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METHODS

Effect of Exercise Level on the Ability of Thallium-201 Tomographic Imaging in Detecting Coronary Artery Disease: Analysis of 461 Patients

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This study examined the effect of the level of exercise on the ability of thallium-201 imaging with single photon emission computed tomography (SPECT) to detect coronary artery disease. Patients in group 1 (n = 164) achieved adequate exercise end points, defined as positive exercise electrocardiograms or ≥85% of maximal predicted heart rate. Patients in group 2 (n = 108) had submaximal exercise.

The SPECT thallium-201 images showed perfusion defects in 74%, 88% and 98%, respectively, of patients with one, two and three vessel coronary artery disease in group 1, compared with 52%, 84% and 79%, respectively, of such patients in group 2 (p < 0.05).

Perfusion defects showed partial or complete redistribution consistent with ischemia in 56%, 80% and 88%, respectively, of patients with one, two and three vessel coronary artery disease in group 1 compared with 35%, 58% and 56%, respectively, of such patients in group 2 (p = 0.08, < 0.03 and < 0.001, respectively).

Of 58 patients with normal coronary angiograms or <50% diameter stenosis, 36 (62%) had normal SPECT images. In a separate group of 131 patients with <5% pretest probability of coronary artery disease, the specificity was 93%. The sensitivity of exercise SPECT imaging in group 1 was higher than that of ST segment depression (p < 0.001).

Thus, the level of exercise affects the results of SPECT thallium imaging in the localization and evaluation of the extent of coronary artery disease and the detection of ischemia.

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Exercise thallium-201 imaging has been wisely used in the diagnosis of coronary artery disease and risk stratification (1–4). Over the past 15 years, important developments have occurred in this technique that have improved the quality of the images and enhanced the accuracy of the results (5–10).

Single photon emission computed tomography (SPECT) with thallium-201 has certain advantages over planar images. Because SPECT images are capable of displaying individual tomographic slices at different levels in multiple planes, there is no problem of superimposition of shallow and deep structures, and, therefore, identification of perfusion defects is easier. Also, with planar imaging, segments of the left ventricular myocardium that are farthest away from the detector are more difficult to visualize than those closest to the detector because of the attenuation effect and the low energy characteristics of thallium-201. This problem is less pronounced with SPECT imaging, which may explain the better detection rate of left circumflex coronary disease with SPECT compared with planar imaging (10–14).

Further, SPECT imaging is inherently three-dimensional in nature, lending itself to quantitative analysis, and, in this regard, several studies (10,15–21) have successfully assessed left ventricular mass and infarct size using SPECT thallium imaging.

An important cause of "false negative" images of the planar technique has been, in some but not all studies, the presence of inadequate exercise (1,22). However, because perfusion defects that reflect flow heterogeneity occur much earlier than symptoms or electrocardiographic (ECG) changes and because SPECT imaging has the advantages discussed over planar imaging, it is not clear whether the level of exercise also affects the result of SPECT thallium imaging.

This study in the largest series of patients undergoing exercise SPECT thallium imaging reported so far, examined

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the effect of the level of exercise on the ability of SPECT thallium imaging to detect coronary artery disease and myocardial ischemia.

Methods

Study patients. The study group included 330 patients who underwent coronary angiography and exercise SPECT thallium-201 imaging within 6 months of each other, and 131 patients who did not undergo cardiac catheterization and who were considered to have a very low (<5%) pretest probability of coronary artery disease based on demographics and risk factors. None of the patients included in this study had previous coronary artery bypass grafting or percutaneous transluminal coronary angioplasty and none had primary valvular disease or congenital heart disease.

In patients who underwent coronary angiography, the exercise studies were performed either before or after the results of angiography were available. In patients who did not undergo coronary angiography, the results of exercise testing were assuring to the patients and physicians, and angiography was not deemed necessary. The most common indication for exercise testing was the evaluation of chest pain suspected of being of cardiac origin.

The results of coronary arteriography were reviewed by two independent observers who were unfamiliar with the results of exercise thallium testing. Similarly, the results of exercise SPECT thallium imaging were interpreted by two independent observers unfamiliar with the results of coronary angiography. All data were subsequently entered into a computer data base that served as the basis for data retrieval and subsequent analysis as reported in this study. For the purpose of this study, coronary artery disease was considered to be present when there was ≥50% diameter stenosis in any one of the major coronary arteries (left main, left anterior descending, left circumflex or right coronary artery) or their major branches.

Exercise testing. All patients underwent symptom-limited upright exercise treadmill testing using either the Bruce or the modified Bruce protocol. It has been our practice for many years that medications are not routinely discontinued before exercise testing. During exercise, three ECG leads were continuously monitored and, at each minute during exercise and recovery, a 12 lead ECG was also obtained. The end points of exercise were defined as angina pectoris of at least moderate severity, ≥2 mm ST segment depression, hypotension, frequent ventricular premature beats or ventricular tachycardia or excessive fatigue, shortness of breath or weakness. Toward the peak of exercise, 3 mCi (111 MBq) of thallium-201 was injected intravenously and flushed with normal saline solution and the patient was asked to continue exercising for 1 additional minute.

The exercise ECGs were interpreted as positive if there was ≥1 mm ST segment depression of the flat or downsloping variety (in the absence of baseline ST segment changes or changes during standing and hyperventilation) or if there was 1.5 mm upsloping ST segment depression. All measurements were obtained 80 ms from the J point. The exercise ECGs were interpreted as negative if there were no changes during exercise provided that the patient achieved ≥85% of the maximal predicted heart rate. In patients with baseline ECG abnormalities or in patients who failed to reach 85% of maximal predicted heart rate, the exercise ECGs were interpreted as nondiagnostic (or inconclusive) (7).

SPECT thallium-201 imaging. SPECT thallium imaging commenced within 5 to 10 min and at 4 h after injection using 180° circular tomography extending from the 45° right anterior oblique to the 45° left posterior oblique projection. During this anterior arc, 32 images were acquired, each for 40 s. The patient was positioned supine on the imaging table with the left arm strapped above the head. A large field-of-view gamma camera was used with a low energy, all purpose parallel hole collimator, utilizing a 20% window centered on the 69 to 83 keV mercury X-ray peak, and 15% window centered on the 167 keV gamma ray peak. All projections were stored on a magnetic disk on a 16 bit, 64 × 64 digital matrix. For reconstruction, images were corrected for nonuniformity of the camera field and the center of rotation was determined with use of a point source. The transaxial tomograms were reconstructed with a filtered-back projection technique with a Ramp-Hanning filter with a cutoff frequency of 0.83 cycles/cm (10,21). Oblique-angled tomograms were reconstructed along the long axis of the left ventricle producing short-axis, vertical long-axis and horizontal long-axis slices (Fig. 1). Our method of interpretation of SPECT images has been previously described (10).

Analysis of SPECT image thallium defects. In summary, all tomographic slices were reviewed in pairs (exercise and 4-h delayed images). Defects were required to be present in at least two adjacent slices and, in general, were visualized in more than one projection. Reversible defects were recognized when redistribution was appreciated visually in at least 25% of the original abnormality. Extension of defects to adjacent segments rather than separate defects in two vascular territories was determined from the number of slices involved in the secondary zone and the extent of abnormality. The information from all tomographic slices was eventually transformed into the three vascular territories in the short-axis view. The data from polar map coordinates were reviewed in each patient but the data were not entered in our computer data base. During image reconstruction, a motion detection algorithm was incorporated using cross correlation function (supplied by GE Medical System). This sinogram was reviewed along the cine display of the original planar data to detect sudden patient movement or upward creep of the heart.

The short-axis slices were divided into anterior, septal, inferior and lateral regions. The anteroseptal areas were considered the territory of the left anterior descending

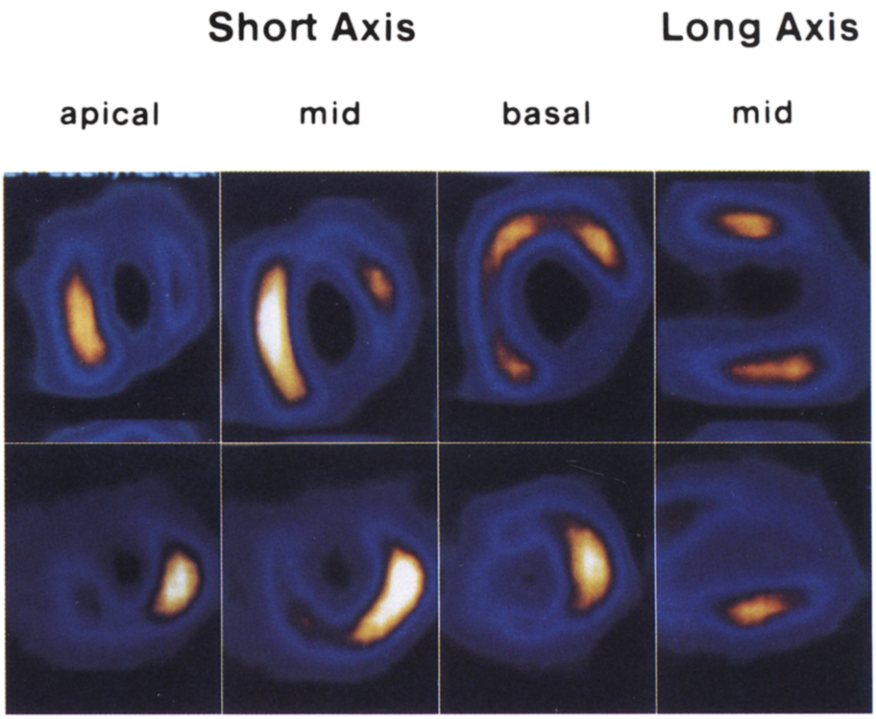

Figure 1. Single photon emission computed tomographic (SPECT) images with thallium-201 showing anterior, lateral, inferior and apical abnormalities in patient 1 (**top**) and anterior, septal, inferior and apical abnormalities in Patient 2 (**bottom**). Both patients had multivessel disease by coronary angiography.

artery; the inferior region, the territory of the right coronary artery and the lateral region, the territory of the left circumflex coronary artery.

Although polar maps (bull's-eye) were routinely available, they were not used in the interpretation of the results in this study (10). The technique for generating the polar coordinate maps has been previously described (Fig. 2).

Segments with perfusion defects were classified as reversible, partially reversible or fixed, depending on the degree of change between the postexercise and the 4-h

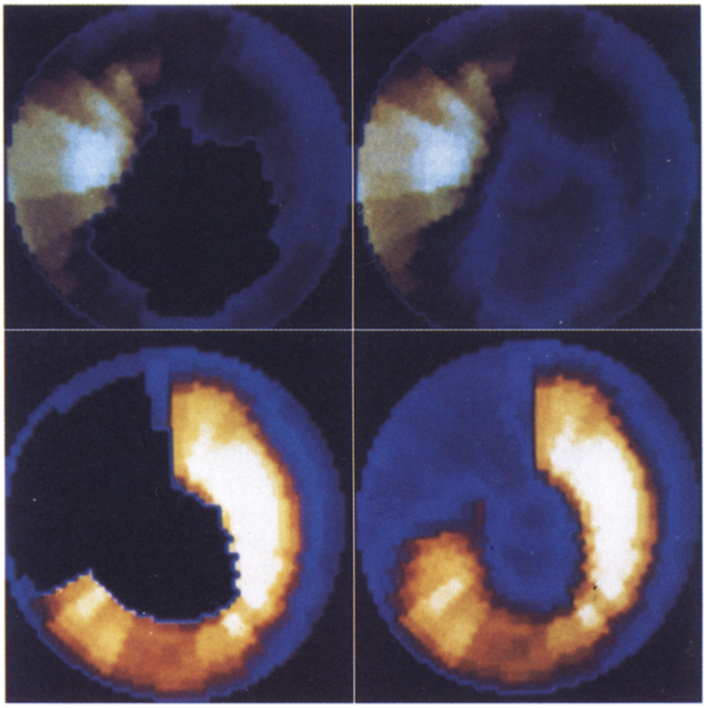

Figure 2. Polar maps or "bull's eye" of the thallium images of the same patients as in Figure 1. The **blackened areas** have tracer uptake >2.5 SD below that in the gender-matched control group. The abnormality in Patient 1 (**top**) involves the anterior, apical, lateral and inferior segments and in Patient 2 (**bottom**), the anterior, apical, septal and inferior segments.

Table 1. Pertinent Data in 164 Patients With Adequate Exercise and End Points (Group 1) and 108 Patients With Submaximal Stress (Group 2)

	Group 1	Group 2	p
Age (yr)	59 ± 1	61 ± 1	NS
Men/women	131/33	73/35	<0.02
History of MI	73 (45%)	52 (48%)	NS
History of hypertension	81 (49%)	52 (48%)	NS
History of diabetes mellitus	25 (15%)	18 (17%)	NS
Q wave MI (ECG)	29 (18%)	21 (19%)	NS
Exercise duration (min)	6.8 ± 0.2	7.4 ± 0.4	NS
Exercise work load (METs)	7.5 ± 0.2	6.1 ± 0.3	<0.0001
Exercise HR (beats/min)	136 ± 2	111 ± 2	<0.001
Exercise SBP (mm Hg)	177 ± 2	166 ± 3	<0.001
Exercise ECG			
Positive	104 (63%)		
Negative	47 (29%)		
Inconclusive	13 (8%)	108	
Exercise-induced angina	77 (47%)	44 (41%)	NS
Medications			
Nitrates	75 (46%)	70 (65%)	<0.01
Beta-blockers	64 (39%)	47 (44%)	NS
Calcium channel blockers	97 (59%)	78 (72%)	<0.04
Coronary artery disease			
One-vessel	39 (24%)	31 (28%)	NS
Two vessel	69 (42%)	38 (36%)	NS
Three vessel	56 (34%)	39 (36%)	NS
Increased lung thallium uptake	37 (23%)	27 (25%)	NS

ECG = electrocardiogram; HR = heart rate; MI = myocardial infarction; SBP = systolic blood pressure.

delayed images. Total elimination of the defect in the 4-h delayed images was considered to reflect complete redistribution. A decrease in the intensity or the extent of perfusion defect by ≥25% was considered to reflect partial redistribution (1). If a defect remained unchanged in the 4-h delayed images, it was considered fixed. Both completely reversible and partially reversible defects were considered to reflect myocardial ischemia; fixed defects were considered to reflect scar.

Statistical analysis. Data were presented as mean values ± SEM when appropriate. The chi-square and the Student's *t* test were used to determine the significance of differences. A probability value <0.05 was considered statistically significant. McNemar's test of symmetry was used with kappa statistic.

Sensitivity was defined as the number of true positives divided by the sum of true positives and false negatives × 100. Specificity was defined as the number of true negatives divided by the sum of the true negatives and false positives × 100. Predictive accuracy was defined as the sum of true positives and true negatives divided by the total number of patients.

Results

Patient groups. Among patients who underwent coronary angiography, there were 272 patients with coronary artery disease and 58 patients with normal or near normal coronary angiograms (<50% stenosis). On the basis of level of exercise and the exercise end points, the patients with coronary artery disease were classified into two groups: group 1 (n = 164) either had a positive exercise ECG or achieved ≥85% of maximal predicted heart rate (or both); group 2 (n = 108) had submaximal exercise, defined as failure to achieve at least 85% of the maximal predicted heart rate; none of these patients had a positive exercise ECG. The exercise ECGs in group 2 were considered nondiagnostic because of submaximal stress.

Pertinent clinical data in the two groups of patients (Table 1). Patients in group 1 were more likely to be men ($p < 0.02$) and achieved a higher exercise work load ($p < 0.001$), exercise heart rate ($p < 0.001$) and exercise systolic blood pressure ($p < 0.001$) than did patients in group 2. The majority of patients in both groups were receiving antianginal medications and a similar proportion in both groups had a history of hypertension, diabetes mellitus and previous infarction. Further, the extent of coronary artery disease defined by the number of diseased vessels was also similar in both groups. Qualitatively, increased thallium uptake in the lung was seen in a similar proportion of patients in both groups.

Results of SPECT thallium imaging (Fig. 3). Abnormal thallium images were significantly more common in group 1

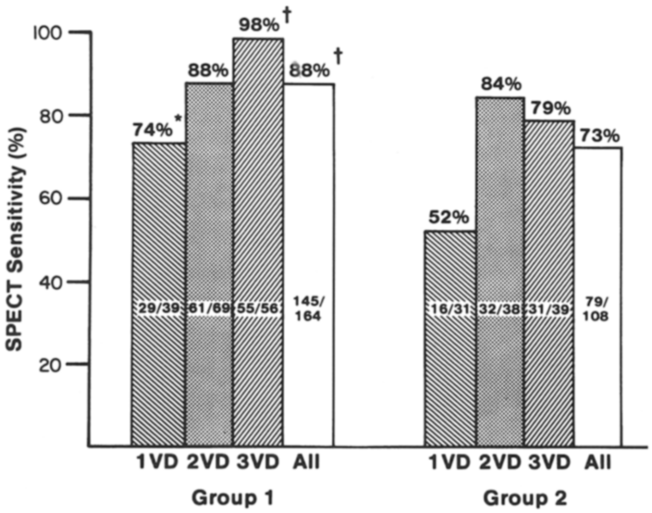

Figure 3. Results of single photon emission computed tomographic (SPECT) thallium imaging in the two groups of patients. 1VD = one vessel coronary artery disease; 2VD = two vessel disease; 3VD = three vessel disease; All = all 272 patients with coronary artery disease. Group 1 includes 164 patients who achieved adequate exercise end points; group 2 includes 108 patients who had submaximal exercise. *p < 0.05; †p < 0.002 versus group 2.

than group 2 in the total patient group and in the subgroup of patients with one, two and three vessel coronary artery disease (Fig. 3). The overall sensitivity was 88% in group 1 and 73% in group 2 ($p < 0.002$); it was 74% versus 52% in patients with one vessel disease ($p < 0.05$), 88% versus 84% in patients with two vessel disease (p = NS) and 98% versus 79% in patients with three vessel disease ($p < 0.02$). When patients with Q wave myocardial infarction were excluded, the sensitivity was still significantly higher in group 1 than group 2 (116 [86%] of 135 versus 58 [67%] of 87, $p < 0.002$).

Detection of myocardial ischemia (Fig. 4 and 5). Significantly more patients in group 1 than group 2 had evidence of myocardial ischemia by SPECT thallium-201 imaging. Ischemia was detected in 22 patients (56%) with one vessel coronary artery disease in group 1 and 11 and patients (35%) in group 2 ($p = 0.08$); in 55 patients (80%) with two vessel disease in group 1 and 22 such patients (58%) in group 2 ($p < 0.03$); and in 49 patients (88%) with three vessel disease in group 1 and 22 such patients (56%) in group 2 ($p < 0.001$) (Fig. 4).

Figure 4. The presence and nature of perfusion abnormality (scar or ischemia) on SPECT imaging in relation to the number of diseased vessels in the two groups of patients.

#Diseased Vessels	Group 1 Normal	Group 1 Ischemia	Group 1 Scar	p (Group 1 vs Group 2)	Group 2 Normal	Group 2 Ischemia	Group 2 Scar
1	10	22 *	7	* p=0.08	15	11	5
2	8	55 †	6	† p<0.03	6	22	0
3	1	49 ‡	6	‡ p<0.001	8	22	9

Group 1 | Group 2

#Diseased Vessels	Group 1: 0	1	2	3	Group 2: 0	1	2	3
1	10	18	11	0	15	10	6	0
2	8	21	32	8	6	12	19	1
3	1	10	23	22	8	6	18	7

Figure 5. The extent of perfusion abnormality on SPECT imaging (number of abnormal vascular territories) in relation to extent of coronary artery disease (number of diseased vessels) in the two groups of patients. Kappa statistic ± SE was 0.24 ± 0.06 for group 1 and 0.19 ± 0.08 for group 2.

The relation between the number of abnormal segments in the territory of the three major vessels by SPECT thallium imaging to the number of diseased vessels by coronary angiography is presented in Figure 5. Although more patients in group 1 than group 2 with two or three vessel coronary artery disease by angiography had abnormal vascular territories involved with perfusion defects, the difference was not statistically significant (85 [68%] of 125 versus 45 [58%] of 77, p = NS).

Comparison between SPECT thallium imaging and exercise ECG. The exercise ECG was positive in 104 patients in group 1 (63%). The sensitivity of ST depression was significantly lower than that of SPECT thallium imaging (88%) ($p < 0.001$). Obviously, the exercise ECG results were not useful in group 2 because these patients had nondiagnostic results. In the 272 patients with coronary artery disease, the overall sensitivity of the ECG was 38%; it was 23% (16 patients) in the 70 patients with one vessel disease, 39% (42 patients) in the 107 with two vessel disease and 48% (46 patients) in the 95 with three vessel disease. The exercise ECG was negative in 25% (18 patients) of those with one vessel disease, 20% (21 patients) of those with two vessel disease and 8% (8 patients) of those with three vessel disease. The remaining patients had inconclusive test results.

Of the 104 patients with a positive exercise ECG 8 had normal SPECT thallium images, 89 had evidence of ischemia and 7 had scar. Of the 47 patients with a negative exercise ECG, 11 had normal images, 29 had ischemia and 7 had scar. Of the 122 patients with an inconclusive exercise ECG, 29 had normal images, 64 had ischemia and 29 had scar (by SPECT thallium images).

Thus, 197 (72%) of the 272 patients with coronary artery disease had either a positive exercise ECG or evidence of ischemia by SPECT thallium-201 imaging, and 233 patients (86%) had either a positive exercise ECG or evidence of scar or ischemia by SPECT imaging.

Table 2. Characteristic Features of 58 Patients With Normal Coronary Angiograms or <50% of Stenosis*

Age (yr)	56 ± 2
Men/women	35/23
History of angina	34 (59%)
History of hypertension	27 (47%)
History of diabetes mellitus	5 (9%)
Medications	
Calcium-channel blockers	32 (55%)
Beta-blockers	9 (16%)
Exercise-induced angina	15 (26%)
Adequate exercise (≥85% MPHR)	37 (64%)
Rest ECG	
LVH	1 (2%)
LBBB	1 (2%)
ST-T abnormality	20 (34%)
Q wave MI	6 (10%)
Exercise ECG	
Positive	9 (16%)
Negative	30 (52%)
Inconclusive	19 (32%)
Exercise duration (min)	8.0 ± 0.8
Exercise work load (METs)	9.7 ± 0.4

LBBB = left bundle branch block; LVH = left ventricular hypertrophy; MPHR = maximal predicted heart rate; other abbreviations as in Table 1.

Patients with normal coronary angiograms. The pertinent data in the 58 patients with normal coronary angiograms are shown in Table 2. These patients had either normal coronary angiograms or <50% diameter stenosis. Most of these patients had typical or atypical angina and one or more coronary risk factors. Of note, 6 patients (10%) had ECG evidence of prior myocardial infarction despite normal coronary angiograms, 9 patients (16%) had a positive exercise ECG and 19 patients had an inconclusive exercise ECG because of submaximal exercise or baseline ST segment and T wave abnormalities. The SPECT thallium images were normal in 36 patients (specificity 62%). The specificity in this group of patients was lower than in the 131 patients with <5% pretest probability of coronary artery disease of whom 123 had normal images (specificity, 93%, $p < 0.0001$). The exercise duration was 8.6 ± 0.3 min and the exercise work load was 9.7 ± 0.3 metabolic equivalents of oxygen consumption (METs) in patients with low pretest probability of coronary artery disease. These patients achieved a mean peak heart rate during exercise of 163 ± 3 beats/min and a mean systolic blood pressure of 185 ± 3 mm Hg (Table 3). In patients with normal coronary angiograms, the specificity of exercise SPECT imaging was not significantly different from that of the exercise ECG (62% versus 72%; p = NS).

Discussion

This large study in patients undergoing exercise testing clearly shows that the results of exercise SPECT thallium imaging are 1) superior to those of exercise electrocardiography, and 2) significantly better in patients with adequate exercise end points than in patients with submaximal exercise. This difference was seen regardless of the extent of coronary artery disease. Further, reversible defects consistent with myocardial ischemia were significantly more common in patients with adequate exercise than in patients with submaximal stress. These results are therefore similar to those of planar thallium imaging. Importantly, among patients with adequate exercise end points, 98% of patients with three vessel coronary artery disease and 88% of those with two vessel disease had abnormal SPECT thallium images, and two-thirds of these patients had multivessel thallium abnormality.

Comparison with previous studies. The sensitivity of 88% in group 1 patients (who achieved adequate exercise end points) is slightly lower than the 97% sensitivity reported by DePasquale et al. (11). However, 26% of their patients compared with only 18% of our patients had Q wave myocardial infarction. Previous studies with SPECT imaging have not examined the effect of the level of exercise on the results of imaging. The current SPECT results are better than our previous results with planar imaging (23). In group 1 patients our sensitivity with SPECT imaging was 88%

Table 3. Comparison Between Normal Subjects With <5% Probability of Coronary Artery Disease; Patients With Normal Coronary Arteriograms; and Patients With Coronary Artery Disease in Groups 1 and 2

	Non-cath Group With <5% Probability of CAD	Patients With Normal Arteriograms	Group 1 (adequate exercise end points)	Group 2 (inadequate exercise)
No. of patients	131	58	164	108
Men/women	51/80	35/23	131/33	73/75
Peak HR (beats/min)	164	163	136	111
SBP (mm Hg)	180	185	177	166
Work load (METs)	10.4	9.7	7.5	6.1
Age (yr)	41	56	59	61
Weight (kg)	73.5	79.8	79.8	81.2
Specificity	93%	62%	...	...

HR = heart rate; non-cath group = patients who did not undergo cardiac catheterization; SBP = systolic blood pressure.

compared with 80% with planar imaging. Further, we included patients with less severe disease in the present study; the current criteria for definition of coronary artery disease was ≥50% diameter stenosis compared with ≥70% stenosis in our previous study (23). In group 2 patients, all patients in the current study had submaximal exercise; however, only half of the patients in our previous study had submaximal exercise (the remaining patients had an inconclusive exercise ECG because of ECG abnormalities at rest).

The study by Esquivel et al. (22) concluded that the level of exercise did not affect the results of thallium-201 imaging. The reasons for differences between their results and ours are not clear but, in our study, patients with a positive exercise ECG were included in the group of patients with adequate exercise end points (group 1). Further, 54% of the patients in the study of Esquivel et al. (22) had documented myocardial infarction, whereas only 18% of our patients had Q wave myocardial infarction. Also, the study by Esquivel et al. used planar imaging whereas our study used SPECT thallium imaging. Unexplained in the Esquivel study is the lower prevalence of redistribution defects in patients with adequate exercise end points than in patients with submaximal exercise.

Image interpretation. The oblique tomograms (short-axis, vertical long-axis and horizontal long-axis) were used in this study in image interpretation and assessing vascular territories. The polar coordinate maps (bull's eye), though available, were not routinely used in image interpretation. In our experience, abnormal polar maps were seen frequently in patients with normal angiograms. These abnormalities were determined on the basis of number voxels with tracer uptake >2.5 SDs below values in the gender-matched control group (24). For these reasons, we routinely interpret our tomograms based on the findings in the individual slices in multiple tomographic planes. Recent data (25) in a larger cohort of gender-matched control subjects may contribute importantly to improvement in the accuracy of this method. The polar map, in essence, represents a series of circumferential count profiles generated from the short-axis slices, arranged in a series of rings extending from the apex (at the center) to the base (at the periphery). Our results, furthermore, were based on subjective analysis of the tomographic images. The study by Garcia et al. (21) suggests no apparent advantage of such analysis when applied to SPECT thallium imaging. This finding is in contrast to that seen in planar imaging whereby quantitative analysis has repeatedly been shown to enhance the ability to detect individual diseased vessels (5). The discrepancy between SPECT imaging and planar imaging in the additive value of quantitative analysis may be related to the fact that in SPECT imaging, no overlap between normal and abnormal segments is present, which makes identification of perfusion defects easier and negates the advantage provided by quantitative analysis.

Correlation with coronary angiography. We did not expect, neither did we find, all stenoses identified by coronary angiography to be correctly identified by SPECT thallium imaging. First, there is sufficient evidence at the present time to indicate that the hemodynamic significance of coronary stenosis cannot be reliably predicted by the percent diameter stenosis (26–30). Measurement of the minimal area stenosis may be more helpful in some patients (30). However, quantitative coronary angiography, which takes into consideration "all dimension stenosis," and measurement of the coronary flow reserve are more appropriate methods to assess the significance of coronary stenosis. Therefore, it is clear that not all vessels with ≥50% diameter stenoses are necessarily hemodynamically significant and should result in a perfusion defect. Second, there is considerable variability in the size, location and distribution of the major coronary arteries. Hence, it is possible that in some patients with proximal left anterior descending artery stenosis, the perfusion defect may not only be seen in the anteroseptal area but also involve the inferior wall. Similarly, in a patient with a large right coronary artery that supplies multiple posterolateral branches a significant stenosis may produce not only an inferior perfusion defect but also posterolateral perfusion abnormality. Third, in patients with multivessel coronary artery disease, the more severe regions might be detected whereas the less severe regions might appear normal, since thallium imaging deals with relative uptake. Fourth, some patients with multivessel disease might have stopped exercise when ischemia was achieved in the worst vascular territory that was at a level below which ischemia would be produced in a territory supplied by a vessel with a less severe stenosis. Our results showed that two-thirds of patients with multivessel coronary artery disease had a pattern of multivessel thallium abnormality.

Comparison between group 1 and group 2. Although the prevalence of previous infarction, hypertension, diabetes mellitus and the extent of coronary artery disease were comparable in groups 1 and 2, the incidence of abnormal images (88% versus 73%) and myocardial ischemia (77% versus 51%) were lower in group 2. The patients with submaximal exercise (group 2) could not be predicted before exercise testing except in obvious circumstances such as peripheral vascular disease, arthritis or severe chronic obstructive lung disease, which were not present in most patients in this study. Such patients are often studied with dipyridamole thallium imaging in our laboratory. Further, the use of beta-blockers was similar in the two groups. It has been our practice for >15 years not to discontinue medications before exercise testing. This practice is supported by a task force report (31) recently issued by the American College of Cardiology and the American Heart Association. It is, nevertheless, important to note that abnormal images were obtained in the majority of patients, even though these patients had submaximal exercise or were receiving antianginal medications. Conceivably, imaging using coronary vasodilatation with pharmacologic agents, such as dipyridamole, papaverine hydrochloride or adenosine, may improve the yield further in the patients with submaximal exercise (9).

Thallium redistribution. Perfusion defects that show partial or complete redistribution 4 h after exercise indicate the presence of ischemia. The lack of redistribution, contrary to earlier predictions, is not necessarily due to scar. Thus, fixed defects have been shown to improve after coronary artery bypass grafting or coronary angioplasty and have also been shown to maintain metabolic activity using positron emission tomography (32,33). Some fixed defects have been observed to show redistribution on delayed images obtained 8 to 24 h after exercise (34). The precise mechanism for the lack of redistribution or the slow process of redistribution is not clear, but a very severe coronary stenosis that compromises the coronary flow, even at rest, has been implicated. Thallium washout depends on concentration gradient between myocardial cells and blood. Slow washout has been noted in patients with submaximal exercise. On the other hand, enhanced washout is seen when blood thallium concentration is decreased, such as after a meal. We routinely ask our patients to have a light meal between initial and redistribution images. It is therefore important to remember that fixed defects should be considered as markers of coronary artery disease.

Patients with normal coronary angiograms. The specificity of exercise SPECT thallium imaging was 62% in patients with normal or near normal coronary angiograms. The low specificity is not unexpected based on the postreferral selection bias; that is, patients with abnormal scans were preferentially selected for cardiac catheterization. These patients had at least an intermediate pretest probability of coronary artery disease based on their symptoms, ECG findings and risk factors (35). In 131 patients with <5% pretest probability of coronary artery disease, the specificity of exercise thallium imaging was 93%. Therefore, the true specificity of the test may be somewhere between these two values.

Pretest bias and posttest probability and referral bias. The sensitivity and specificity of exercise thallium imaging in the early published reports was 80% to 90%. Recent studies report the same sensitivity of 80% to 90% but the specificity has fallen to approximately 60%. Referral bias is one explanation offered for this lower specificity. The argument is that normal subjects have been excluded from the catheterization population in recent years and, therefore, the study group is skewed toward greater prevalence of disease by the exclusion of these normal subjects. According to Bayes' theorem, as the population is skewed toward greater prevalence of disease, the number of true-negative tests or apparent specificity of that study group falls. The term "referral bias" can therefore be defined as skewing of the study population toward greater disease prevalence. In support of this argument is the normalcy rate of about 90% in uncatheterized patients having <5% probability of coronary artery disease by virtue of age, lack of risk factors or family history of premature coronary atherosclerosis.

An alternative explanation for the recent low specificity of thallium testing is that the study group in early reports comprised patients who had sufficiently advanced coronary artery disease to warrant cardiac catheterization without additional data derived from exercise thallium imaging. More recently, stress thallium imaging has been used in patients who have no clear clinical evidence of coronary artery disease are, therefore, likely to have a lower prevalence of disease. Supporters of this hypothesis argue that, in populaitons recently studied with lower prevalence of disease in whom a noninvasive test is most needed, thallium imaging results must be disappointing because of the lower specificity and, hence, lower diagnostic accuracy.

According to Hamilton et al. (36,37), a posttest probability of 62% for a normal coronary arteriogram as reported in our study requires a pretest prevalence of disease of 85%; if correct, these data imply that the posttest probability of disease should be 100% in patients with abnormal test results. Because in our study the sensitivity of the test was only 82%, our results tend to suggest that the lower specificity cannot be explained by the higher prevalence of disease provided by the referral bias.

Finally, it can also be argued that patients with low pretest probability of disease cannot be used to derive normalcy rate because of differences in risk factors, age and anatomy, including the greater chest diameter, greater body mass, bone density and the greater prevalence of diaphragmatic and breast attenuation in the older patients with a normal coronary angiogram, which may cause false positive thallium images (Table 3).

Clinical implications. These two viewpoints on specificity of SPECT thallium imaging cannot be reconciled completely, but several points of our study and our large experience are worth mentioning: 1) the pretest probability of coronary artery disease was 82%; that is, 272 of 330 patients who underwent cardiac catheterization had coronary artery disease. 2) There is no real standard for defining hemodynamic significance of coronary artery disease, as discussed earlier. 3) Abnormal coronary flow reserve has been observed in patients with normal coronary angiograms; therefore, abnormal thallium studies in such patients may not be truly false positive. 4) Our results suggest that the level of exercise should be taken into consideration in interpreting the results of SPECT thallium imaging. For example, 98% of patients with multivessel disease and adequate exercise end points had abnormal thallium images. It may be that alternative techniques are necessary in patients who had normal scans but did not achieve adequate exercise end points. The use of coronary vasodilatation with dipyridamole or with adenosine may be such an alternative. 5) There definitely is a learning curve in interpreting SPECT thallium results in recognizing artifacts. For example, acquisition of SPECT images in the prone rather than the supine position may eliminate most diaphragmatic attenuation artifacts. Also, taping the breast away from the field may decrease the chance of breast attenuation artifacts. Strict attention to motion artifacts, upward creep, reconstruction artifacts, image quality and artifacts due to hot spots within or outside the left ventricular myocardium would certainly decrease the false positive rates and improve the specificity (38–40).

Some abnormalities such as those seen in patients with left bundle branch block or regional wall motion abnormality may not be truly false positive but may represent unrecognized cardiomyopathy or abnormality in the left anterior descending artery flow, conceivably because of prolongation of systole and encroachment on diastole. A mild decrease in the perfusion pattern in the posterolateral wall was recently also described in patients with left ventricular hypertrophy due to systemic hypertension (40). Therefore, not all abnormal scans in the absence of obstructive coronary artery disease may be truly false positive. The standard of normalcy may be as difficult to define as the standard for defining the hemodynamic significance of coronary stenosis.

Finally, the use of newer imaging agents, such as technetium-99m isonitrile (RP-30A), which has a higher energy level, may improve the results (8,41). We continue to believe that exercise thallium imaging is a very important technique in patient managment for screening patients with coronary artery disease, identifying patients at low or high risk and studying the effects of complications such as acute infarction or results of interventions such as medical therapy, coronary artery bypass grafting or coronary angioplasty.

Conclusions. The results of exercise SPECT thallium imaging are significantly better in patients with adequate exercise end points than in patients with submaximal exercise. Furthermore, the results of SPECT thallium imaging are significantly better than those of exercise electrocardiography, regardless of the extent of coronary artery disease.

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