Differentiation of False- from True-Positive ECG Responses to Exercise Stress by Thallium 201 Perfusion Imaging

Timothy E. Guiney, M.D.;* Gerald M. Pohost, M.D.;*† Kenneth A. McKusick, M.D.; and George A. Beller, M.D., F.C.C.P.

It is well known that a positive ischemic ECG response to exercise stress in asymptomatic patients and patients with atypical chest pain may be nonspecific. The aim of this study was to determine the value of myocardial imaging using thallium 201 in differentiating between false-positive and true-positive ECG responses to exercise stress. Thirty-five patients referred for coronary angiography because of an exercise test interpreted as positive for ischemic ST segment changes (1.0 mm or more reversible horizontal or downsloping ST depression), but who were asymptomatic or had a history of atypical chest pain, underwent repeated exercise testing in conjunction with $^{201}$Tl$^+$ perfusion imaging. All patients received 1.5 mCi of $^{201}$Tl$^+$ at maximal exercise, and imaging began five minutes after exercise.

Stress electrocardiography has been widely used both in the assessment of patients with chest pain syndromes and as a routine screening procedure in asymptomatic populations. A number of recent studies have called attention to the high percentage of false-positive results when stress electrocardiography is compared with coronary angiography in an asymptomatic patient population or in patients with atypical chest pain. The predictive value of a positive ST segment response during exercise testing when considered in the absence of other information, such as chest pain, is largely dependent on the population under study.

Thallium 201 myocardial imaging in conjunction with exercise testing has been demonstrated to improve the predictive value of the ECG alone. Exercise-induced defects in $^{201}$Tl$^+$ uptake that fill in with $^{201}$Tl$^+$ activity over time seem to represent viable but underperfused or transiently ischemic myocardial segments. Persistent defects observed over a two- to four-hour postexercise period usually represent regions of irreversible cell damage consistent with infarction or scar. Certain persistent defects, particularly those not associated with pathologic E waves, revert to normal thallium uptake after coronary bypass graft surgery, suggesting that they might represent severe ischemia or a mixture of scar and hypoperfused but viable myocardium.

In the present study, we sought to determine if $^{201}$Tl$^+$ imaging could be used to differentiate false-positive from true-positive ECG responses to exercise stress. We have defined the false-positive exercise test as 1.0 mm or more of reversible horizontal or downsloping ST segment depression appearing with exercise but unaccompanied by either angina pectoris or demonstrable significant coronary stenoses at angiography.

MATERIALS AND METHODS

Criteria for Patient Selection

The study group was made up of 35 patients referred for coronary angiography by their physicians on the basis of an exercise test judged to be positive on the basis of ECG criteria alone. Twenty of the initial stress tests were performed in our laboratory and 15 at other institutions. These
patients were accumulated over an 18-month period. Approximately 2,000 patients were exercised in the laboratory during that time. The true prevalence of "false-positive" tests could not be estimated, since not all patients with a positive ischemic ECG response had catheterization. No patient had classic angina pectoris, and none reported angina during the initial stress test. Seventeen patients were men (mean age, 47 ± 9.8 [SD] years), and 18 were women (mean age, 54 ± 7.1 years). For each patient, a detailed history was obtained with particular emphasis on cardiovascular symptoms. Additionally, physical examinations were performed and resting ECGs obtained in all patients. Each of the 19 women and 12 of the men patients were judged to have atypical symptoms not suggestive of angina. Five men were asymptomatic. Each patient underwent another exercise test in conjunction with $^{201}$TI$^+$ imaging before angiography. No patient was taking propranolol, digitalis, or diuretics at the time of testing. Informed consent was obtained in each instance.

**Exercise Stress Methodology**

All patients were exercised on either a motorized treadmill using the Bruce protocol or on a bicycle ergometer. Bicycle ergometry was used for the first 18 patients for the repeated exercise test.

Bicycle exercise was of the continual type, with three-minute work periods of increasing loads of 300, 600, 900, and 1,200 KPM. The end point for both treadmill and bicycle exercise protocols was fatigue. The patients were urged to continue working until they felt they could no longer continue. These were "symptom limited" exercise tests, although in no case was the symptom angina pectoris. Specific heart rate targets were not used. Arterial blood pressure was recorded during each minute of exercise using a standard sphygmomanometer of the aneroid type. Twelve ECG leads (Viagraph, Denver) were recorded once per minute during treadmill exercise and during a five-minute recovery period in which the patient was supine. Leads 2, 3, aVF, and V₅ were recorded once per minute during the bicycle tests.

**Electrocardiographic Criteria**

The criterion of ECG positivity was one full millimeter of horizontal or downsloping ST depression beyond the abnormality observed at rest, if present.

**Myocardial Imaging Technique**

The sequential imaging protocol used in this study has been described previously. Briefly, a bolus of $^{201}$TI$^+$ chloride (1.5 mCi) was injected intravenously (IV) at maximal exercise via an indwelling IV catheter. The activity was flushed with a solution of 5 percent dextrose in water. The patient was then encouraged to continue exercising for another 30 sec. Within five to six minutes after $^{201}$TI$^+$ administration, the patient was positioned under a gamma camera (Ohio Nuclear, Cleveland) equipped with a parallel-hole, low-energy, all-purpose collimator. Images were obtained in the anterior, 50° and 70° left anterior oblique projections. This series of images was repeated at one hour and two to four hours after exercise. Imaging data from the first 20 patients were collected using a PDP-9 computer system and displayed on a 64 × 64 matrix interpolated to 128 × 128. With this system, uniform image intensity and contrast were maintained between initial and delayed images, using a high-sensitivity cadmium sulfide exposure meter equipped with a fiberoptics probe (Gossen Luna Pro, West Germany). Scintigraphic data from the remaining patients were processed and displayed using the VIP 45° imaging computer system (Ohio Nuclear, Cleveland). Image processing consisted of 20 percent background subtraction with this system. Hard copy from both display systems was obtained on both 35-mm celluloid film and Polaroid film.

All scintigrams were reviewed independently by each investigator, and when differences in interpretation occurred a consensus interpretation was derived for each series of images. Initial postexercise images were scored as either normal, ie, showing uniform myocardial $^{201}$TI$^+$ activity, or abnormal, ie, showing segmental defects in $^{201}$TI$^+$ uptake. If areas of decreased $^{201}$TI$^+$ uptake on initial postexercise images filled in with $^{201}$TI$^+$ activity on delayed rest images, then redistribution was noted to have occurred. Defects were designated as persistent if no $^{201}$TI$^+$ redistribution was visually apparent in the delayed images.

**Coronary Angiography**

Coronary cineangiography was carried out in each patient by either the Judkins or Sones technique. Each angiogram was analyzed by two investigators. A significant coronary stenosis was one in which the luminal diameter in two or more projections was reduced by 50 percent or greater. Differences in scoring were resolved by the interpretation of a third investigator.

**Results**

**Electrocardiographic Findings**

The resting ECG was entirely normal in 18 patients (14 men, four women). Minor nonspecific T wave abnormalities in the inferior or lateral leads ranging from slight flattening of the T waves to T wave inversion without ST depression were present in five men and 11 women. In one woman, ST segment depression of 2 mm was present at rest and increased to 5 mm with exercise.

**Heart Rate and Blood Pressure Responses to Exercise**

There were no significant differences in heart rates, blood pressures, or rate pressure products (HR × SBP/100) between the initial test and the test repeated for purposes of imaging. Observed maximum heart rates ranged from 120 to 180 beats/min (mean, 154.9 ± 3.05 SEM) in the initial test and from 120 to 185 (mean, 149 ± 3.27 SEM) in the subsequent test. When compared with maximum heart rates expected on the basis of age, they ranged from 66 to 109 percent (mean, 89.3 percent ± 1.8 SEM) on the first test and from 66 to 105 percent (mean 86.3 percent ± 1.9 SEM) on the later test.

Similarly, maximum systolic blood pressure levels ranged from 120 to 220 mm Hg (mean, 174.5 ± 4.4

CHEST, 80: 1, JULY, 1981

DIFERENTIATION OF ECG RESPONSES TO EXERCISE STRESS 5
SEM) initially and from 140 to 240 (mean, 181.3 ± 4.8 SEM) subsequently. Rate pressure products ranged from 144 to 385 (mean, 272.5 ± 8.9 SEM) and from 168 to 378 (mean, 269.4 ± 10.3 SEM). None of these values demonstrated any significant differences when compared by paired t testing. Because of the different exercise protocols used, the duration of exercise could not be compared.

**Imaging Data**

Of the 35 patients studied with positive ischemic ST segment responses, 24 (69 percent) had normal postexercise 201TI+ scans and 11 (31 percent) demonstrated segmental defects in thallium uptake on initial postexercise images, eight of which disclosed complete or partial redistribution on delayed images (Fig 1).

Of the 24 patients with normal stress 201TI+ scans, 23 had no significant coronary stenoses at angiography, while one patient had an 80 percent proximal narrowing of a short left anterior descending coronary artery. In this patient the distal left anterior descending vessel did not reach the apex, and perfusion to the apex appeared to be supplied by a very long posterior descending branch originating from a normal right coronary artery. This patient's exercise effort was believed to be adequate (heart rate rose to 130 beats/min, 86 percent of maximum, and blood pressure rose to 180/100 mm Hg in the course of 6.5 minutes of treadmill exercise). Of the 24 patients with no coronary artery disease, 15 were women (52.6 ± 7.6 years) and nine were men (47.7 ± 11.1 years).

Of the 11 patients with an abnormal postexercise scintigram, eight were found to have significant stenoses of one or more vessels and all eight showed evidence of 201TI+ redistribution on delayed scans. Three patients with scans interpreted as abnormal proved to have no significant coronary stenoses. Two of these, however, had lesser stenoses (30 to 40 percent) in each of two vessels but no vessel with 50 percent or greater narrowing of vessel diameter. The third patient had normal coronary arteries and prolapse of the posterior leaflet of the mitral valve. It is of note that the two patients with positive scans but lesser stenoses showed persistent defects in a distribution corresponding to their angiographically demonstrated disease. Figure 1 summarizes these data. The mean age of the nine patients with significant coronary artery disease (CAD) was not significantly different from the mean age of patients without CAD. Of the nine CAD patients with significant stenoses, seven were male and two were female (eight with positive scans and one with a negative scan). One woman was the only patient with significant disease not associated with a positive scan. Of the two patients with lesser stenoses, one was a man and the other woman. The prevalence of men was significantly greater in the group with CAD (P < 0.05) compared with the group with normal coronary arteries.

Figures 2A and B show the exercise ECG, postexercise and delayed 201TI+ images, and pertinent
frames from the coronary angiogram in a representative patient with a positive exercise ECG and normal coronary arteries.

As shown, this patient with angiographically normal coronary arteries had a false-positive ST segment response to exercise stress but a normal $^{201}$TI myocardial imaging study. Figures 3A and B show the exercise ECG, postexercise and delayed thallium images, and illustrative frames from the coronary angiogram in an asymptomatic patient with a positive ST segment response to exercise stress and significant CAD.

**Discussion**

Several criteria other than ST segment changes have been proposed to help distinguish between asymptomatic patients with true- and false-positive ECG responses to exercise. A lower maximum heart rate, a shorter duration of exercise, and prolonged duration of ST segment depression in recovery have been cited as providing some ability to better identify those patients with a true-positive test result.\(^7\) Change in amplitude of the R wave following exercise has recently been proposed as an index of exercise-induced left ventricular dysfunction, and by extension, suggests the presence of severe coronary disease.\(^8\) These criteria all are of potential value in differentiating true- from false-positive responses, but they are often more useful in characterizing groups than individuals. Thus, among the nine pa-
patients with significant CAD, seven exercised for eight minutes or more, and all but one achieved 85 percent of maximum heart rate predicted for age. Among the 26 patients without CAD or insignificant disease by angiography, 13 had "ischemic" ECG changes persisting for at least one minute into recovery. Five of the 13 patients had entirely normal resting ECGs. Hypertension, digitalis, and diuretics are well known to influence the ST segment response. Abnormalities in the resting tracing or labile repolarization changes with standing or hyperventilation have been reported in association with false-positive stress tests. In the present study, standing and posthyperventilation tracings were done voluntarily before the repeated test and had no predictive value. Two of the male patients with normal coronary arteries were hypertensive both at rest and with exercise and had exercise-induced ST segment abnormalities in the absence of digitalis and diuretics. R wave amplitude increased in one and decreased in the other. With these findings it is impossible to make a reasonable prediction that a given test is likely to be false-positive by virtue of hypertension when hypertension is a known risk factor for the development of coronary atherosclerosis.

While many patients with a typical chest pain can be evaluated on the basis of history alone, and many

---

**Figure 3A.** Rest and exercise ECG, initial and delayed postexercise $^{201}$TI$^+$ myocardial scintigrams and coronary angiographic findings in 50-year-old asymptomatic male patient. Marked ST segment depression observed in lead V$_5$ on the exercise ECG.

**Figure 3B.** Initial postexercise $^{201}$TI$^+$ scintigram in anterior view (left panel) demonstrates apical and inferior perfusion defects that fill in with $^{201}$TI$^+$ activity in delayed image (right panel). Selected frames from the coronary angiogram (below) show severe multivessel coronary artery disease.
others can be reassured on the basis of a normal exercise test result, there are patients with atypical or no symptoms who have an abnormal ECG response to exercise. Certain of these may be managed successfully on the basis of good clinical judgment, and some reassured on the basis of the non-ST-segment changes mentioned above. Often, however, the patient and the physician are dissatisfied with mere reassurance.

In patients with a history of typical angina, particularly males, standard ECG stress testing provides valuable confirmation of the presence of ischemia. Recent reports have also underlined the prognostic value of the duration of exercise with or without ischemic changes. However, in patients who are truly asymptomatic or in those with atypical symptoms, ECG stress testing has been shown to have a distressingly high percentage of false-positive results. Redwood et al have postulated that at least theoretically, populations may exist in which exercise testing would reveal more false-positives than true-positives. In three recent studies, which included subgroups of patients with ECG abnormalities on exercise but no history of angina and no anginal symptoms during exercise testing, between 33 and 54 percent had angiographically normal coronary arteries.

The results of the present study show that myocardial imaging after 201Tl+ administration at peak exercise can be used successfully to differentiate between the true- and false-positive ST segment response to exercise stress in the asymptomatic or atypically symptomatic patients. All 35 patients undergoing conventional treadmill or bicycle exercise testing in this study had unequivocally abnormal ECG changes characterized by 1 mm or greater horizontal or downsloping ST segment depression. All were either asymptomatic or had atypical chest pain. No patient related a history consistent with classic Heberden’s angina pectoris. Twenty-three of 28 patients with angiographically normal coronary arteries or stenoses of less than 50 percent of the diameter of the vessel in two or more projections had normal exercise 201Tl+ scans in association with an ischemic ECG response. On the other hand, eight of nine patients with greater than 50 percent stenosis of at least one coronary artery had exercise-induced defects on 201Tl+ initial images, which demonstrated redistribution on delayed rest images. Thus, for this group of patients the sensitivity of 201Tl+ imaging was 89 percent and the specificity was 88 percent yielding a predictive value of 73 percent. These values are comparable to those reported previously. Although the numbers in this study are relatively small, the predictive value of standard stress electrocardiography in the same group was 28 percent. Sensitivity and specificity for the exercise ECG are not meaningful in this context, since all patients had 1 mm or greater ST segment depression and there were no “negative” responders.

These data indicate that addition of 201Tl+ imaging to the ECG stress test offers the physician a noninvasive alternative to coronary arteriography to distinguish between true- and false-positive ST-segment responses. Of three patients with false-positive 201Tl+ scans, two had coronary artery disease with stenoses of 30 to 40 percent. Neither of these two patients showed redistribution of activity on delayed images, but had persisting defects. The explanation of this finding is presently not evident. Possible explanations might include underestimation of the degree of stenosis by angiography, previous small infarction with recanalization of a thrombus, possible exercise-induced spasm at the region of stenosis, or that these were false-positive scans.

The remaining patient without significant CAD in whom the scan was positive had totally normal coronary arteries. This patient demonstrated mitral valve prolapse. None of the remaining 34 patients had either echocardiographic or ventriculographic evidence of mitral prolapse. Mitral valve prolapse has been reported by some investigators occasionally to be associated with a false-positive 201Tl+ exercise scan. Other reports, however, have failed to find such correlation. Careful auscultation and echocardiography should identify patients with mitral valve prolapse before the 201Tl+ study. It must be remembered that mitral prolapse does not exclude concomitant coronary disease.

Only one patient with significant CAD had a normal exercise 201Tl+ scan. This patient had an 80 percent stenosis of a short left anterior descending coronary artery, and the entire left ventricular apex was supplied by an unusually long posterior descending coronary artery originating from the right coronary artery. The false-positive scan in the patient may have been related to a relatively small myocardial zone perfused by this vessel.

Other investigators have reported the clinical utility of myocardial imaging with 201Tl+ in conjunction with ECG exercise stress testing in patients with either suspected or CAD. In these studies, the sensitivity had specificity of thallium 201 perfusion imaging was found to be significantly greater in the detection of significant coronary artery stenosis than stress electrocardiography alone.

The results of the present study suggest a possible approach to some patients with atypical symptoms or with no symptoms who are found to have a positive stress ECG unaccompanied by typical angina.
nal-type chest pain. It is under these circumstances that the ischemic ECG response may be nonspecific. If the exercise test is repeated in conjunction with \(^{201}\text{Tl}^+\) imaging and the postexercise scintigrams reveal uniform myocardial uptake of the radionuclide, then the likelihood of significant CAD can be judged to be quite low. If the postexercise scintigrams reveal focal defects in \(^{201}\text{Tl}^+\) uptake with delayed redistribution, the likelihood of CAD is quite high. Patients showing only a focal persistent defect in thallium uptake with no delayed redistribution and no ECG evidence of prior myocardial infarction, may have false-positive scans.

In conclusion, this study demonstrates that myocardial perfusion imaging with thallium 201 is of considerable value in differentiating between true- and false-positive ST segment responses to exercise stress in asymptomatic patients or patients with atypical chest pain syndromes.

ACKNOWLEDGMENT: The authors are grateful for the technical assistance rendered by Mr. William H. Shea and the secretarial assistance of Ms. Nancy Durham.

REFERENCES

7 Lozner EC, Morganroth J. New criteria to enhance the predictability of coronary artery disease by exercise testing in asymptomatic subjects. Circulation 1977; 57:796-802
9 Kawai C, Hiltgren HN. The effect of digitalis upon the exercise electrocardiogram. Am Heart J 1964; 68:409-20

10 Guiney ET AL