Maximum Treadmill Exercise Test in Patients with Abnormal Control Electrocardiograms

By Joseph W. Linhart, M.D. and Howard B. Turnoff, M.D.

SUMMARY
To determine the validity and safety of exercise induced ST changes (1 mm ischemic depression or further depression in ECG lead V5) as an indication of coronary artery disease (CAD) in patients with abnormal control electrocardiograms (ECG), 121 such patients were compared to 87 patients with a normal control ECG. All underwent a maximum graded treadmill exercise test and coronary arteriography. Among those patients with normal control ECGs, there were no false positives and five false negatives (sensitivity-85%, specificity-100%). In 61 patients with abnormal ECG (no drug therapy except nitrates) there were four false positives and nine false negatives (sensitivity-76%, specificity-79%). In this group of patients T waves reverted from negative to positive in four patients with CAD and 10 patients with no CAD, but T inversion during exercise only occurred in those with CAD (6 patients). Three of 12 patients (25%) with ECG evidence of old infarction and four of eight with single vessel disease had false negative tests. In 60 patients with abnormal ECG on drug therapy there were 10 false positives (17%) and 15 false negatives (sensitivity-55%, specificity-63%). Not helpful in differentiation were resting T vs ST changes, induction of arrhythmias or exercise induced chest pain.

The validity of exercise induced ST changes in differentiating CAD is excellent when the control ECG is normal and is only slightly reduced with control ST-T wave abnormalities. When the latter occur in association with cardiovascular drug therapy, other than nitrates, the exercise ECG is of no use in differential diagnosis although still valid and safe for the determination of exercise tolerance.

Additional Indexing Words:
ST segment depression  Coronary arteriography  Coronary artery disease

The recent tendency in exercise testing has been to determine a patient’s maximal exercise capacity through graded increases in work load.1-4 This permits a measurement of maximum oxygen intake (VO2 max), the international standard for physical fitness,5 and the stress applied is usually sufficient to separate the normal from the abnormal in terms of myocardial ischemia. Little information is available regarding the value and safety of this technique in patients with abnormal control electrocardiograms. This report documents our experience in such patients in whom the status of the coronary arteries was determined by coronary arteriography.

Methods
One hundred and seventy-eight patients having both maximum graded treadmill exercise tests and coronary cineangiographic studies were evaluated. They were divided into three groups. Group I—normal resting electrocardiogram (50 males, 7 females; average age 49.5 years). The patients in this group without coronary artery disease had atypical chest pain without evidence of any other disease entity. Group II—abnormal resting electrocardiogram and no drug therapy except for nitroglycerin (49 males, 12 females; average age 48.3 years). The patients without coronary artery disease were similar to those in group I except that they had isolated nonspecific ST-T wave abnormalities. Careful evaluation disclosed no definite etiology for these changes. Group III—Abnormal resting electrocardiogram plus various cardiovascular drugs (39 males, 21 females; average age 46.9 years). Resting electrocardiographic abnormalities included previous myocardial infarction, left ventricular hypertrophy (voltage and ST-T changes), right and left bundle branch block, T wave flattening or inversion and ST segment depression of 0.5 mm or more. These patients had no electrolyte abnormalities, anemia, valvular heart disease, pericardial or myocardial disease or any known factor other than those mentioned which might influence the resting electrocardiogram. Most patients were considered to have "nonspecific" ST-T wave changes.

After complete clinical examination and informed written consent was obtained, a multistage treadmill test of maximum exercise was performed according to
the protocol described by Bruce and his associates.1–4
The patients were studied several hours postprandially and they had neither smoked nor taken nitroglycerin in the preceding three hours. The test began with the subject walking at 1.7 mph on a 10% grade with the speed and grade increased every three minutes according to the following protocol.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Speed</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.7</td>
<td>10%</td>
</tr>
<tr>
<td>2</td>
<td>2.5</td>
<td>12%</td>
</tr>
<tr>
<td>3</td>
<td>3.4</td>
<td>14%</td>
</tr>
<tr>
<td>4</td>
<td>4.2</td>
<td>16%</td>
</tr>
<tr>
<td>5</td>
<td>5.0</td>
<td>18%</td>
</tr>
<tr>
<td>6</td>
<td>5.5</td>
<td>20%</td>
</tr>
</tbody>
</table>

Testing was done with constant ECG and blood pressure (clinical sphygmomanometer) monitoring and under medical supervision. The ECG lead system employed a negative lead over the manubrium and the positive lead at the V5 position. The patients were not permitted to hold onto a hand rail, but only to rest one or two fingers of one hand on the rail, if necessary, to maintain a fixed position on the treadmill. The end point for exercise was determined by the patient when severe dyspnea, fatigue, angina, claudication, dizziness, etc. occurred. In addition, the medical supervisor could terminate the procedure if ataxic gait, arrhythmia, ST depression of 5 mm or more, or hypotension was noted. The electrocardiogram was recorded with the patient seated and standing prior to exercise, every minute during exercise, and standing and seated immediately at the end of exercise. The patients were monitored closely after the exercise period for 10 minutes with electrocardiographic recordings every two minutes.

Within the boundaries of patients’ safety an attempt was made to reach each patient’s maximum exercise level. A stop watch was used to measure the duration of exercise and this was compared to standard values related to body weight, sex, age and ordinary level of activity to determine each patient’s functional aerobic impairment.1

The exercise electrocardiogram was scrutinized for changes in QRS and T wave morphology, conduction disorders, arrhythmias and ST segment depression or elevation. J junctional changes alone, with upward sloping ST segments, were considered as normal responses.6 Ischemic or positive changes were interpreted as horizontal or downward sloping ST segments of at least 1 mm depression below the corresponding PR segment measured at the point .06 sec after the QRS complex.6 In patients with depressed ST segments in the resting tracing a further depression of at least 1 mm was considered as an abnormal response to exercise stress.

Cardiac catheterization with coronary cineangiography was carried out by standard techniques. Multiple coronary artery injections with many projections were used and each film was interpreted by at least two observers. The number of diseased coronary arteries was determined in each patient with significant disease considered to coincide with an obstruction of 50% or more. The extent of angiographic coronary artery disease was compared to each patient’s treadmill exercise response.

Results

There were no differences between the groups with regard to age, maximum heart rate achieved during exercise or the average functional aerobic impairment (FAI) as determined by nomogram.1 Maximum heart rate was greater in those patients in whom exercise was discontinued because of fatigue rather than angina, but the rates were also similar in each group (see table 1).

**Group I**

Thirty-four of these 57 patients had significant coronary artery disease (CAD). There were no false positive tests and 5 false negative responses (see table 2). All the latter had at least 50% occlusion of the left anterior descending coronary artery (LAD) with two patients having disease of three vessels, two having disease of two vessels, and one having disease of a single vessel. The percent occlusion for each main coronary artery in the 5 false negative patients were as follows:

<table>
<thead>
<tr>
<th>Patient</th>
<th>Right</th>
<th>Descending</th>
<th>Circumflex</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>80</td>
<td>50</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>85</td>
<td>55</td>
<td>55</td>
</tr>
<tr>
<td>3</td>
<td>75</td>
<td>85</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>70</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>60</td>
<td>0</td>
</tr>
</tbody>
</table>

In one patient (number 1) the negative result may be accounted for by inadequate stress as his heart rate reached only 81 beats/min. The average rate in the other four patients was 158 beats/min. Two patients with CAD had positive tests with only 50 to 60% obstruction in their right and left circumflex coronary arteries, respectively. Two patients with CAD had exercise induced ventricular premature contractions.

**Group II**

Thirty-seven of 61 patients had CAD. Resting

| Table 1 |

<table>
<thead>
<tr>
<th>Results of Exercise Tests</th>
<th>Pts</th>
<th>Ex HR</th>
<th>HR angina</th>
<th>No angina</th>
<th>FAI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>57</td>
<td>142</td>
<td>144</td>
<td>150</td>
<td>20.3%</td>
</tr>
<tr>
<td>Group II</td>
<td>61</td>
<td>146</td>
<td>134</td>
<td>159</td>
<td>19.8%</td>
</tr>
<tr>
<td>Group III</td>
<td>60</td>
<td>144</td>
<td>131</td>
<td>152</td>
<td>17.3%</td>
</tr>
</tbody>
</table>

Abbreviations: Ex HR = mean maximum heart rate in beats/min during exercise; HR angina = mean maximum heart rate when angina necessitated discontinuing exercise; No angina = exercise discontinued due to fatigue; FAI = functional aerobic impairment.

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electrocardiographic abnormalities in patients with no CAD included one with right bundle branch block, 21 with nonspecific ST-T changes and two with left ventricular hypertrophy (LVH) by voltage and ST-T changes. In patients with CAD two had LVH, three had right bundle branch block, 12 had a previous myocardial infarction and 20 had nonspecific ST-T abnormalities. There were 4 false positive and 9 false negative tests. Of the latter, 4 had disease of a single vessel (3-LAD), one had disease of two vessels and four had disease of three vessels. Four of 8 (50%) with single, one of 10 (10%) with double and 4 of 18 (22%) with triple vessel disease had false negative tests. The presence of only resting T, only ST or a combination of ST and T wave changes did not influence the incidence of false positive or negative responses in those either with or without CAD. Three patients of 12 (25%) with electrocardiographic evidence of old myocardial infarction had negative tests. One of four patients with left ventricular hypertrophy (25%) had a false negative result. In 14 patients reversal of T wave polarity occurred (negative to positive) and ten of these patients had no coronary artery disease. All six patients in whom the T waves became inverted with exercise had CAD. Except for one patient, in whom they returned to normal levels, resting ST abnormalities always became further depressed during exercise. One patient with CAD and two with no CAD had exercise induced ventricular premature contractions.

**Group III**

Coronary artery disease was present in 33 of 60 patients. Ten patients had false positive and 15 false negative studies. Five patients with an old myocardial infarction on electrocardiogram had negative results. Although this could reflect true lack of ischemia secondary to scar formation after infarction, all of these patients had disease of more than one vessel and clinically, hemodynamically and angiographically they had evidence and were studied because of myocardial ischemia. T wave reversal (negative to positive) occurred in 10 patients with CAD and 14 patients with no CAD. The T waves became negative in 9 patients, 7 of whom had CAD. False positive or negative results occurred with various drugs as follows: One false positive out of 3 patients on, digoxin, one false positive out of 7 on propranolol, one false positive and one false negative out of 6 on a diuretic, one false positive and five false negative out of 13 patients on phenothiazines, 0 out of 4 on quinidine, one false positive out of 1 on aldotrem, and 5 false positives and 9 false negatives out of 26 patients on various combinations of these drugs. Exercise induced ventricular premature contractions in 8 of these patients, 3 of whom had no CAD.

There was no correlation between the extent of ST segment depression in these patients and the degree of coronary artery disease. When all of the patients with CAD are considered, the extent of ST depression was 2.0 mm for single, 2.5 mm for double and 2.3 mm for triple vessel disease.

Ventricular premature contractions (in all groups) occurred in 5 of 74 (7%) patients with no CAD and in 8 of 104 (8%) patients with CAD.

Table 2 also shows the sensitivity and specificity of the exercise studies in each group. These results were compared statistically to four other studies which used submaximal exercise protocols. The increased specificity in our group I patients was significant (P < .01) but no increased sensitivity was apparent. The results in our group II patients with abnormal resting electrocardiograms was similar to the results in these same studies which primarily involved patients with normal but also some with abnormal control electrocardiograms.

### Table 2

<table>
<thead>
<tr>
<th></th>
<th>Pts</th>
<th>CAD</th>
<th>True POS</th>
<th>False NEG</th>
<th>SENS</th>
<th>No CAD</th>
<th>True NEG</th>
<th>False POS</th>
<th>SPEC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>57</td>
<td>34</td>
<td>29</td>
<td>5</td>
<td>85</td>
<td>23</td>
<td>23</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Group II</td>
<td>61</td>
<td>37</td>
<td>28</td>
<td>9</td>
<td>76</td>
<td>24</td>
<td>19</td>
<td>4</td>
<td>79</td>
</tr>
<tr>
<td>Group III</td>
<td>60</td>
<td>33</td>
<td>18</td>
<td>15</td>
<td>55</td>
<td>27</td>
<td>17</td>
<td>10</td>
<td>63</td>
</tr>
</tbody>
</table>

Abbreviations: Pts = patients; CAD = pts with coronary artery disease; POS = positive and NEG = negative exercise tests; SENS = sensitivity (9) = no. of true positives + (no. of true positives + no. of false positives) × 100; SPEC = specificity (9) = no. of true negatives + (no. of true negatives + no. of false positives) × 100.
Discussion

The exercise electrocardiogram is a valuable noninvasive technique for aiding in the clinical diagnosis of myocardial ischemia. This is especially true with the newer protocols due to higher levels of exercise stress. Various reports have appeared confirming the sensitivity, specificity and above all the relative safety of this procedure. Most of these studies, though, were based on patients with essentially normal control electrocardiograms as it was considered dangerous to exercise in the face of electrocardiographic abnormalities or it was believed that no additional information could be elucidated. When some patients with abnormal resting electrocardiograms were included later, a separate analysis or correlations with coronary arteriography was not always available.

Roitman et al. have recently reported on submaximal exercise test and angiographic correlations in 100 patients, 49 of whom had various QRS and/or ST-T wave abnormalities. A good correlation between test results and angiography was noted in patients with no resting electrocardiographic abnormalities or clinical or pharmacological factors other than coronary artery disease known to affect the electrocardiogram. However, in their patients with left ventricular hypertrophy, aortic valve disease, mitral valvular regurgitation, systemic hypertension, digitalis therapy or ST changes at rest the development of “ischemic” ST changes with exercise was of no help in diagnosing coronary artery disease.

Subsequently, Cohn et al. also reported on the response of a similar group of patients with resting ST-T abnormalities (on no drug therapy) to a submaximal form of exercise, the double Master’s two-step test. Their criteria differed somewhat from others as they considered 0.5 mm ST depression or any further ST depression of at least 0.5 mm as representing a positive ischemic response. A negative response was an ST change of lesser degree with a heart rate of at least 110 beats/min. They found that the presence of any pre-existing electrocardiographic abnormality did not influence either the frequency or the severity of positive responses and therefore the two-step test was safe and of clinical value in patients with chest pain and abnormal control electrocardiograms. Our study extends this conclusion to patients undergoing maximum exercise tests, but additionally discloses that concomitant drug therapy essentially invalidates the usual interpretation.

Many factors other than coronary artery disease with myocardial ischemia may cause ST segment changes in the resting and/or the exercise electrocardiogram. Digitalis, even with a normal resting tracing, may cause false positive exercise results. Also, right and left bundle branch block, left ventricular hypertrophy, rheumatic heart disease, hypokalemia, Wolff-Parkinson-White syndrome, autonomic disorders, meals, smoking and various pharmacologic agents may distort the electrocardiographic response to exercise. This study has shown, however, that using a maximum graded treadmill exercise protocol, the exercise electrocardiogram is still of value in patients with resting abnormalities in the absence of drug therapy. An increase of 1 mm horizontal or downsloping ST segment depression over the abnormal control value was indicative of a positive ischemic response (fig. 1). Since our study included only those patients with coronary artery disease or with chest pain in whom only coronary artery disease was suspected, these conclusions are only valid under those circumstances. This includes the majority of patients that we study but may not be correct in patients with other forms of cardiac disease.

The protocol was safe for patients with various electrocardiographic abnormalities including previous myocardial infarction after three months (fig. 2). Eleven patients of 121 with resting abnormalities did develop some ventricular premature contractions during or after exercise, but in no instance did arrhythmia or other complication necessitate interruption of exercise. Despite the use of maximum stress it was impossible to separate patients with coronary artery disease from those without this disease when electrocardiographic abnormalities were associated with concomitant drug therapy. Forty-two percent of these patients had either false
positive or false negative tests based on coronary arteriographic correlation. Although, under these circumstances, ST changes are not valid for diagnosing the presence or absence of coronary artery disease, a maximum treadmill test may still be valid for measuring the patient's physical performance capacity. In this manner, electrocardiographic changes excepted, exercise performance may be evaluated before and after surgical or medical intervention.

It has been shown that only ST changes during and after exercise have predictive value regarding coronary artery disease.\(^6\),\(^3\) Isolated T wave negativity is of no predictive use.\(^6\) However, there has been some speculation that "paradoxical" reversal of T wave polarity with exercise means coronary artery disease with myocardial ischemia.\(^3\) This was not confirmed by our patients (group II) where reversal of negative T waves occurred ten of fourteen times in patients with normal coronary arteries and no other cause for myocardial ischemia (fig. 3).

Ventricular premature contractions were induced by exercise in 13 of our 178 patients (7%) with no difference in incidence between those with and those without coronary artery disease. This incidence is similar to other studies that used submaximal exercise and confirms and extends the belief that this arrhythmia alone cannot be used as a criterion for a positive (ischemic) exercise test.\(^3\) However, ventricular arrhythmias developing during exercise in patients with known coronary artery disease represent an ominous sign, as these patients generally have severe coronary as well as significant myocardial disease.\(^3\)

It is generally believed that greater degrees of ST segment depression occur with progressive increases in coronary artery disease and that most false negative exercise studies (with sufficient stress) occur with single right or left circumflex artery obstruction.\(^22\),\(^3\) Neither of these concepts were confirmed in our maximum exercise study either in patients with resting normal or abnormal electrocardiograms. The same average extent of ST segment depression occurred with disease of one, two, or three vessels in this study. All five of our false negative patients with normal resting electrocardiograms had significant obstruction of the left anterior descending coronary artery; two had disease of two vessels and two had disease of three vessels.

This study has shown that maximum treadmill exercise studies are feasible and safe in patients with abnormal resting electrocardiograms including patients studied at least three months following an acute myocardial infarction. The specificity of the exercise electrocardiogram (table 2) in our patients with normal resting electrocardiograms was even better and the sensitivity as good as in some other reports.\(^10\),\(^36\)-\(^38\) probably because we employed a maximum stress test. In our patients with abnormal resting tracings, on no drugs except for nitroglycerin, the correlation with other studies was also good.\(^10\),\(^22\),\(^36\)-\(^38\) indicating the validity of this exercise protocol in these subjects. However, when in addition to an abnormal resting electrocardiogram, the patient is taking various frequently used cardiovascular medications the exercise electrocardiogram is of no use in differential diagnosis.

References


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