Noninvasive Prediction of Multivessel Disease After Myocardial Infarction

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SUMMARY  In 65 patients with a previous transmural myocardial infarction (anterior in 33, inferior in 32), exercise thallium scanning was compared with 12-lead exercise electrocardiography to see if multivessel disease could be detected. At coronary arteriography 40 patients were shown to have multivessel disease (≥ 70% diameter stenosis in two or three vessels) and 25 patients had one-vessel disease. On the exercise scan thallium defects corresponding to the electrocardiographic site of infarction were present in all patients.

Patients with one-vessel and multivessel disease were separated by exercise-induced angina, perfusion defects on the exercise thallium scan in more than one specific vascular area, and a positive exercise ECG associated with angina, but not by a positive exercise ECG alone. Of the 40 patients with multivessel disease, 85% had defects in more than one vascular area on the thallium scan and 70% had a positive exercise ECG (p = NS). Of the 37 patients with thallium defects in more than one specific vascular area, 92% had multivessel disease, compared with 72% of the 39 patients who had a positive exercise ECG (p < 0.05).

Perinfarctional ischemia was present in 38 of the 65 patients (58%) (14 of 25 with one-vessel disease and 24 of 40 with multivessel disease), and did not correlate with the severity of the corresponding coronary artery disease. When thallium defects that resolved were noted in a second vascular area, they were associated with a resolving rather than a constant defect in the vascular area where the infarction had occurred (p < 0.005). In patients after a transmural myocardial infarction, multivessel disease can be better differentiated from one-vessel disease by thallium scanning than by exercise electrocardiography.

PROGNOSIS after myocardial infarction depends on the extent of coronary artery disease.1-2 A positive stress ECG after myocardial infarction is reported to predict multivessel disease with a sensitivity of 41–91%.3-5 Comparative studies of thallium-201 myocardial perfusion scanning and electrocardiography have shown thallium scanning to be more sensitive in detecting coronary artery disease.6-8

In this study exercise electrocardiography and exercise thallium-201 myocardial scanning were compared and related to coronary arteriographic findings in patients with a previous transmural myocardial infarction to see if one-vessel and multivessel disease could be differentiated.

Methods

Sixty-five patients (63 males and two females) with ECG evidence of a single previous transmural myocardial infarction defined according to the Q-wave criteria of the American Heart Association9 underwent exercise stress testing with thallium-201 myocardial perfusion scanning 3–72 months after infarction (mean 30 months). The mean age of the patients was 50.4 years (range 32–64 years). Fifty-one of the 65 patients complained of angina pectoris after the myocardial infarction, and 42 of the 65 (65%) were taking β blockers.
Coronary Arteriography and Ventriculography

All patients underwent coronary arteriography using the Judkins or Sones technique. Each study was reviewed by an independent observer. One-vessel disease was diagnosed if one coronary vessel was significantly (≥ 70% diameter) stenosed and multivessel disease was diagnosed if two or more vessels were significantly stenosed. Left ventriculograms were performed in all patients in the right anterior oblique projection. Wall motion abnormalities were localized according to the criteria of the American Heart Association.9

Exercise Thallium Myocardial Perfusion Scanning

Exercise myocardial perfusion scanning was performed within a mean time of 10 days (range 1 day to 5 months) from coronary arteriography. The patients exercised maximally on an upright bicycle ergometer using a graded, multistage, continuous protocol1 until chest pain, breathlessness or fatigue occurred. Leads were placed in the standard location by Mason et al.10 and a 12-lead ECG was recorded before and during each minute of exercise and recovery. At peak exercise, 1.5–2 mCi of thallium-201 were injected through an intravenous cannula previously inserted. All patients continued exercising for another 60 seconds to allow blood clearance and myocardial uptake of the thallium during conditions of stress.

Scanning was begun in the exercise laboratory 5 minutes after the thallium injection (exercise scan). With the patient supine, four views (anterior, 40° left anterior oblique, 60° left anterior oblique and left lateral) were taken using an Ohio Nuclear Sigma 420 mobile camera and a high-resolution, parallel-hole collimator. In the initial view, 220,000 counts were collected in an average time of 400 seconds. Counts in the other three views were taken to an equal time. The four scans were usually completed within 40 minutes after exercise. Scans were repeated 4 hours later in the same four views without further administration of thallium (4-hour redistribution scan).11, 12

Exercise Stress Test Interpretation

The exercise ECG was positive if during or after exercise there was (1) 1 mm or greater horizontal or downsloping ST-segment depression, compared with baseline, lasting 0.08 second, and present in three consecutive beats or (2) 1 mm or greater horizontal or upsloping ST-segment elevation, compared with baseline, in three consecutive beats in any lead without a Q wave. The exercise ECG was considered negative if these ST-segment changes did not occur during maximal, symptom-limited exercise. Patients with a negative exercise ECG who reached less than 85% of their predicted maximum heart rate were included in the study only if exercise was limited by angina or if they were taking β blockers and exercised for more than 10 minutes. Only three patients were in this latter group, and all reached at least 70% of their predicted maximal heart rate. As 65% of our patients were on β blockers, a low achieved heart rate or low blood pressure response was not used to discriminate between left ventricular dysfunction and coronary artery disease.

Thallium Scan Interpretation

Thallium scans were interpreted by three unbiased observers from the original Polaroid scintiphotos without computer enhancement or background subtraction. The three observers reached a consensus concerning the presence or absence of a defect, the location of a defect and any change in defect size or intensity between the two scans. The interconsensus variability of these three factors was 7%. A thallium defect was considered present if there was a visually estimated discrete reduction of radionuclide activity greater than 50%, involving at least 15% of the left ventricular circumference.7 Thallium defects were localized to three specific vascular areas previously shown to correlate with the distribution of the three major coronary arteries13, 14 (fig. 1).

Multivessel coronary artery disease was considered to be present if the exercise scan showed thallium...
defects in two or more specific vascular areas and these scans were considered positive. One-vessel disease was considered present if the exercise scan showed thallium defects limited to one specific vascular area and these scans were considered negative. Exercise and 4-hour redistribution thallium scans were then compared, and a thallium defect on the exercise scan was classified as resolving, if the extent or intensity of the defect improved, or constant, if there was no change on the 4-hour scan. Perinfarctional ischemia was inferred if a thallium defect on the exercise scan corresponding to the site of previous infarction decreased in size or intensity on the 4-hour scan.

Antianginal medications were not changed before any of the procedures, and there were no complications.

Statistical Analysis

The sensitivities and predictive accuracies of a positive thallium scan, exercise-induced angina and a positive 12-lead exercise ECG for detecting multivessel disease were compared. Sensitivity was calculated as true positives divided by the sum of true positives plus false negatives. Predictive accuracy was calculated as true positives divided by the sum of true and false positives.

Data were analyzed using Yates corrected chi-square test, the exact test of Fisher, Irwin and Yates for the 2 × 2 contingency table or the McNemar test.

Results

Sixty-five patients with a previous transmural infarction were studied. Thirty-three had anterior Q waves and 32 had inferior Q waves. The ECG site of infarction corresponded to both the site of abnormal ventricular wall motion and coronary artery obstruction (≥70%) at angiography except in one patient who had a clinically documented infarction with 100% obstruction of the right coronary artery but a normal ventriculogram. One-vessel coronary disease was present in 25 of the 65 patients and multivessel disease was present in 40 (25 with two-vessel disease and 15 with three-vessel disease).

In all 25 patients with one-vessel disease, thallium defects on the exercise scan were present in the vascular area corresponding to the ECG site of Q waves. In three of the 25 patients (12%), thallium defects were also present at a second specific vascular site (table 1). Defects in the second area in these patients were seen in only one view and were not associated with stenosis greater than 50% but less than 70% in the corresponding coronary artery. In eight of these 25 patients (32%), angina developed during exercise, and 11 (44%) had a positive exercise ECG. Three patients (12%) had both exercise-induced angina and a positive exercise ECG (table 1 and fig. 2).

In all 40 patients with multivessel disease, thallium defects on the exercise scan were present in the vascular area corresponding to the ECG and angiographic site of infarction. In 34 of the 40 patients (85%), thallium defects were also present at a second specific vascular area (table 1) that corresponded to a stenotic coronary artery. Table 2 also shows the results of the exercise stress test in the 40 patients who had multivessel disease. Angina during exercise developed in 32 patients (80%), the 12-lead exercise ECG was positive in 28 (70%) and angina on exercise with a positive exercise ECG developed in 25 (63%) (fig. 3). The exercise thallium scan with defects in two or more specific vascular areas (positive thallium scan) was more sensitive for detecting multivessel disease than the positive exercise ECG (85% vs 70%, p = NS), exercise-induced angina (85% vs 80%) and a positive exercise ECG with angina (85% vs 63%, p < 0.05) (figs. 4–6).

Table 1 and figure 7 are a comparison of the results of the exercise test and the exercise thallium scan in patients with multivessel and one-vessel disease. Patients with multivessel disease were differentiated from those with one-vessel disease by exercise-induced angina (80% vs 32%, p < 0.0005), defects on the exercise thallium scan in two or more vascular areas (85% vs 12%, p < 0.0001) and a positive exercise ECG with angina (63% vs 12%, p < 0.0001), but not by a positive 12-lead exercise ECG alone.

The predictive accuracy of the exercise test and exercise thallium scan for multivessel disease is shown in figure 8. Multivessel disease was present in 32 of 40 patients (80%) with exercise-induced angina, 28 of 39

| Table 1. Comparison of Exercise Test and Thallium Scan in Patients with One-vessel and Multivessel Disease |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| | Exercise-induced angina | Positive exercise ECG | Exercise-induced angina + positive exercise ECG | Exercise thallium defects in two vascular areas |
| | ECG infarction site | Total (n = 25) | ECG infarction site | Total (n = 40) | p |
| | ANT (n = 13) | ANT (n = 20) | ANT (n = 20) | ANT (n = 22) | INF (n = 12) |
| Exercise-induced angina | 6 | 18 | 32 | 0.0005 |
| Positive exercise ECG | 4 | 14 | 28 | NS |
| Exercise-induced angina + positive exercise ECG | 2 | 13 | 25 | 0.0001 |
| Exercise thallium defects in two vascular areas | 0 | 17 | 34 | 0.0001 |

Abbreviations: ANT = anterior; INF = inferior; p = p value for comparison of sensitivity of each of the four tests for detecting one-vessel and multivessel disease.
patients (72%) with a positive 12-lead exercise ECG, 25 of 28 patients (89%) with a positive 12-lead exercise ECG and angina, and 34 of 37 patients (92%) with thallium defects in two or more vascular areas. The predictive accuracy of a positive thallium scan for detecting multivessel disease was significantly higher than that of the 12-lead exercise ECG ($p < 0.05$).

Figure 9 shows the predictive accuracy of the exercise ECG and exercise thallium scan for detecting one-vascular disease. One-vascular disease was present in 17 of 25 patients (68%) without exercise-induced angina, 14 of 26 patients (54%) with a negative 12-lead exercise ECG, 22 of 37 patients (59%) with a negative exercise ECG and no angina, and in 22 of 28 patients (79%) with thallium defects in one vascular area. The predictive accuracy of a negative thallium scan for one-vascular disease was better than that of the 12-lead exercise ECG, but this difference did not reach statistical significance.

The relationship of the changes on serial thallium scanning (exercise and 4-hour redistribution) at the site of infarction in the 25 patients with one-vascular disease to coronary artery anatomy and to the exercise ECG is shown in Table 2. Thallium defects at the infarct site were constant in 11 patients (44%) — eight with a single 100% coronary artery obstruction and three with either incomplete obstruction or 100% obstruction of one branch and a stenosis of another branch of the same artery. Thallium defects at the infarct site showed serial improvement in 14 patients (56%) — seven with a single 100% coronary artery obstruction and seven with either incomplete obstruction or more than one stenosis of the same artery. In 13 of the 14 patients, persistent defects were present

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**Figure 2.** An exercise thallium scan (Ex) and 4-hour redistribution scan (R) in the 60° left anterior oblique (LAO) view (D), showing a resolving anteroseptal (ANT SEPT) and apical defect at the site of an infarction (periinfarctional ischemia) with a residual mild defect on the redistribution scan. The scans were performed in a 40-year-old male patient who had sustained a transmural anteroseptal myocardial infarction 4 months before the exercise test, and subsequently complained of effort angina (New York Heart Association functional class II) treated with propranolol. The exercise ECG was positive, with 2 mm of ST depression in the inferolateral leads, but there was no exercise-induced angina. Cardiac catheterization (C/C) the following day revealed anterolateral hypokinesis, 99% stenosis of the left anterior descending coronary artery (LAD) and 90% stenosis of the first diagonal branch.

**Figure 3.** Comparison of the sensitivities of the exercise test and exercise scan for detecting multivessel disease. The asterisk indicates that the thallium scan was significantly more sensitive than exercise ECG with angina ($p < 0.05$).
FIGURE 4. A negative exercise ECG in a patient with a previous anterior infarction. There is upsloping inferolateral ST-segment depression, and ST-segment elevation over QS waves in leads V₁ to V₃. Ex ECG = exercise ECG; Wmax = maximal, symptom-limited work capacity or exercise.

FIGURE 5. The 60° left anterior oblique (LAO) and left lateral views (D) of the exercise thallium scan (EX) and 4-hour redistribution scan (R) of the patient in figure 4. There are thallium defects in two specific vascular areas on the exercise scan (LAD vascular area, dotted; and RCA/LCX vascular area, striped). There is complete resolution of the posteroinferior defect and partial resolution of the anteroapical infarct defect, leaving a persistent defect in this area. The result of coronary angiography (C/C) is shown on the right. The thallium scan predicted the presence of multivessel disease. Abbreviations as in figure 1.
Figure 6. The anterior and 60° left anterior oblique (LAO) views of an exercise thallium scan (EX) and 4-hour redistribution scan (R) in a patient with a previous anteroseptal (ANT SEPT) infarction. The exercise ECG was negative, with ST elevation over Q waves. The scan shows constant defects in two specific vascular areas: LAD vascular area (dotted) and RCA/LCX vascular area (blackened). The results of coronary angiography (C/C) are shown at the bottom. It was felt that the posteroinferior (POST INF) defect was caused by the LCX stenosis. See figure 1 for abbreviations.

Figure 7. Comparison of the exercise (EX) test and exercise thallium scan in patients with one-vessel disease (open bars) and multivessel disease (cross-hatched bars). Positive thallium scan refers to defects in more than one specific vascular area.

Table 2. Relation of Serial Thallium Scan Changes and Severity of Coronary Artery Obstruction Corresponding to the ECG Site of Myocardial Infarction

<table>
<thead>
<tr>
<th>Serial scan changes</th>
<th>One-vessel disease (n = 25)</th>
<th>Multivessel disease (n = 40)</th>
<th>Total (n = 65)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coronary obstruction*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>100%</td>
<td>&lt; 100%</td>
<td>100%</td>
</tr>
<tr>
<td>Constant</td>
<td>8 (4)†</td>
<td>3 (2)</td>
<td>10 (6)</td>
</tr>
<tr>
<td>Resolving</td>
<td>7 (3)†</td>
<td>7 (2)</td>
<td>19 (17)</td>
</tr>
</tbody>
</table>

*100% refers to complete obstruction and < 100% refers to incomplete obstruction or complete obstruction and a stenosis of another branch of the coronary artery corresponding to the ECG site of infarction.
†Numbers in parentheses refers to number of patients with a positive exercise ECG.
The predictive accuracies of a positive exercise (Ex) and thallium scan for detecting multivessel disease are shown in Figure 8. The asterisk indicates that the thallium scan was significantly more accurate than the exercise ECG (p < 0.05). Positive exercise scan refers to defects in more than one specific vascular area.

Changes in serial thallium scanning at the site of infarction in the 40 patients with multivessel disease were related to the severity of corresponding coronary artery obstruction and the exercise ECG (table 2). Thallium defects at the infarct site were present on both scans in all 40 patients. The defects were constant in 16 patients (40%) and improved in 24 (60%). The relationship to coronary anatomy is shown in table 2. In the combined group (one-vessel plus multivessel disease), the presence of a resolving infarct site defect was equally distributed between patients with total obstruction in the corresponding coronary artery (59%) and those with incomplete obstruction or more than one stenosis (57%).

Changes in serial scanning were compared in the 34 patients with defects in two vascular areas. The defect in the second vascular area was constant in nine patients and improved in 25. A resolving defect in a second vascular area was seen in 20 of 24 patients with a resolving defect at the site of infarction, but in only five of 16 with a constant defect at the site of infarction (p < 0.005). The exercise ECG was positive in 28 patients — 17 with a resolving defect at both the site of infarction and a second site, two with a resolving defect only at the site of infarction, three with a resolving defect only at a second site and six with no resolving defects.

Discussion

Oberman et al. showed that the prognosis of patients with coronary artery disease depends on the number of vessels obstructed. Miller et al. found that 63% of asymptomatic patients after an uncomplicated inferior myocardial infarction have significant left anterior descending coronary artery obstruction. When angina develops after myocardial infarction it is important to ascertain whether the patient has one-vessel or multivessel disease. Although a positive exercise ECG is more frequently found in patients with multivessel than in patients with one-vessel disease, the exercise ECG poorly localizes myocardial ischemia and cannot distinguish between perfusional ischemia in patients with one-vessel disease and a second area of ischemia in patients with multivessel disease. In contrast, the site of coronary artery disease may be predicted from the pattern of defects on the exercise thallium scan. Thallium defects in one
specific vascular area suggest one-vessel disease, whereas defects in more than one specific vascular area suggest multivessel disease.

Perfusion defects in more than one specific vascular area identified 85% of our patients with multivessel disease. In a similar study, Lenaers et al. found that the thallium scan correctly identified multivessel disease in 71% of their patients. The higher sensitivity in our study may be due to differences in the patient groups, as all our patients had documented myocardial infarction, compared with only 36% in Lenaers’ study. In six of our patients (15%) with multivessel disease, thallium defects were present in only one specific vascular area, a false-negative result. Three were thought to show periinfarctional ischemia, which may have limited exercise before perfusion in a second obstructed coronary artery was compromised. In the other three patients, the difficulty of recognizing areas of reduced radionuclide uptake in the presence of other areas of more severely reduced radionuclide uptake, as occurs with infarction, may explain why a defect in a second area was not seen.

Thallium defects on the exercise scan in only one specific vascular area identified 88% of the patients with one-vessel disease. In the remaining 12% (three patients) with one-vessel disease, thallium defects were found in two specific vascular areas. In all three patients, defects in the second vascular area were seen in only one view and were not associated with greater than 50% but less than 70% stenosis in the corresponding coronary artery. These defects may represent an error in classification of the vascular area as a result of variation in the cardiac position, or may be artifactual and represent attenuation by other tissue structures.

A positive exercise ECG after myocardial infarction is said to predict multivessel disease. In our study, a positive exercise ECG did not separate patients with multivessel and one-vessel disease, as there was a high incidence of a positive exercise ECG in patients with one-vessel disease. Eleven patients (44%) with one-vessel disease had reversible ST-segment changes on exercise. In five of the 11, ischemia was considered periinfarctional because the thallium defect at the site of infarction was smaller on the 4-hour scan than on the exercise scan. In the other six patients, the defect did not change between the serial scans. The ST-segment changes in these patients were false positives or due to ischemia not detected by the thallium scan. The specificity of the exercise test for predicting multivessel disease was increased when both exercise angina and positive exercise ECG were combined.

The incidence of a positive exercise ECG in patients with multivessel disease after myocardial infarction has varied between 41–91%, depending upon patient selection and the lead system used. Castellanet et al. using a three-lead ECG system, found that the exercise ECG was more sensitive in identifying multivessel disease in patients with previous inferior (84%) than anterior infarction (52%). In our 65 patients, a 12-lead ECG system was used and the exercise ECG was equally sensitive (70%) in patients with previous inferior and anterior infarction. The difference in the two studies may be related to the different ECG lead systems used. Although the exercise thallium scan in our patients was more sensitive than the exercise ECG in detecting multivessel disease (85% vs 70%), the number of patients was insufficient for the difference to be significant.

The thallium scan in our patients was both sensitive (85%) and highly predictive (92%) of multivessel disease. Lenaers et al. also reported a high predictive accuracy (88%) of the thallium scan for detecting multivessel disease, but with a lower sensitivity (71%) than in our study. Paine et al. reported a high predictive accuracy of the exercise ECG for detecting multivessel disease in patients after myocardial infarction, but with a sensitivity of only 41%. Our exercise ECG was less accurate but more sensitive than Paine’s exercise ECG. The lower accuracy of the ECG in our study is related to the relatively high incidence of a positive exercise ECG in patients with one-vessel disease.

In 58% of our patients, periinfarctional ischemia was inferred from the serial changes on the exercise and 4-hour thallium scans. A similar incidence of serial redistribution of thallium (62%) at the site of chronic infarction was found by Verani et al. In some of our patients, the periinfarctional ischemia could be explained by incomplete obstruction of the corresponding coronary artery or complete obstruction with a stenosis in another branch of the same artery. In the others with only a single complete obstruction in the corresponding artery, a potential explanation is the role of collateral blood flow. We did not consider the adequacy of collateral circulation, but Verani et al. showed a relationship between the extent of thallium redistribution at 4 hours and the adequacy of collaterals. In patients with multivessel disease, myocardial ischemia in a second vascular area inferred from serial thallium scan changes was commonly associated with periinfarctional ischemia. This association has not been reported previously and may be related to collateral blood flow to the infarcted area becoming inadequate with stress when blood flow in another coronary artery is compromised.

At a second site, constant defects were present without previous myocardial infarction and corresponding Q waves in nine of our patients with multivessel disease. This has been reported, and may be due to infarction undetected by the ECG or to an area of severe myocardial ischemia that at 4 hours has not yet started to show redistribution. In these patients, repeat scanning at 12–24 hours, or a separate study at rest may show improvement.

Although our patients after myocardial infarction were partially selected because they were referred predominantly for angina pectoris, multivessel disease could be distinguished from one-vessel disease by the exercise thallium scan, but not by the exercise ECG. The thallium scan showing defects in two or more vascular areas was more sensitive and predicted multivessel disease more accurately than a positive exercise ECG. The accuracy of the exercise ECG was increased when a positive exercise ECG with angina was taken to predict multivessel disease, but the sensitivity decreased.
Acknowledgment

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