Maximum Treadmill Exercise Electrocardiography in Female Patients

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SUMMARY
Exercise testing has become standardized for the diagnostic and functional evaluation of male patients but little data is available regarding its specificity and sensitivity in the female. Therefore, maximum treadmill exercise (Bruce protocol) was performed on 98 consecutive females and compared to coronary arteriography. Using 50% obstruction as indicating coronary artery disease and 1 mm ST-segment depression (horizontal or downsloping) as positive for ischemia, 24 patients had coronary artery disease with seven false-negative results (sensitivity = 71%) and 74 patients had no coronary artery disease with 16 false-positive responses (specificity = 78%).

Five of seven false-negative tests were in patients with single-vessel disease. Eleven of 16 false-positive responses were in patients on digitalis, diazepam, or methyldopa. In 39 patients on no drug therapy except for nitroglycerin there were no false negatives and only four false-positive tests. There were no false negatives and only two false-positive tests in 34 patients with normal resting electrocardiograms. Only one of 18 patients with both normal resting electrocardiograms and on no drug therapy had a false-positive test result. Eleven false-positive and seven false-negative results occurred in 40 patients with both an abnormal resting electrocardiogram and associated drug therapy.

The exercise electrocardiographic response in female patients is similar to the male when patients with resting electrocardiographic abnormalities and concomitant drug therapy are eliminated.

Additional Indexing Words:
Functional aerobic impairment (FAI)
Digitalis
ST segment
Coronary arteriography
Coronary artery disease
Angina pectoris

ALTHOUGH EXERCISE TESTING has become a standard technique for diagnostic and functional evaluation of patients, little information is available regarding its specificity and sensitivity in the female. Some studies have indicated that women are more likely to have electrocardiographic abnormalities during exercise testing in the absence of coronary artery disease and that segmental ST-segment depression is, therefore, less specific. Nevertheless, a review of some recent exercise investigations discloses that the large majority of studies were performed on men (7268 men as compared to 935 women) and/or no distinction was made between the male and female electrocardiographic response to stress.

In order to help answer this question, the present investigation was performed on 98 consecutive female patients who had both a graded maximum treadmill exercise test and coronary arteriography. The results form the substance of our report.

Methods

Ninety-eight consecutive female patients who had undergone both maximum graded treadmill exercise tests and coronary cineangiographic studies were evaluated. Their average age was 46 years, with a range of 18 to 66 years. Most (89 patients) were being investigated for chest pain which varied from highly atypical to true angina pectoris. The exercise tolerance test was used to confirm or deny the presence of ischemic heart disease. Cardiac catheterization and coronary angiography were performed to define the status of the coronary circulation and myocardial function. The other nine subjects were exercised because of dyspnea, fatigue, or an abnormal resting electrocardiogram. Two patients were mildly hypertensive and were receiving methyldopa therapy. No other forms of cardiovascular disease were present in any other patient.

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. The patients were studied several hours postprandially, and they had neither smoked a cigarette nor taken nitroglycerin in the preceding three hours. Fifty-seven patients had been receiving various cardiovascular and/or tranquilizer medications (see below), which had not been discontinued prior to the test. The stress began with the subject walking at 1.7 mph on a 10% grade
with the speed and grade changed every 3 min 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 under 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. Although multiple lead monitoring may increase sensitivity (approximately 5%), we elected to use the most commonly used, practical, clinically evaluated single lead system. 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, or dizziness 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 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 min with electrocardiographic recordings every 2 min.

Within the boundaries of patient safety an attempt was made to reach each patient's maximum exercise performance. 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.

The exercise electrocardiogram was scrutinized for changes in QRS and T wave morphology, ST-segment depression, or elevation, arrhythmias or conduction disorders. "J" junctional changes alone, with upward sloping ST segments, were considered as normal responses. Ischemic or positive changes were interpreted as horizontal or downward sloping ST segments of at least 1 mm depression below the preceding P-R segment measured .06 seconds after the end of the QRS complex. 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 (fig. 1).

Cardiac catheterization with coronary cineangiography was carried out by standard techniques. Multiple coronary artery injections with several 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 in two views. The extent of angiographic coronary artery disease was compared to each patient's treadmill exercise response.

Results

General

Twenty-four of the patients had significant angiographically proven coronary artery disease (CAD) and 74 did not. Although both groups had similar resting heart rates, the average maximum heart rate during exercise in patients with CAD was 138 ± 4 SEM/min while in those with no CAD it was 157 ± 2 (P = 0.001) (table 1). The FAI was greater in those with CAD (18 ± 5.5%) than in those without CAD (6 ± 2.8%) (P = 0.05). The exercise duration averaged 349 seconds in those with CAD and 411 seconds in those patients without CAD.

Table 2 lists the electrocardiographic response in comparison to coronary arteriography. There were seven false-negative responses in the CAD group and 16 false-positive responses in patients without CAD. This resulted in a sensitivity of 71% and a specificity of 78%.

In 39 patients on no drug therapy except for nitroglycerin (normal and abnormal ECG) there were no false-negative and only four false-positive tests (table 3). There were no false-negative and only two false-positive tests in patients with normal resting electrocardiograms (on or off drugs). One of 18 patients with both a normal resting electrocardiogram and on no drug therapy had a false-positive test result while two of 19 patients with an abnormal resting electrocardiogram and no drug therapy had false-positive tests. Patients with both abnormal resting electrocardiograms and drug therapy had 11 false-positive and seven false-negative results.

<table>
<thead>
<tr>
<th>Table 1</th>
</tr>
</thead>
</table>

**Exercise Testing in Female Patients**

<table>
<thead>
<tr>
<th></th>
<th>Heart rate</th>
<th>FAI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAD</td>
<td>Resting</td>
<td>94 ± 4</td>
</tr>
<tr>
<td>(24)</td>
<td>Exercise</td>
<td>138 ± 4</td>
</tr>
<tr>
<td>No CAD</td>
<td>Resting</td>
<td>95 ± 4</td>
</tr>
<tr>
<td>(74)</td>
<td>Exercise</td>
<td>157 ± 2</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± standard error of the mean.

Abbreviations: CAD = patients with coronary artery disease; FAI = functional aerobic impairment; ( ) = number of patients.
Circulation, Volume 50, December 1974

Table 2

Exercise Electrocardiographic Responses in Female Patients

<table>
<thead>
<tr>
<th></th>
<th>True Pos</th>
<th>False Neg</th>
<th>SENS</th>
<th>True Neg</th>
<th>False Pos</th>
<th>SPEC</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAD</td>
<td>17</td>
<td>7</td>
<td>71%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No CAD</td>
<td>58</td>
<td>16</td>
<td>78%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CAD = patients with coronary artery disease; SENS (sensitivity) = number of true positives + (number of true positives + false negatives) × 100; SPEC (specificity) = number of true negatives + (number of true negatives + false positives) × 100.

Patients with Coronary Artery Disease

Five of the seven false-negative tests occurred in patients with single-vessel coronary artery disease. The disease involved the left anterior descending alone in three instances and the right coronary artery only in two. The other two patients had double-vessel disease but in each case the left anterior descending was also involved. The average maximum heart rate in these seven patients was 145 beats/min. However, three patients had an average exercise heart rate of 133 beats/min which may have been inadequate stress and contributed to the negative test result.

Seven patients were not on any cardiovascular drug therapy and seven others had a normal resting electrocardiogram. No false-negative responses were elicited in these patients.

Chest pain was the reason for ceasing exercise in one of seven false-negative results and was the reason in 11 of 16 true-positive tests.

Patients without Coronary Artery Disease

False-positive tests occurred in 11 of 42 (26%) patients taking various medications and in only five of 32 (16%) patients not on drug therapy. The medications associated with the false-positive responses were digitalis in six, diazepam in three, and methyldopa in two instances.

Chest pain was the reason for stopping in five of 16 false-positive (31%) and seven of 58 true-negative (12%) results.

Discussion

Proper interpretation of the exercise electrocardiographic response in women patients is more difficult than in the male since much less testing has been done on these patients. The available information indicates that women are more likely to have exercise-induced electrocardiographic abnormalities, but in age-matched groups, the incidence of coronary artery disease and its complications is less. The studies that have been performed have utilized differing techniques and interpretations of the abnormal response, and most have not had any anatomic and/or functional standard for comparison.

ST-segment depression has been considered the hallmark of myocardial ischemia ever since Feil and Siegal described its association with spontaneous angina pectoris in 1928. Subsequent clinical studies and the results of stress testing procedures have confirmed this relationship. Difficulties have arisen, however, as to the extent of ST depression to be considered abnormal, the configuration of the ST segment itself, and the importance of "J"-junctional depression.

The present weight of evidence favors horizontal or downsloping ST-segment depression of at least 1 mm below the preceding P-R segment as an indication of an ischemic response. When the P-R interval and the ST segment are influenced by atrial repolarization during exercise (the Ta wave), a method of measurement proposed by Lepeschkin can be used. The ST depression is measured from a line drawn tangent to the last portion of the P-R segment where it intersects a vertical line at the end of the QRS complex.

"J"-junctional depression with an upsloping ST segment is usually considered a normal physiologic response to stress since a long-term follow-up study by

Table 3

Exercise Response Related to Resting Electrocardiogram and Therapy

<table>
<thead>
<tr>
<th>Group</th>
<th>State</th>
<th>Patients</th>
<th>False positive</th>
<th>False negative</th>
<th>Percent false positive or negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Normal resting ECG</td>
<td>34</td>
<td>2</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>II</td>
<td>No drug therapy</td>
<td>39</td>
<td>4</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>III</td>
<td>Normal resting ECG + no drug therapy</td>
<td>18</td>
<td>1</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>IV</td>
<td>Abnormal resting ECG + no drug therapy</td>
<td>19</td>
<td>2</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>V</td>
<td>Abnormal resting ECG + drug therapy</td>
<td>40</td>
<td>11</td>
<td>7</td>
<td>45</td>
</tr>
</tbody>
</table>

Some patients in groups I and III are the same as are some patients in groups II and III. Group I patients may be on medications and some group II patients have abnormal resting ECGs.
Robb and Marks indicated no increased risk of coronary events in such patients. However, some investigators believe that even isolated "J" point depression, over 2–3 mm, is indicative of coronary artery disease.

Another problem in interpretation related to junctional depression is that of ST depression which is not quite horizontal but is slowly ascending. McHenry et al. and Lester et al. have defined slowly ascending as a slope of less than 1 mV/sec, Profant et al. as an ST segment depressed at least 0.1 mV at a point 0.06 second after the nadir of the S wave, and Punsar et al. define it as an ST segment not reaching the isoelectric point before the next T wave. In addition, Kattus defines it as an ST segment not reaching the isoelectric point before the next T wave. Unfortunately, no one of these criteria seem to be better than any other in defining proper interpretation. In addition, Kattus and our own group have observed nonischemic "J" point depression may be a forerunner to true ischemic changes in the postexercise period or in subsequent exercise tests.

Based upon our past experience correlating exercise tests with coronary arteriographic findings, plus the other available evidence, we elected to use as "positive" criteria a 1 mm ST-segment depression (measured 0.06 sec after the QRS complex) with a downsloping or horizontal configuration or exhibiting a slope of less than 1 mm/sec. Our prior study indicated that excellent results can be obtained (no false positives, 15% false negatives) using this method of exercise testing interpretation when patients with abnormal control tracings who are also on drug therapy are eliminated. In our group of female patients, most of whom were middle aged (mean age 46), there were 22% false-positive and 29% false-negative test results. These results are similar to a recent study from our laboratory in which there were 28% false-positive and 19% false-negative results in a group of patients that were 80% male.

Although the results of the present study also compare favorably with those of other exercise coronary angiographic investigations, they are even better when only patients with both normal resting electrocardiograms and no cardiovascular drug therapy are considered. In 18 such patients, only one false-positive result was obtained.

Many factors other than coronary artery disease with myocardial ischemia may cause ST-segment changes in the resting and/or exercise electrocardiogram. Digitalis, even with a normal resting tracing, right and left bundle branch block, left ventricular hypertrophy, rheumatic heart disease, hypokalemia, Wolf-Parkinson-White syndrome, autonomic disorders, hyperventilation, meals, smoking and various pharmacologic agents have all been implicated. This is an especially important consideration in many of our women patients who present with various forms of chest pain. The discomfort may be typical for angina in some but in others it is rather ill defined and nonspecific. They frequently present, as in this study, with resting electrocardiographic abnormalities (usually nonspecific ST-T changes) and on some form of therapy, the latter most often being a tranquilizer.

As in our previous study, to evaluate patients with abnormal resting tracings, an increase in ST-segment depression of 1 mm over the control was considered a positive test indicating ischemia. In our past experience, 43% of the results were false positive or false negative in patients with both resting abnormalities and sedative or cardiovascular drug therapy. Similar results are evident in the present study in which the greatest proportion of false-positive (15 of 16) and of false-negative (7 of 7) responses were in patients on drug therapy other than short-acting nitrates and/or who had an abnormal control electrocardiogram. False-negative results were associated with diazepam in five patients and procaine amide and furosemide, one instance each. False positive tests occurred in patients administered digitalis (6 instances), furosemide (2), diazepam (3) and methyl dopa (2). Thus, the value of the exercise response in detecting myocardial ischemia under those circumstances is greatly diminished.

There are a number of pitfalls in obtaining adequate exercise tests. If insufficient stress is applied more falsely negative tests will occur. Three of our patients may have been inadequately stressed and this may have been a contributing factor in their negative results despite all other evidence indicating myocardial ischemia.

Since, in most studies, the extent of ST-segment depression is proportional to the severity of the coronary artery disease, it would be anticipated that false-negative responses would be most common in patients with single-vessel disease. This has been a common but not absolute finding in other reports. In our female population, five of seven false negatives occurred with single-vessel lesions.

It is notable that 24 of the 98 patients stopped because of chest pain. Sixteen of these tests were positive, 11 true-positive and five false-positive results. Thus, the occurrence of chest pain with exercise is not synonymous with the presence of ischemic heart disease.

As expected, the exercise tolerance in our patients with coronary artery disease (FAI = 18%) was reduced compared to the normal subjects (FAI = 6%). This reflects the fact that those with cor-
FEMALE EXERCISE RESPONSE

Coronary disease are forced to discontinue exercising because of the occurrence of angina pectoris or myocardial dysfunction. The functional aerobic impairment of only 6% in our normal group and a mean heart rate of 157 signifies that they did exercise to an essentially maximum level. The FAI would be only 4% if the three poorly motivated patients are eliminated. These findings help confirm the value of Bruce’s nomogram in the determination of oxygen consumption and FAI from exercise duration.

This study has disclosed that exercise electrocardiography, when carried out in this laboratory using the Seattle protocol, is as valid for women as for men. This holds true in circumstances when the resting electrocardiogram is normal despite drug therapy or in patients on no drug therapy who have resting ST-T wave abnormalities (table 3). However, it must be remembered that the results are not valid, in either sex, when both electrocardiographic changes are present and cardiovascular drug therapy is being given. If feasible, drug therapy should be discontinued before exercise testing as valid electrocardiographic responses might be obtained if the therapeutic influence of the drug has been eliminated.

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Circulation. 1974;50:1173-1178
doi: 10.1161/01.CIR.50.6.1173
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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