Clinical usefulness of thallium-201 scintigraphy in the study of coronary artery disease: a comparison of two exercise systems

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Exercise-related thallium-201 (^{201}Tl) scintigraphy has become an established diagnostic technique in the study of coronary artery disease.[1-4] Its predictive value, like that of stress electrocardiography or any other diagnostic test, varies according to the likelihood of the disease in any given population,[5] but in the study of symptomatic patients, or those identified as at risk, it often provides information about the extent as well as the presence of disease. A recent review by Okada et al,[1] which combines the results of many studies (1817 patients), gives an overall sensitivity of 87% and specificity of 91%. This paper will review the experience at the Cleveland Clinic with thallium testing in daily clinical practice and compare the results from two test protocols.

Materials and methods

The patients involved in the study were referred to the Cleveland Clinic for evaluation of a chest pain syndrome, possibly representing coronary insufficiency, or for study following documented myocardial infarction. The records of patients from two, separate, 3-month periods who underwent exercise and equilibrium myocardial imaging with ^{201}Tl were reviewed; those who had undergone coronary angiography within 6 weeks of the procedure were included in the analysis. Patients who had undergone myocardial revascularization procedures were excluded.

The two exercise systems are shown in *Table 1.* These differed in terms of type of exercise, dose of ^{201}Tl and interval between exercise and imaging. An abnormal electrocardiographic response was considered to be an ST-segment depression $\geq$ 1 mm, either horizontal or downsloping in quality. A diagnostic test either showed an abnormal response or was carried to limiting symptoms and a pulse rate greater than 85% of the age-predicted maximum (estimated as 220 minus the age of the patient). Both systems used continuous graded exercise protocols. In the first group, a bicycle ergometer with graded 300 kpm (kilopond-meter) stages of 3 minutes each was utilized. In the second, a treadmill (with use of the Bruce protocol) was the mechanism of stress.

Thallium images were obtained in the standard fashion: at peak effort, 1.5 mCi (Group 1) or 2.0 mCi (Group 2) of ^{201}Tl was injected through a previously placed free-flowing intravenous line and exercise continued for an additional 30 to 60 seconds. After a 3–6 minute recovery period, the patient was then transported to the imaging area and three sequential images were obtained: 45° left anterior oblique view; 60°–70° left anterior oblique view; and an anterior view, in that order. Counts were collected for a 10-minute period for each image. Approximately 3–4 hours after exercise, the same views were repeated in the same time sequence and the two sets of images compared. An abnormal thallium image was defined as one or more segments showing count-rate activity below 80% of that identified in the most intense segment for each view. Ischemia was diagnosed if an abnormal region improved in the recovery (equilibrium) phase. Scar was indicated by a persistent or incompletely resolved perfusion defect.

Table 1. Exercise technique

	Group 1	Group 2
Work system	Bicycle ergometer	Treadmill
Protocol	Graded 3-min 300 kpm stages	Bruce
ECG system	Frank leads + bipolar V_5	12-lead ECG
Thallium dose	1.5 mCi	2.0 mCi
Exercise imaging delay	10–12 min	4–6 min

Coronary angiography was done in the standard fashion via the Sones technique.[6] In the sensitivity calculation for this study, significant disease was considered present if any major coronary vessel showed atherosclerotic changes reducing the vascular lumen by 70% or more from an estimated normal caliber.

Sensitivity was calculated as true-positive divided by true-positive plus false-negative responses ($TP/TP + FN$). In the calculation of specificity, only coronary lesions blocking less than 50% of the vessel lumen were considered. Specificity equaled true-negative divided by true-negative plus false-positive responses ($TN/TN + FP$).

Between August 1 and November 1, 1979, 80 patients had exercise thallium imaging and accompanying catheterization who had not undergone prior bypass surgery. Of these, 48 had at least one coronary artery lesion $\geq$ 70% of the vessel lumen; 13 had lesions measuring 50%–59%, and 19 had minor or no coronary irregularities.

The second group comprising 78 acceptable patients was studied between April 1, and July 1, 1980. Forty-eight had coronary lesions of 70% or more of the vessel lumen. Lesions in 10 measured between 50% and 69%, and 20 had mild or no disease.

Thallium images

Sensitivity of thallium imaging in detecting significant coronary artery disease (70% of the lumen or greater) for the two groups is shown in *Table 2.* Thirty-five of 48 (73%) and 41 of 48 (85%) were identified as having either scar or ischemia; the sensitivity for exercise-related abnormalities (transient defects) alone was 54% (26 of 48) and 71% (34 of 48) for Groups 1 and 2, respectively. If images showing only reversible defects were considered, this rose to 67% and 83% for each group, respectively. Specificity for each group for coronary artery disease < 50% was 84% (3 of 19 false-positives) and 35% (13 of 20 false-positives), respectively.

Electrocardiography

Sensitivity for the two ECG stress systems is shown in *Table 3.* Thirty of 48 (63%) and 41 of 48 (85%) in Groups 1 and 2 had exercise-related ST-segment changes or significant Q-waves on the resting ECG, suggesting prior myocardial infarction. For ST-segment changes alone, the sensitivity in Group 1 was 35% and in Group 2, 50%. The specificity for ECG responses, excluding coronary artery disease of less than 50% narrowing, was 100% (0 of 19 false-positives) for the first group and 90% (2 of 20 false-positives) for the second.

The value of the test in patients without resting electrocardiographic evidence of myocardial infarction was reviewed. Twenty-nine of 48 patients in Group 1, and 21 of 48 patients in Group 2 did not have electrocardiographic evidence suggestive of myocardial infarction. *Table 4* compares the sensitivity of thallium imaging and ST-segment changes between these groups. Thallium was more sensitive than the ECG in both groups and the combined tests tended to result in higher sensitivity than either alone. The sensitivity of both thallium imaging and stress ECG for the two groups based on the presence of single-vessel and multivessel disease is shown in *Tables 5 and 6.* With more advanced disease, abnormal results are more likely and the testing technique used in Group 2 tended to be more sensitive than that used in Group 1.

Table 2. Sensitivity of thallium-201 in identifying patients with significant coronary artery disease*

	Group 1 (n = 48)	Group 2 (n = 48)
Rest and exercise PD†	73% (35/48)	85% (41/48)
Exercise PD	54% (26/48)	71% (34/48)

* Significant CAD = 70% or more. Sensitivity = TP/TP + FN.
† PD = perfusion defect.

Table 3. Sensitivity of rest and exercise electrocardiography in patients with significant coronary artery disease

	Group 1 (n = 48)	Group 2 (n = 48)
Abnormal rest or exercise ECG	63% (30/48)	85% (41/48)
Exercise-induced ST changes	35% (17/48)	50% (24/48)

Table 4. Thallium and stress ECG sensitivities in the absence of Q waves on the resting electrocardiogram

	Group 1	Group 2
Thallium images	69% (20/29)	71% (15/21)
Exercise-induced ST changes	41% (12/29)	67% (14/21)
Combined	72% (21/29)	86% (18/21)

Discussion

The electrocardiographic results are in agreement with those recently reported by others. Bailey et al[7] and Rit-

Table 5. Relative sensitivity of thallium-201 and stress electrocardiography in patients with single-vessel coronary disease

	Group 1 (n = 32)	Group 2 (n = 27)
Thallium		
Rest and exercise PD	63%	81%
Exercise PD	44%	67%
ECG		
ST changes	31%	44%

Table 6. Relative sensitivities of thallium-201 and stress electrocardiography in patients with multivessel coronary disease

	Group 1 (n = 16)	Group 2 (n = 21)
Thallium		
Rest and exercise PD	94%	90%
Exercise PD	69%	76%
ECG		
ST changes	50%	57%

chie and associates[8] obtained sensitivity values of 38% and 45%, respectively for exercise-induced ST-segment depression using comparable exercise and electrocardiographic lead systems. Although the use of multiple leads was introduced for our second group, and the stress environment was switched from the bicycle to the treadmill, the exercise-related ST-segment sensitivity rose to only 57%.

Test results in this population confirmed the value of exercise thallium scintigraphy in the identification of coronary artery disease. The sensitivities of ^{201}Tl testing in Groups 1 (73%) and 2 (85%) are similar to those of Bailey et al[7] (75%), Ritchie et al[8] (76%), and Okada et al[1] (82%).

Comparison of the two groups demonstrates the importance of the testing technique for increasing sensitivity. In Group 2, a larger dose of ^{201}Tl was administered, resulting in a greater number of counts, which decreases the effects of statistical randomization. In addition, the exercise for patients in Group 2 was carried out in a room immediately adjacent to the gamma camera, permitting the onset of imaging within 4–5 minutes after termination of exercise, thus minimizing early redistribution. In Group 1, there was usually a 10–12-minute delay because the patient had to be transported to another floor for imaging.

The specificity for thallium was reduced in the second group. The false-positive values appear to result from subcritical occlusion or other abnormalities of the heart muscle simulating perfusion defects.

It has been shown that primary myocardial diseases or hypertrophic changes can produce false-positive thallium images in the absence of coronary artery disease. Lösse et al[9] studied 39 patients with chest pain who had normal coronary arteriograms and left ventriculograms. Twenty-seven had ^{201}Tl defects and of these, 20/27 showed abnormal stress ECG responses, 10/22 had abnormal pulmonary artery pressure changes with effort, and 12/12 had abnormal right ventricular biopsy specimens, which suggests an underlying myocardial abnormality. Pitcher et al[10] found a high incidence (18/23) of abnormal and variable ^{201}Tl distribution in young patients with hypertrophic cardiomyopathy. In 14/44 patients with sarcoidosis without cardiac involvement, Kinney et al[11] found abnormal thallium perfusion patterns associated with echocardiographic suggestion of left ventricular dysfunction.

Myocardial bridging may also reduce

specificity. Ahmad and associates[12] demonstrated abnormal exercise thallium images in 3 of 4 patients with high-grade systolic narrowing of a coronary artery by a myocardial bridge, whereas Greenspan et al,[13] using the same classification, found no abnormalities in 7 patients referred for ^{201}Tl testing. The inclusion of subcritical disease in the calculation of specificity reduces test reliability. Mews et al[14] saw 7/13 "appropriately located" ^{201}Tl perfusion defects in patients with coronary lesions occluding 30–45 percent of the lumen. In our second group of patients, there were 13 false-positive scans. Appropriately located subcritical lesions (< 50%), or myocardial bridges were seen in 4. Myocardial changes of left ventricular hypertrophy, primary myocardial dysfunction, or more classic hypertrophic cardiomyopathy were present at the time of catheterization in 6. Of the remaining 3 subjects, 2 had definite defects that could not be explained which were thus thought to represent true false-positive results. The other patient was an obese woman; breast-tissue absorption was thought to explain the apparent anterior perfusion defect.

These results reflect the use of this technique in the day-to-day assessment of patients with possible occlusive coronary artery disease. The present protocol of Group 2 has a high sensitivity but lower specificity, apparently related to detection not only of critical lesions, but also of subcritical occlusion and other types of cardiac disease. True false-positive images (those for which no explanation of perfusion defect is possible) are uncommon. This is merely a part of the overall assessment of patients who present with possible coronary artery disease. The technique is useful in deciding whether coronary angiography should be performed. With the second protocol, subcritical coronary lesions or noncoronary cardiac abnormalities may be placed in a group for extended study but significant, occlusive coronary disease, especially multivessel disease, is less likely to be ignored.

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