of the heart, thereby creating the short-axis, vertical long-axis and horizontal long-axis tomograms with each slice being 1-pixel thick. In 72 patients, first-pass radionuclide angiograms were obtained using the Sim-400 gamma camera/computer system (Scintacor, Milwaukee, WI) with a bolus injection of ^{99m}Tc-sestamibi for the rest SPECT images. The acquisition and processing of the first-pass radionuclide angiograms was described previously (7). The wall motion was assessed in two segments for each patient (anterior and inferior) as showing asynergy (moderate hypokinesis, severe hypokinesis, akinesis or dyskinesis) or normal. The perfusion pattern in each segment was assessed from the corresponding segments on the SPECT images.

Statistical Analysis

Results were presented as mean ± s.d. when appropriate. Student's t-test was used for comparison of continuous variables and chi-square for discrete variables. A p value of <0.05 was considered significant. A coefficient correlation was calculated using the Pearson correlation method.

RESULTS

Pertinent patient data are listed in Table 1. There were 112 men and 20 women aged 60 ± 11 yr. All patients had CAD and 33 had one-vessel, 45 had two-vessel and 54 had three-vessel disease. The exercise results are summarized in Table 2. The mean exercise duration was 7.6 ± 3.2 min. The exercise electrocardiographic (ECG) response was positive in 37 patients (28%). The exercise was adequate (85% of maximum predicted heart rate or positive S-T response) in 79 patients and submaximal in 53 patients with CAD. It was adequate in 45

TABLE 2
Exercise Results

	CAD (n = 132)	Low pretest (n = 61)
Exercise duration (min)	7.6 ± 3.2	8.1 ± 3.1
Exercise workload (METs)	8.2 ± 3.7	9.1 ± 3.6
Exercise heart rate (bpm)	132 ± 24	163 ± 21
Exercise systolic blood pressure (mmHg)	168 ± 4	179 ± 26
Exercise ECG response		
Positive	37 (28%)	0 (0%)
Negative	42 (32%)	45 (74%)
Inconclusive	53 (40%)	16 (26%)
Exercise-induced angina	29 (22%)	0 (0%)

subjects with a low pretest probability of CAD. The sestamibi results are shown in Table 3. The overall sensitivity of SPECT imaging was 88%: it was 76% in one-vessel, 84% in two-vessel and 98% in three-vessel disease (p = 0.01 versus one-vessel and two-vessel disease) (Fig. 1). The sensitivity was 86% when patients with transmural myocardial infarction were excluded. The normalcy rate in 61 patients with a low pretest probability of CAD was 95% (Fig. 1). Of the 16 patients with CAD but normal images, eight had submaximal exercise (Patients 1, 3, 4, 7, 8, 9, 11 and 16), and four had mild-to-moderate stenosis (Patients 2, 3, 14 and 15) (Table 4). In 116 patients with abnormal images, 80 had reversible perfusion defects (complete or partial), and 36 had fixed perfusion defects.

Correlation between Perfusion and Function

In the 72 patients who had radionuclide angiography, the left ventricular ejection fraction was 54 ± 6% in those with normal images, 39 ± 9% in those with fixed defects and 50 ± 12% in those with reversible defects (p = 0.0004 versus fixed defects). There was a modest correlation between the size of the perfusion abnormality (number of abnormal segments) and ejection fraction (r = -0.31, p < 0.01). The relation between segmental perfusion and wall motion is shown in Figure 2. The wall motion was normal in 18 of 18 segments with normal perfusion, 60 of 88 segments with reversible defects and 8 of 38 segments with fixed defects (p < 0.01).

DISCUSSION

The present study shows that the same-day stress-rest protocol is reliable in detecting CAD. The results are comparable to data obtained with ²⁰¹Tl or other sestamibi protocols (1–7,9). The main advantage of this protocol is that the results of stress images are available much earlier than with other protocols that not only may expedite patient care but also eliminate the need for rest studies if the images are normal (2,3,10). This improves laboratory throughput and decreases cost which is a major issue in current managed health care. It is also possible that, in patients with mild-to-moderate stenosis, this protocol is preferred to the rest-stress protocol because the difference in ischemic to normal zone may be small and may be difficult to

TABLE 3
Results of SPECT Sestamibi Images

	CAD (n = 132)	Low pretest (n = 61)
Abnormal images	116 (88%)	3 (5%)
Ischemic abnormality	80 (61%)	1 (2%)
Cavity dilation	35 (27%)	2 (3%)
Extent abnormality (%)	17 ± 11	4 ± 6
Severity score	410 ± 300	75 ± 115

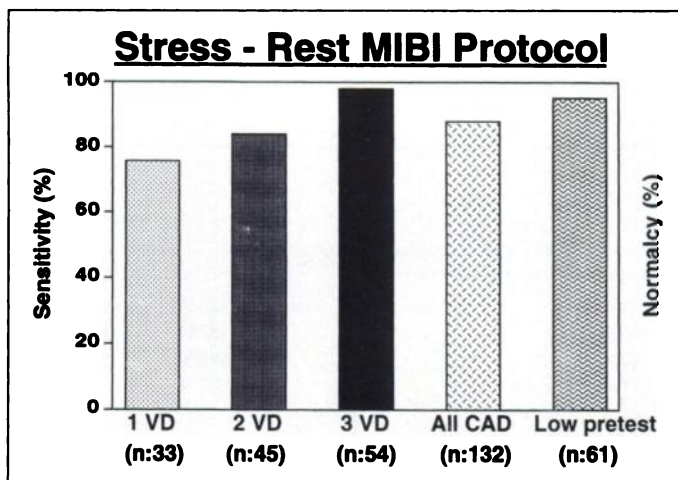


FIGURE 1. Sensitivity and normalcy rate of SPECT imaging.

detect if the myocardium has residual activity from the rest study. This issue cannot be addressed for this or other studies in the literature because of the difficulty in defining such stenosis from angiography alone and because the results may be affected by the choice of tracer and choice of stress (exercise versus vasodilator). In any large study, these patients are often diluted by patients with more severe stenosis in whom the choice of protocol is not essential. The rest study in the rest-stress protocol, however, represents genuine rest images since there is no carry-over activity from the stress images in rest-stress protocol. This may be the reason why rest-stress protocol is preferred for viability assessment (11–13). The issue of detecting a reversible etiology for severe left ventricular dysfunction, however, is not of major concern in most patients studied because of chest pain syndromes (14–17). In the study of Taillefer et al., 18 patients underwent both ^{99m}Tc-sestamibi protocol, rest-stress and stress-rest (2). The perfusion abnormality was assessed as normal, ischemic or scarred in 16 segments per study. There was agreement in 283 of 324 segments (87%) between rest-stress and stress-rest sequences. However, 24 segments (7.4%) were classified as ischemic in rest-stress

TABLE 4
Patients with Coronary Artery Disease and False-Negative SPECT Images

Patient no.	Age/Sex (yr)	Exercise heart rate	Exercise ECG	Exercise angina	% Stenosis		
					LAD (%)	LCx (%)	RCA (%)
1	50/F	118	I	N	30	0	80
2	51/M	182	N	N	30	30	60
3	52/F	113	I	N	30	30	70
4	52/M	132	I	N	90	30	50
5	53/M	160	P	N	60	70	90
6	56/M	144	N	N	80	40	0
7	58/M	134	I	N	100	100	0
8	60/F	104	I	N	80	50	20
9	61/F	104	I	N	0	80	100
10	62/M	136	N	N	80	20	20
11	63/F	107	I	N	70	0	100
12	64/F	146	N	P	60	100	20
13	65/F	115	P	N	75	80	0
14	67/M	154	N	N	50	0	0
15	75/F	143	N	N	60	30	40
16	89/M	129	I	N	80	30	20

I = inconclusive; N = negative; P = positive.

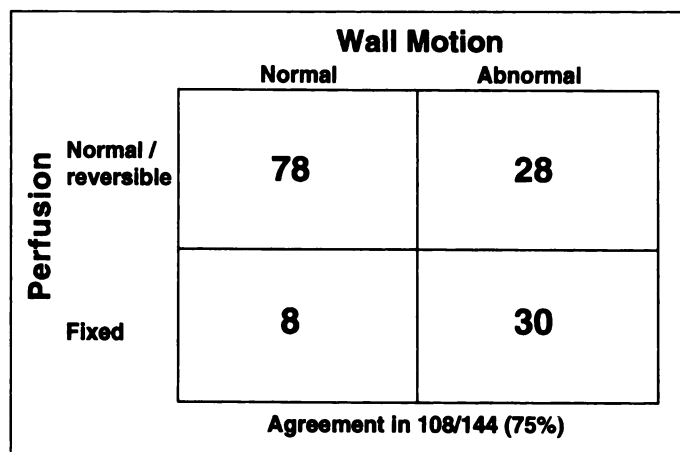


FIGURE 2. Correlation between wall motion and perfusion.

protocol but were considered as scarred by stress-rest protocol. In one segment, ischemia was better appreciated on stress-rest sequence. Thus, reversible abnormalities were better appreciated by the rest-exercise sequence. In our previous work, 32 patients were enrolled in the same-day protocols (3). Both protocols (rest-exercise and exercise-rest) were performed within 10–14 days of each other after randomization. Segmental analysis was interpreted as normal, scarred or ischemia (20 segments per patient). There was an agreement between the two protocols in 593 of 640 segments (93%). Both protocols provided high-quality images. The rest-exercise protocol showed greater differences between abnormal and normal zones on exercise images with better normalization of the abnormality on rest images than exercise-rest protocol. Although in the stress-rest protocol the stress dose of sestamibi is smaller than the rest dose, it should be stated that 10 mCi of ^{99m}Tc-sestamibi is a threefold higher dose than ²⁰¹Tl, and sestamibi has a higher energy with less attenuation and scatter. Therefore, this dose is adequate in most patients. Regardless of the sequence, one of the two studies in a one-day protocol will be done with a low dose, and thus, the issue of low(er) counts cannot be eliminated. In overweight patients, the two-day stress-rest protocol is preferred. We now take into consideration the gender, height and weight of the patients in selecting a one- or two-day protocol. From a physics standpoint, the two-day protocol is ideal since there is no background activity carried over from the first study; however, it is not convenient for patients and the image information is not available until completion of the second study. On the other hand, the same-day protocol is completed within 6 hr as is the thallium protocol.

Simultaneous Perfusion/Function Imaging

Because of its favorable dosimetry, sestamibi imaging allows simultaneous acquisition of first-pass radionuclide angiography or gating (18–21). A first-pass study may be obtained (preferably) with a multicrystal gamma camera but can also be obtained with a digital single-crystal gamma camera.

The addition of functional information to perfusion data may improve differentiation between attenuation artifact and a true defect, improve detection of viable myocardium (for example, a perfusion defect in a segment with preserved wall motion or wall thickening is likely to be viable) and measure left ventricular ejection fraction that is prognostically important (22). With the stress-rest protocol, we obtained the radionuclide angiogram at rest using the higher dose of ^{99m}Tc-sestamibi with the patient in supine and resting position, hence without motion artifact. It should be noted that, when gating is used, the gated images also reflect rest function. First-pass radionuclide angiography, like

gated perfusion imaging, increases observer confidence in interpretation of perfusion images. Several studies show a considerable degree of variability between perfusion defect size and ejection fraction (23,24). Our results are consistent with these observations. The combination of perfusion and function studies is especially important in patients with primary cardiomyopathy who may have normal or near normal perfusion but severe left ventricular dysfunction.

In summary, the exercise-rest same-day sestamibi protocol provides high diagnostic accuracy for the detection of CAD. The protocol may also eliminate the need for rest studies in patients whose exercise images are normal.

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Effect of Haloperidol Dose on Iodine-123-IBZM Brain SPECT Imaging in Schizophrenic Patients

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Studies have suggested that antipsychotic drug therapy with haloperidol in schizophrenic patients requires an optimal dose that blocks the brain dopamine D2 receptors. We evaluated the effect of different doses of haloperidol on D2 receptor occupancy in schizophrenia. **Methods:** Three normal subjects and three patients with acute schizophrenia had serial brain SPECT imaging studies (every 5 min) for 3 hr following the injection of [¹²³I]IBZM. The patients had IBZM studies off medication and at different doses (1–10 mg) of haloperidol. **Results:** The basal ganglia (BG) were well visualized in normals and in schizophrenics off medication. After haloperidol therapy, SPECT images showed qualitatively diminished activity in the basal ganglia. ROIs were drawn over the basal ganglia and cerebellum (CE). The results were expressed as BG/CE ratios. At 2 hr postinjection of IBZM, the mean BG/CE ratio in normals was 1.75 ± 0.025 . In schizophrenics, the BG/CE ratio off medication was 1.54 ± 0.12 . The BG/CE ratio showed an inverse relationship to

haloperidol dose; 1.46 at 1 mg, 1.25 at 4 mg and 1.05 at 10 mg, respectively. **Conclusion:** These results demonstrate that IBZM brain SPECT imaging studies are potentially useful to relate the antipsychotic drug D2 receptor occupancy with the administered dose in schizophrenic patients and may ultimately help optimize antipsychotic treatment.

Key Words: iodine-123-IBZM; receptor imaging; schizophrenia

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According to the dopamine hypothesis, the antipsychotic effect of neuroleptic drugs is mediated by the blockade of dopamine D2 receptors (1,2). This hypothesis has been supported by the observations of Farde et al. who showed, with PET studies using [¹¹C]-raclopride (a dopamine D2 receptor antagonist), that clinical doses of classic antipsychotic drugs cause a substantial blockade of central dopamine D2 receptors (3–6). For dopamine receptor SPECT imaging studies, Kung et al. developed ¹²³I-labeled iodobenzamide (IBZM), an analog of raclopride (7). In patients with different neuropsychiatric dis-

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