Potassium-43 Myocardial Perfusion Scanning for the Noninvasive Evaluation of Patients with False-Positive Exercise Tests


SUMMARY

Twelve patients with false-positive ECG exercise tests presented with ischemic ECG responses (greater than one mm ST segment depression) during graded maximal treadmill exercise testing in the absence of exercise-induced chest pain or clinical coronary heart disease. Coronary arteriography, left ventriculography and hemodynamic evaluation revealed no significant abnormality in these patients. Transmyocardial lactate analysis during atrial pacing revealed a normal extraction (mean 21%) during pacing stress in five patients.

Nine of 12 patients were evaluated with exercise potassium-43 myocardial perfusion imaging whereby the radioactive tracer was administered intravenously during exercise at a time when abnormal ECG changes were present. Myocardial images in these nine patients all showed a normal homogeneous pattern of radioisotope distribution. These results are in direct contrast to findings in patients with coronary heart disease in whom reproducibly demonstrable abnormal regions of decreased potassium-43 accumulation have been noted in myocardial images obtained following injection of the radioactive tracer during exercise. Potassium-43 exercise myocardial perfusion scanning thus appears to be an accurate noninvasive method of assessing patients with suspected false-positive exercise tests and provides a means of increasing the specificity of exercise testing.

Additional Indexing Words:
Atrial pacing  Cardiac imaging  Maximal exercise tests  Radioisotope techniques

Rectilinear scanner

The appearance of abnormal ST segment depression during ECG monitoring of patients undergoing exercise stress tests has been traditionally equated with the presence of occlusive coronary atherosclerosis, transient myocardial ischemia, and shortened life expectancy.1-5 Recently, however, several comparative studies of the results of exercise testing and coronary arteriography have noted the occurrence of ischemic or "positive" exercise tests in patients with normal coronary arteriograms, raising the question of a relative lack of specificity of exercise electrocardiography.6-18 The frequency of "false-positive" exercise tests in the general population is presently undetermined, but it may be as high as 10% of patients undergoing complete cardiac evaluation.

In order to document the presence or absence of coronary atherosclerosis in subjects with ECG responses suggesting ischemia, coronary arteriography has been required. This procedure, which is costly and requires hospitalization, is not without risk. We have recently described an alternative, noninvasive approach for the evaluation of regional myocardial perfusion and the detection of myocardial ischemia.16,17 The technique utilizes precordial imaging following the intravenous injection...
during exercise of potassium-43 (\(^{43}K\)), a radioactive tracer which is rapidly extracted by the myocardium. This report describes 12 subjects with false-positive exercise tests and our experience with potassium-43 myocardial imaging in distinguishing these individuals from those with coronary heart disease.

Methods

Patient Selection

The 12 patients comprising this study were included among 70 patients undergoing both coronary arteriography and graded exercise testing at our institution from April 1971 to December 1972. Five were referred because of minor abnormalities in T wave configuration in a routine resting ECG. These changes were most frequently in the inferolateral leads and were labile. Five patients were referred for evaluation of chest pain which was clinically considered to be noncardiac by at least two experienced observers, and two were referred for a history suggestive of a paroxysmal arrhythmia. Five of the 12 were active duty military personnel on flying status, in whom it was critical to establish the presence or absence of coronary heart disease.

All were relatively young men with a mean age of 39 years (range 24–47 years) (table 1). At the time of evaluation, six of 12 were smoking at least 20 cigarettes per day. Five of 12 had a family history of coronary heart disease. Physical examination was normal in all 12. Seven of 12 demonstrated abnormalities in fasting serum lipids, while none exhibited abnormalities in glucose tolerance. Ten of 12 had normal resting 12 lead ECGs, while two exhibited minor nonspecific T wave abnormalities. There were no abnormalities of blood pressure, heart size or electrolytes. None had undergone treadmill exercise testing prior to the test which resulted in their inclusion in this study.

Exercise Testing

Maximal graded exercise testing was performed on a motorized treadmill in a standard fashion with increments in rate and incline occurring at three minute intervals. The initial rate was 1.7 mph at a grade of 10% with stepwise increases to a potential maximum of 6.0 mph at 20% grade during the final stage.\(^{18}\) ECG monitoring was constant, employing a four lead system with positioning of recording electrodes at standard positions V\(_4\) and V\(_1\), and over the xiphoid and suprasternal notches. Recording was accomplished each minute on an electrocardiograph machine conforming to American Heart Association recommendations for frequency response.\(^{19}\) Exercise was continued to the end point of severe fatigue, and was not terminated in the presence of abnormal ST segment changes. Blood pressure was recorded by auscultation in the control state, at the end of each three minute stage, and at the termination of exercise.

An abnormal response (positive exercise test) was defined as persistent flat or downsloping ST segment depression of 1 mm (0.1 mV) or greater for at least 0.06 sec during and/or immediately following exercise in a lead which had an isoelectric ST segment and upright T wave in the control tracing. A repeat exercise test, which duplicated the positive response noted initially, was performed in each patient prior to further study.

Laboratory Studies

Because of markedly abnormal ECG responses to exercise, selective coronary cineangiography was performed in all patients. Arteriograms were filmed at 60 frames/sec on 35 mm film using both the six and nine

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**Table 1**

Clinical Characteristics in Twelve Patients with False Positive Exercise Tests

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex/Age</th>
<th>Reason for referral</th>
<th>Rest ECG at time of evaluation</th>
<th>Family history of CHD</th>
<th>Cigarette smoking</th>
<th>Cholesterol mg%*</th>
<th>Triglyceride mg%†</th>
<th>Glucose tolerance(%)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>T.H.</td>
<td>M/45</td>
<td>Minor labile NSSTTWC</td>
<td>Normal</td>
<td>Positive</td>
<td>Yes</td>
<td>219</td>
<td>121</td>
<td>Normal</td>
</tr>
<tr>
<td>J.O.S.</td>
<td>M/39</td>
<td>Atyp chest pain</td>
<td>Normal</td>
<td>Negative</td>
<td>No</td>
<td>286</td>
<td>330</td>
<td>Normal</td>
</tr>
<tr>
<td>J.S.</td>
<td>M/24</td>
<td>Atyp chest pain</td>
<td>Normal</td>
<td>Negative</td>
<td>No</td>
<td>180</td>
<td>110</td>
<td>Normal</td>
</tr>
<tr>
<td>F.M.</td>
<td>M/37</td>
<td>Minor labile NSSTTWC</td>
<td>Normal</td>
<td>Positive</td>
<td>No</td>
<td>224</td>
<td>75</td>
<td>Normal</td>
</tr>
<tr>
<td>N.L.</td>
<td>M/34</td>
<td>Atyp chest pain</td>
<td>Normal</td>
<td>Negative</td>
<td>Yes</td>
<td>259</td>
<td>331</td>
<td>Normal</td>
</tr>
<tr>
<td>W.L.</td>
<td>M/42</td>
<td>VPBS</td>
<td>Normal</td>
<td>Negative</td>
<td>Yes</td>
<td>230</td>
<td>207</td>
<td>Normal</td>
</tr>
<tr>
<td>R.L.</td>
<td>M/39</td>
<td>Minor NSSTTWC</td>
<td>NSSTTWC, II, III, aVF</td>
<td>Negative</td>
<td>Yes</td>
<td>250</td>
<td>173</td>
<td>Normal</td>
</tr>
<tr>
<td>G.G.</td>
<td>M/47</td>
<td>Atyp chest pain, VPBS</td>
<td>Normal, VPBS</td>
<td>Positive</td>
<td>Yes</td>
<td>228</td>
<td>78</td>
<td>Normal</td>
</tr>
<tr>
<td>R.G.</td>
<td>M/31</td>
<td>? cardiac arrhythmia</td>
<td>Normal</td>
<td>Negative</td>
<td>No</td>
<td>237</td>
<td>139</td>
<td>Normal</td>
</tr>
<tr>
<td>J.B.</td>
<td>M/36</td>
<td>Atyp chest pain</td>
<td>NSSTTWC</td>
<td>Negative</td>
<td>No</td>
<td>336</td>
<td>112</td>
<td>Normal</td>
</tr>
<tr>
<td>R.S.</td>
<td>M/38</td>
<td>Labile NSSTTWC</td>
<td>Normal</td>
<td>Positive</td>
<td>No</td>
<td>240</td>
<td>125</td>
<td>Normal</td>
</tr>
<tr>
<td>G.A.</td>
<td>M/40</td>
<td>Labile NSSTTWC</td>
<td>Normal</td>
<td>Positive</td>
<td>No</td>
<td>183</td>
<td>206</td>
<td>Normal</td>
</tr>
</tbody>
</table>

*Cholesterol normal <250 mg %; †triglyceride normal < 150 mg %; ‡either three hour glucose tolerance or fasting and two hour postprandial determinations.

Abbreviations: CHD = coronary heart disease; M = male; NSSTTWC = nonspecific ST and T wave changes; VPBS = ventricular premature beats; Atyp = atypical.

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inch fields of a variable field image intensifier. Biplane left ventricular cineangiography was performed in all patients following the intracavitary injection of 45–60 cc of sodium and meglumine diatrizoate* over three seconds. Films were independently evaluated by three of the authors.

In five patients atrial pacing stress tests were accomplished in conjunction with transmural myocardial lactate analysis.20 Atrial pacing was performed with a bipolar pacing catheter positioned either in the right atrium or coronary sinus. A heart rate sufficient to induce 1.0 mm of flat ST segment depression was obtained in all patients tested. Simultaneous coronary sinus and brachial artery blood samples were obtained in duplicate in the resting state, at the close of a five minute pacing period, and ten minutes following pacing. Lactate analysis was performed spectrophotometrically using Sigma Company kit #826.21

Potassium-43 Myocardial Imaging

Nine of 12 patients were evaluated with 43K exercise myocardial imaging. This technique is a means of evaluating the presence, site, and extent of regional myocardial ischemia and has been shown to correlate well with coronary arteriographic abnormalities (fig. 1).21 The procedure is associated with a low incidence of false-negative results and no false-positive results to date. Briefly, subjects underwent graded maximal treadmill exercise to the end point of severe fatigue (or chest pain in patients with angina pectoris), at which time 0.5 to 0.1 mCi of 43K was injected intravenously. Exercise was continued for an additional 30–45 sec, allowing for relatively complete distribution of the radioactive tracer. The patient was then immediately transported to the adjacent scanning laboratory where myocardial imaging was accomplished with a rectilinear scanner (Picker Magnascanner 500). A five inch crystal with a 31 hole Picker Model 2112 collimator was employed. A 0.34-0.70 MeV window was chosen, since scanning at this broad window includes both major energy peaks of 43K and thus provides a greater count rate than could be obtained with either peak alone, yet is associated with a minimal increase in image degradation.17 Myocardial images were obtained at 1000 information density employing contrast enhancement (40–50 count rate differential). Duplicate images were obtained in both anterior and 40–50° left anterior oblique positions. The time from injection of 43K to the beginning of scanning was less than five minutes. ECG monitoring was halted for no more than two minutes during movement from one laboratory to another. An individual scan was obtained in from five to ten minutes.

Images were interpreted by two of the authors who were not present at the time of the exercise procedure and who were not aware of the clinical diagnosis or arteriographic findings if such were already available. The interpretation of these images was qualitative with an assessment made as to whether 43K activity within the visualized myocardium was homogeneous (normal), or whether regions of decreased activity were present (abnormal). Although visual interpretation of data is of necessity subjective, reproducibility of this technique has been established by repeated tests in six patients.16 Reproducibility of interpretation has also been demonstrated by an independent retrospective reinterpretation of 50 consecutive studies by three of the authors without patient identification; results were consistent both among the three viewers and with the previous interpretations.

Results

Exercise testing was considered unequivocally positive in all 12 patients (fig. 2). The positive ECG responses noted in lead V5 and/or V4 developed during and persisted following exercise in 11 patients, and occurred only immediately following exercise in one patient. The mean duration of exercise was 11 minutes (range 6–15 minutes), and the mean maximal heart rate achieved was 171 beats/min (range 150–188). The average duration of exercise at which a positive response was first recorded was six minutes (range

Figure 1

Potassium-43 myocardial perfusion scans in the anterior (ANT) and left anterior oblique (LAO) views obtained following injection of radioactive tracer during exercise to onset of angina pectoris in a patient with coronary heart disease. Note the large region of decreased potassium-43 accumulation in the anterior view in which the LAO view is seen to involve the posterolateral and inferior walls of the left ventricle as well as the proximal portion of the interventricular septum. Scans obtained in the resting pain-free state were normal. Coronary arteriography revealed three vessel obstructive disease with the most severe obstructive lesions involving the proximal circumflex and right coronary arteries. The V4 ECG lead at the time of potassium-43 injection is shown below.

*Hydralazine 75%
pain, a significant arrhythmia, or hypotension during exercise testing. Heart rate response to positional changes was normal (mean increase in heart rate from supine to upright position was 12 beats/min), and there were no ECG abnormalities associated with change in position.

Coronary arteriography demonstrated either an entirely normal coronary vascular tree (nine patients) or a single vessel with minimal irregularity of 20% or less of the luminal diameter (three patients) (fig. 3). Biplane left ventricular cineangiograms were likewise normal and in no instance demonstrated regions of dyssnergy or increased left ventricular wall thickness. Measurements of cardiac output (mean 3.3 L/min/m²) and left ventricular end diastolic pressures (mean 10 mm Hg) were also normal. A normal pattern of myocardial lactate extraction was noted in all five patients studied during atrial pacing (mean paced heart rate 165 beats/min with a range from 150–180 beats/min), the mean lactate extraction being 21% with a range of 7–40%.

All nine patients evaluated with exercise ⁴³K myocardial perfusion imaging demonstrated a normal homogeneous pattern of radioactive tracer distribution within the left ventricular wall (fig. 4, 5). This pattern—previously described in a series of 12 normal subjects—is suggestive of absence of obstructive coronary atherosclerosis. These results are in direct contrast to findings in an initial series of patients with positive exercise tests and angiographically proven coronary heart disease in whom reproducibly demonstrable abnormal regions of decreased radioactive tracer accumulation have been noted in the myocardial images obtained following injection of ⁴³K during exercise (fig. 1).¹⁶ We have to date increased our series to 50 patients with coronary heart disease and transient myocardial ischemia, and have noted only one false-negative and one equivocal exercise ⁴³K image. Of particular importance, two patients with coronary heart disease who were initially suspected of having false-positive ECG exercise tests, had exercise potassium-43 myocardial scans which were abnormal in the posterolateral left ventricular region (fig. 6). Subsequently, coronary arteriography demonstrated...

Figure 2

Typical false-positive exercise test (patient G.A.). Note the normal control tracing and the ischemic appearing ST segment depression which persists through nine minutes following exercise.
a single high grade proximal obstruction in the circumflex marginal coronary artery in both patients.

Our results appear to indicate that ischemic regions of decreased 42K accumulation are not obscured by overlying activity in normal myocardium. The contrast enhancement used probably contributes to ease of visualization of these abnormal areas. When only a single vessel demonstrates high grade obstruction, the left anterior oblique view is often most helpful. However, both anterior and left anterior oblique views are necessary for complete evaluation. Visualization of the inferior wall of the left ventricle is facilitated in the exercise image because of reduction in overlying hepatic activity secondary to redistribution of blood flow away from the splanchnic bed during exercise.16, 17 The central region of decreased radioactivity due to the left ventricular cavity is small and surrounded by a halo of uniform radioactivity within the myocardial wall. Centrally located cold areas which are the result of myocardial ischemia are larger and extend to the peripheral margin of the image in both the anterior and left anterior oblique views.

Discussion
The association of abnormal or positive exercise tests with clinical and preclinical coronary heart disease has been established. ST segment depression is the hallmark of the positive exercise test.1-5 The mechanism of this surface electrophysiologic event has not been completely defined, and may be due in part to neural and hormonal events or electrolyte shifts which occur regularly during myocardial hypoxia, but which may also occur under nonpathologic circumstances. With the recent widespread use of coronary arteriography, in fact, the less than ideal specificity of positive exercise tests has been appreciated.6-13 Although the occurrence of false-positive responses to exercise has been documented in several studies, little clinical detail concerning such patients has been

Figure 4
Myocardial perfusion scans in the anterior (ANT) and left anterior oblique (LAO) views obtained following injection of potassium-43 during exercise in a patient with a false-positive exercise test (Patient J.S.). Note the normal homogeneous pattern of radioisotope distribution in both views and a small central clear space corresponding anatomically to the left ventricular cavity. The ECG at the time of tracer injection is below.

Figure 5
Anterior (ANT) and left anterior oblique (LAO) exercise myocardial perfusion scans in another patient (G.A.) with a false-positive exercise test. Note again the normal homogeneous potassium-43 myocardial distribution. The ECG at the time of tracer injection is below.

Figure 3
Left coronary arteriogram in a 30 degree right anterior oblique projection, 6 inch field (top) and right coronary arteriogram in an anterior projection, 9 inch field (bottom) in a patient with a false-positive exercise test (Patient J.S.). Note the normal coronary arteriographic pattern.
Figure 6
Anterior (ANT) and left anterior oblique (LAO) myocardial scans obtained following injection of potassium-43 during exercise in a patient initially suspected of having a false-positive ECG response to exercise. He was subsequently demonstrated to have a high grade proximal stenosis of a large circumflex marginal coronary artery. The patient experienced no chest pain during the exercise test; the exercise ECG at the time of tracer injection is shown below. Note a region of relatively decreased potassium-43 concentration at the lateral border of the anterior image. In the LAO view this region is seen to involve the posterolateral wall of the left ventricle.

available. The 12 patients in this report all presented with unequivocally positive ECG exercise tests; yet their age, exercise capability, lack of exercise-induced chest pain, and relative lack of high risk factors did not favor the unequivocal clinical diagnosis of coronary heart disease. Cardiac catheterization and coronary arteriography in multiple projections demonstrated the absence of significant coronary atherosclerosis or left ventricular dysfunction, and there was no evidence of myocardial ischemia by lactate analysis. Thus, the ECG responses to exercise of the subjects in this report appear to represent true false-positive results.

The absence of myocardial lactate production during pacing stress and the absence of exercise-induced chest pain differentiate these patients from those with "angina and normal coronary arteries" described by others. Likewise, the absence of marked posturally-related heart rate changes and ECG responses distinguish our patients from those described by Friesinger et al. in whom the false-positive exercise tests and other ECG changes were ascribed to "vasoregulatory abnormalities."25

Even though the clinical suspicion of coronary heart disease was very low in our patients, asymptomatic ischemic heart disease could not be excluded and, in fact, was present in two patients presenting with a similar clinical pattern. Potassium-43 exercise myocardial perfusion scanning proved to be accurate in excluding the diagnosis of coronary heart disease in patients with false-positive exercise tests. In none of these subjects was an abnormal scan noted; this is in direct contrast to our results in patients with coronary heart disease and angina pectoris, as well as our results in two asymptomatic patients with positive exercise tests and angiographically proven coronary atherosclerosis.

This noninvasive technique is safe, easy to perform, and reproducible. A quantitative approach to this as yet qualitative technique would be desirable. This will require use of the scintillation camera with modification of currently available collimation in order to reduce the loss of resolution associated with imaging of a high energy tracer such as K with this instrument. Our current imaging instrument, the rectilinear scanner, is the simplest of currently available scanning instruments and is available in most hospitals. The radionuclide is available commercially, and the radiation dose is well within accepted limits. It would thus seem appropriate to employ potassium-43 myocardial imaging as described in the screening of patients with positive ECG exercise tests, but otherwise little suspicion of coronary heart disease. We believe that in this manner a significant increase in the specificity of exercise testing can be achieved.

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