Correlation of Exercise $^{201}$Thallium Myocardial Scan with Coronary Arteriograms and the Maximal Exercise Test*

Antonio P. Carrillo, M.D.; ** Daniel S. Marks, M.D.;†
Sol D. Pickard, M.D.; ‡ Fareed Khaja, M.D.; § and Sidney Goldstein, M.D.||

Myocardial scans obtained by injecting radioactive $^{201}$thallium during exercise were correlated with electrocardiograms obtained at rest and during exercise, with coronary arteriographic abnormalities, and with left ventriculograms in 55 patients suspected of having coronary arterial disease. Thirty-nine patients had significant coronary arterial disease, 34 of whom had abnormal myocardial scans after exercise and 21 of whom had abnormal ECGs during exercise. The myocardial scan after exercise was most frequently abnormal in the presence of significant abnormalities in the Q wave or localized left ventricular asynergy and when ST-segment depression persisted for longer than ten minutes after exercise. All patients with single-vessel disease had abnormal myocardial scans after exercise, whereas five of 29 patients with two or more abnormal vessels had normal scans. Patients with coronary arterial disease were more likely to have a normal myocardial scan after exercise when the resting ECG and left ventriculogram were normal and when exercise-induced ST-segment depression persisted for less than ten minutes. The combination of the myocardial scan after exercise and the ECG during maximal exercise had a sensitivity of 98 percent. The myocardial scan after exercise alone had a specificity of 100 percent. These observations indicate that the myocardial scan obtained by injecting $^{201}$thallium during exercise is an important diagnostic adjunct in the identification of patients with coronary arterial disease.

A continuing need exists for the noninvasive determination of both the presence and the extent of coronary arterial disease in the general population and in patients suspected of having the disease. Although the electrocardiogram during rest and exercise is widely used, it is increasingly clear that it lacks the high level of specificity desirable for optimal clinical use. We, therefore, must continue to rely upon coronary arteriograms as the final standard for identification of coronary disease, as well as its quantification and localization. Recent reports indicate that the maximal exercise test has a considerable limitation in terms of both false-positive and false-negative results when compared to coronary arteriograms.1–4

Radionuclide imaging of the heart using a number of different agents has recently been shown to be very effective in both identifying areas of infarcted myocardium and defining regions of myocardial hypoperfusion.5–7 The experience using radioactive $^{201}$thallium in the resting state has been recently described in patients with myocardial infarction3 and during episodes of angina.8 Bailey and associates9 have suggested that myocardial perfusion scans obtained with $^{201}$thallium following maximal exercise may add significantly to the specificity of the maximal exercise test. These authors7 indicated that the perfusion scan with $^{201}$thallium after exercise was more sensitive when compared to exercise-induced ST-segment changes alone and was particularly helpful in identifying patients with coronary arterial disease when the resting ECG was abnormal. From these reports, it appears that perfusion scans obtained following injection of $^{201}$thallium at peak exercise may be more definitive than those obtained at rest. In this report, we correlated the myocardial scan obtained with $^{201}$thallium at rest and after exercise with ECGs obtained at rest and during exercise, with coronary arteriograms, and with ventriculograms, in an effort to show the limitations of the myocardial scan obtained with $^{201}$thallium after exercise, as well as the use of this scan as a diagnostic tool in coronary arterial disease.

**MATERIALS AND METHODS**

The group of patients consisted of 55 individuals who were being evaluated for suspected or proven coronary disease. Coronary angiographic studies were indicated on clinical grounds, either because patients were severely symptomatic.
with angina pectoris or because the diagnosis of coronary disease could not be established otherwise.

All patients had ECGs obtained at rest and at maximal exercise and had a myocardial scan obtained with \(^{201}\)thallium after exercise. In 17 of the patients, resting scans with \(^{201}\)thallium were also obtained in the same projections, usually three to five days prior to the study with exercise. All patients had either a maximal treadmill exercise test according to the Bruce protocol or a maximal bicycle exercise test using a protocol for maximal graded continuous exercise with a single electrocardiographic monitoring lead in the V5 position. In 19 patients, both exercise protocols (treadmill and bicycle) were performed. A comparison of both tests, using the maximal heart rate and systolic blood pressure as an end point, indicated that equal workloads were achieved.\(^9\) Patients were exercised to the point at which symptoms occurred, the ECC became diagnostic, a maximal heart rate for the patient's age and conditioning was achieved, or the patient could continue no further because of fatigue. The results were interpreted as abnormal if the ST-segment depression was 1 mm at 80 msec from the J point and had a downward-sloping or horizontal pattern. The test was considered equivocal when the exercise was suboptimal (maximal heart rate achieved was less than 85 percent of that predicted by age and conditioning), when changes in the ST segment were present in a previously abnormal tracing obtained at rest, or when J-point depression was associated with an upward-sloping ST-segment depression of 1 mm at 80 msec.

Two millicuries of \(^{201}\)thallium were injected intravenously at peak exercise or when symptoms of angina pectoris or electrocardiographic changes of myocardial ischemia developed. The amount of time elapsed between the injection of the radioisotope and the imaging was minimized as much as possible and usually was five minutes or less. The exercise was continued for another 60 seconds, and the imaging was begun five minutes after the injection of the isotope. Scintiscans were obtained in the anterior, left lateral, and 30° and 60° left anterior oblique projections using a gamma camera (Picker Dyna model 4C). A converging collimator was used in the initial 25 cases, and a parallel-hole collimator was used in the subsequent 30 cases, with a 35 percent and 20 percent window, respectively. Peak energy of 80 kev was used, with a ten-inch field of view. There was no difference in the diagnostic quality of the image using these different collimators and windows in ten patients who were scanned with both methods.

In ten patients in whom both techniques were used, identical images were produced. Imaging was completed when 350,000 counts were detected, which required five to seven minutes for each view. The scan was considered normal when an image of homogeneous distribution of radioactivity was seen in an ovoid pattern that corresponds anatomically to the left ventricle. Areas of inhomogeneity in the image were considered to be abnormal. The scintiscans were interpreted by three observers in a "blind" manner, without knowledge of angiographic or electrocardiographic findings. The final decision was reached by a majority if unanimity was not achieved.

All patients had left ventriculographic studies in the right and left anterior oblique projections and selective coronary arteriographic studies performed using 35-mm cinearteriograms in the right and left anterior oblique and cephalo-caudal views. Coronary vessels were interpreted as abnormal if greater than 75 percent narrowing of the diameter was present. The relative sensitivity and specificity of the maximal exercise test and the myocardial scan with \(^{201}\)thallium after exercise were calculated separately and together, using the following three equations: (1) percent sensitivity = No. of true positive/(No. of true positive + No. of false negative) \(\times\) 100; (2) percent specificity = No. of false negative/(No. of false positive + No. of true negative) \(\times\) 100; and (3) percent predictive accuracy = No. of true positive/(No. of true positive + No. of false positive) \(\times\) 100.

**Results**

Of the 55 patients studied, 39 had angiographically proven coronary disease. Their ages ranged from 32 to 66 years (mean, 51 years), and there were 34 men and five women. Clinical features were disabling angina in 32 patients, and atypical pain in the chest, recurrent ventricular tachycardia, mitral regurgitation, and significantly abnormal treadmill exercise test in one patient each. The remaining three patients were studied because they were under 40 years of age and had had recent myocardial infarctions. In this group of 39 patients, 22 had a history of myocardial infarctions, 17 patients showed Q waves in the resting ECG, eight had nonspecific ST-T abnormalities, four showed a delay in intraventricular conduction, one showed left ventricular hypertrophy, and in nine the resting ECG was normal.

Sixteen of the 55 patients showed normal coronary arteries on angiographic studies. Their ages ranged from 33 to 64 years (mean, 52 years), and there were eight men and eight women. All had atypical pain in the chest, and two had a questionable history for myocardial infarction. The resting ECG was normal in seven and showed nonspecific ST-T abnormalities in eight patients and left anterior hemiblock in one patient. In the 39 patients with abnormal coronary angiograms, ten patients had one-vessel involvement, 15 patients had two-vessel involvement, and 14 patients had three-vessel involvement.

The relationship of coronary arteriograms to the maximal exercise test and the \(^{201}\)thallium scan after

<table>
<thead>
<tr>
<th>Data</th>
<th>Normal</th>
<th>Abnormal</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial scan after exercise</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>16</td>
<td>5</td>
<td>21</td>
</tr>
<tr>
<td>Abnormal</td>
<td>0</td>
<td>34</td>
<td>34</td>
</tr>
<tr>
<td>Total</td>
<td>16</td>
<td>39</td>
<td>55</td>
</tr>
<tr>
<td>Maximal exercise test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Abnormal</td>
<td>4</td>
<td>21</td>
<td>25</td>
</tr>
<tr>
<td>Equivocal</td>
<td>11</td>
<td>16</td>
<td>27</td>
</tr>
<tr>
<td>Total</td>
<td>16</td>
<td>39</td>
<td>55</td>
</tr>
</tbody>
</table>
exercise in the total group of evaluated patients is shown in Table 1. No false-positive exercise 201thallium scans were observed. In the 16 patients with normal exercise 201thallium scans and normal coronary arteriograms, the maximal exercise test was abnormal in four and equivocal in 11 (Table 1).

The results of the maximal exercise test were compared to the myocardial scans obtained with 201thallium after exercise in 39 patients with proven coronary arterial disease (Table 2). Eighteen patients developed angina during the maximal exercise test.

In 15 of 16 cases in which the maximal exercise test was equivocal and coronary arterial lesions were present, the myocardial scan after exercise was abnormal. Thus, the myocardial scan with 201thallium after exercise was helpful in clarifying abnormalities in patients with equivocal maximal exercise tests. There were five falsely normal myocardial scans after exercise. It is important to note that the combination of both the myocardial scan after exercise and the maximal exercise test identified all but one patient with abnormal coronary arteriograms. Also, a normal myocardial scan obtained with 201thallium after exercise and a normal maximal exercise test virtually ruled out the presence of significant coronary arterial disease.

In an attempt to establish the determinants of an abnormal myocardial scan after exercise in patients with coronary arterial disease, the results were correlated with the resting electrocardiographic patterns. Of the 30 patients with an abnormal resting ECG, 29 had abnormal myocardial scans after exercise. Thus, the myocardial scan after exercise was more likely to be abnormal in patients when resting electrocardiographic abnormalities were present. Of the nine patients with a normal resting ECG, the myocardial scan after exercise was abnormal in five.

We also correlated the duration of the exercise-induced ischemic electrocardiographic changes with the findings on the myocardial scan after exercise (Table 3). It seemed possible that a brief period of ischemia might be missed by the scan, which took a considerable length of time to obtain, relative to the duration of ST-segment abnormality. In four of the five patients with normal myocardial scans after exercise, the resting ECG was normal, and the ischemic ST-segment abnormalities persisted for less than ten minutes. The fifth patient had ST-segment abnormalities at rest, with ventricular hypertrophy and equivocal changes during exercise. Of the 21 patients with abnormal maximal exercise tests, ischemic ST-segment changes persisted for more than ten minutes in 14 patients, and all of them had abnormal myocardial scans after exercise. In the seven patients in whom ST-segment abnormalities persisted for less than ten minutes, only three showed abnormal myocardial scans after exercise, and two of them had Q waves on the resting ECG. From these observations, it appears that the persistence of electrocardiographic abnormalities for more than ten minutes was of significant importance (P < 0.01) for an abnormal myocardial scan after exercise to occur in patients with normal resting ECGs. If the electrocardiographic changes lasted less than ten minutes and the resting ECG was normal, there was a greater probability of having a falsely normal myocardial scan after exercise.

Patterns of ventricular wall motion were also correlated with the myocardial scan obtained with 201thallium after exercise (Table 4). The left ventriculogram was abnormal in 21 of 39 patients with coronary arterial disease. The ventriculogram showed hypokinesia in 11 patients, akinesia in eight patients, and dyskinesia in two patients. All 21 patients had an abnormal myocardial scan after exercise. Areas of ventricular dysfunction correlated in all instances with the area of abnormalities on the myocardial scan after exercise. Although abnormal

### Table 2—Myocardial Scan with 201Thallium after Exercise and the Electrocardiographic Response to Exercise in Patients with Abnormal Coronary Arteriograms

| Maximal Exercise Test (ECG) | Myocardial Scan |  |
|-----------------------------|-----------------|--
|                             | Normal | Abnormal | Total |
| Normal                      | 0      | 2        | 2     |
| Abnormal                    | 4      | 17       | 21    |
| Equivocal                   | 1      | 15       | 16    |
| Total                       | 5      | 34       | 39    |

### Table 3—Duration of Exercise-Induced Changes in ECG and Myocardial Scan with 201Thallium after Exercise in Patients with Proven Coronary Arterial Disease and Abnormal Maximal Exercise Test

| Duration of Exercise-Induced ST-Segment Abnormality | Myocardial Scan |  |
|----------------------------------------------------|-----------------|--
| <10 min*                                           | 4               | 3 | 7  |
| >10 min*                                           | 0               | 14| 14 |
| Total                                              | 4               | 17| 21 |

*P < 0.01 (x² test).

### Table 4—Segmental Abnormalities on the Ventriculogram and Myocardial Scan with 201Thallium after Exercise in Patients with Coronary Arterial Disease

| Ventriculogram | Myocardial Scan |  |
|----------------|-----------------|--
| Normal         | 5               | 13| 18 |
| Abnormal       | 0*              | 21| 1  |
| Total          | 5               | 34| 39 |

*P < 0.05.
ventriculograms were always associated with abnormal myocardial scans after exercise (P < 0.05), the presence of a normal ventriculogram did not exclude the occurrence of an abnormal myocardial scan after exercise, since 13 of 18 patients with normal ventriculograms had such abnormal scans.

The extent of coronary arterial disease was also considered. Since the interpretation of the myocardial scan obtained with $^{201}$thallium after exercise depends upon focal defects in perfusion, it is possible that a cause for falsely normal myocardial scans after exercise could be related to the lack of focal lesions or the presence of equal coronary arterial narrowing in all three major coronary arteries. Our data tend to suggest this, since all ten patients with single-vessel disease had an abnormal myocardial scan after exercise, whereas the five patients with normal myocardial scans after exercise had two or more vessels involved and tended to have a relatively uniform degree of vascular involvement. The other 24 patients with abnormal myocardial scans after exercise had two-vessel or three-vessel disease; however, this difference was not statistically significant (P < 0.5). These five patients with normal myocardial scans also had normal ventriculograms and absent Q waves; four of them had a normal resting ECG.

In 17 of 55 patients, myocardial scans obtained with $^{201}$thallium at rest and after exercise were compared. Ten of the 17 were patients with proven coronary arterial disease; two had one-vessel disease, three had two-vessel disease, and five had three-vessel disease. The resting scan was abnormal in seven patients, and the myocardial scan after exercise showed an increase in the defect in perfusion in five patients and showed no change in two. In all three patients with a normal resting scan, the myocardial scan after exercise became abnormal. Six of the seven patients with an abnormal resting scan had Q waves on the ECG and an abnormality of segmented wall motion on the ventriculogram. In the remaining seven patients with normal coronary arteries, myocardial scans both at rest and after exercise were normal. The ECGs did not show Q waves, and the ventriculograms were normal. The number of coronary vessels involved did not seem to affect the presence of abnormalities on the myocardial scan obtained with $^{201}$thallium, either at rest or after exercise.

Figure 1 illustrates the development of an abnormal hypoperfused area that can be seen after exercise, but which was absent at rest. Thus, the study after exercise appears to be more sensitive in detecting the presence and extent of abnormalities in myocardial perfusion, since this study either expressed a new defect or exaggerated a previous one in ten cases.

Consideration of the relative sensitivity of the tests indicated that the maximal exercise test had a sensitivity of 40 percent and the myocardial scan after exercise a sensitivity of 86 percent. When the two tests were considered together, their sensitivity increased to 97 percent. The predictive accuracy of the tests in this highly selected group of patients indicated that the myocardial scan after exercise had a specificity of 100 percent, since we had no false-positive scans.

**Discussion**

One of the most challenging and frequent problems in clinical cardiology is the detection of the presence and extent of coronary arterial disease. The exercise ECG, specifically the graded maximal exercise test, appears to be an excellent method for screening but is also limited by equivocal and falsely positive and negative results. Its sensitivity and specificity are inversely related. The correlation of the maximal exercise test to coronary arteriographic findings depends upon the population studied. In asymptomatic individuals, an abnormal response of the ST segment to exercise will identify those with a higher risk of developing coronary events in the future. In symptomatic patients with heart disease, the predictive accuracy of the test increases considerably, but its sensitivity generally remains unchanged. The use of this method is even more

**Figure 1.** Myocardial scans obtained with $^{201}$thallium at rest and after exercise. At rest, myocardial image with $^{201}$thallium appears normal, but after exercise a significant decrease in uptake of isotope can be seen in inferior and septal region of left ventricle. ANT, Anterior; and LAO, left anterior oblique.
limited when it is necessary to evaluate patients with an abnormal ECG at rest or patients who are unable to discontinue cardiac drugs that can alter the results of the exercise ECG.

Recently, radionuclide imaging using potassium ion analog tracers has been suggested as an important adjunct to the noninvasive diagnosis of coronary arterial diseases. The initial distribution of these substances in the myocardium depends upon the regional flow of blood.\(^5\,\,10,\,11\) 201thallium is a metallic element with properties that closely resemble potassium in biologic systems.\(^12\) The half-life of 201thallium is 73 hours, and its physical properties make it suited for imaging with systems using a scintillation camera; however, its relatively long half-life precludes multiple serial examinations. Wackers and associates\(^5\) have shown the 201thallium scan, when performed at rest, is closely correlated to the presence of an acute transmural myocardial infarction when the scan is obtained within the first 24 hours of the event. Maseri and associates\(^6\) have demonstrated that defects in perfusion may develop quickly during spontaneous angina in patients with coronary arterial spasm.

Bailey and associates\(^7\) suggested an increase in the sensitivity of the test when the isotope is administered at peak exercise. Similar findings have been reported with radioactive 45potassium\(^10,\,13,\,14\) and 81rubidium.\(^15\) During exercise the decrease in the uptake of the isotope in areas that were adequately perfused at rest may be due to a number of different mechanisms. It is presumed that during exercise the disparity of flow to normal and abnormal tissue is exaggerated.

The relative sensitivity and specificity of this test during ischemia in our experience is in accord with previous reports.\(^7,\,10,\,16-18\) Although the sensitivity of the 201thallium scans increases when the injection is made at peak exercise, normal studies are also found in patients with significant coronary arterial disease. In this regard, the dynamics of the radiisotope when injected intravenously indicate that the initial distribution depends upon the regional flow of blood to the myocardium, and the final distribution tends to be proportional to the pool of potassium ions in the tissue, which reflects the total myocardial mass.\(^6\) It has been shown that the myocardial clearance is slower than the clearance from the blood and that the maximum ratio of the concentration in the heart to the concentration in the blood in the mouse is approximately 3:1 at ten minutes, 2:1 at 20 minutes, and 1:5 at 30 minutes.\(^11\) Based on this finding, it is possible that if the ischemia does not persist when the arterial concentration is still high, the initial regional differences in myocardial uptake may rapidly disappear because of the larger blood-tissue gradient of tracer in the ischemic area. If the ischemia is relatively more severe and lasts until the arterial concentration of 201thallium is reduced, the initial differences in distribution will persist for longer periods of time.\(^6\) Thus, it is possible that the duration of ST-segment depression and the defect in perfusion on the myocardial scan after exercise may be indicators of the severity of ischemia. Our clinical observations tend to support this concept in that most of the patients with an abnormal myocardial scan after exercise either had a defect in perfusion at rest or the ischemic event persisted for periods longer than ten minutes. We did not observe a normal myocardial scan after exercise in a patient with proven coronary arterial disease and electrocardiographic ischemic changes that lasted longer than ten minutes. Pohost and associates\(^19,\,20\) reported a significant redistribution of 201thallium within ischemic myocardium after experimental transient coronary occlusion. This fact is used to differentiate the transient ischemic from the infarcted myocardium and may explain the false-negative myocardial scans after exercise that were observed in our study.

It is also possible that the defect in perfusion may not be of significant size to be detected, since reports\(^21\) indicate that in animal models, a total of 5 gm of myocardium with a relative decrease in perfusion of more than 45 percent is required to show an abnormal scan. The scintillation camera also compresses the image of a three-dimensional object into a single-plane, and, thus, the activity contained in tissues overlying and underlying the region of interest are superimposed.\(^22\) Areas of uneven distribution are considered to represent regions of underperfusion. If the defect in perfusion is homogeneous, such as in patients with equal degrees of triple-vessel disease, the differential density of the scan used to interpret abnormality perhaps could be lost due to a homogeneous decrease in perfusion. The five patients with false-negative myocardial scans after exercise had disease that involved two or more vessels. All five patients had a normal left ventriculogram, an absence of significant Q waves, and exercise-induced ST-segment depression that persisted for less than ten minutes. The level of exercise at which the 201thallium is injected may also relate to the sensitivity of the scan obtained after exercise. It has been determined that submaximal exercise will have a lower yield than maximal exercise in uncovering areas of myocardial hypoperfusion.\(^23\) In our study using maximal exercise, it is unlikely that this factor played a role, since exercise was maximal in all patients.

The myocardial scan obtained with 201thallium

**Correlation of Exercise Scan, Arteriograms and Maximal Exercise Test**

CHEST, 73: 3, MARCH, 1978

Downloaded From: http://journal.publications.chestnet.org/pdfffacess.ashx?url=/data/journals/chest/21004/ on 06/27/2017
after exercise was particularly helpful in dealing with the clinical diagnosis of pain in the chest in patients with abnormal resting ECGs and when exercise ECGs were equivocal. The presence of a normal myocardial scan after exercise in the setting of an abnormal resting ECG excluded coronary arterial disease. This is helpful in excluding a large number of patients from the hazards, discomfort, and expense of needless coronary angiographic studies. It was somewhat disappointing that in the patients in whom diagnostic techniques are most needed (i.e., patients with normal resting ECGs), the myocardial scan after exercise was least helpful.

The major determinant of an abnormal myocardial scan after exercise appears to be the severity of ischemia, which is expressed either by a prolonged persistence of the ST-segment changes in a maximal exercise test or by evidence of a previous myocardial infarction. The number of vessels involved, by itself, did not seem to correlate with the severity of the ischemia.

Our studies support the concept that the myocardial scan obtained with 201thallium after exercise is an important adjunct to the diagnostic techniques used in identifying patients with coronary arterial disease. Our studies also indicate that in patients with normal ECGs without left ventricular dysfunction and with two or more vessels involved, the myocardial scan obtained with 201thallium after exercise is not particularly reliable in itself, but when it is coupled with a maximal exercise test, the two are highly sensitive indicators of coronary arterial disease.

REFERENCES
8 Robinson BF: Relation of heart rate and systolic blood pressure to the onset of pain in angina pectoris. Circulation 35:1073, 1967
22 Ter-Pogassian MM: Limitations of present radionuclide methods in the evaluation of myocardial ischemia and infarction. Circulation 53 (suppl 1):119, 1976