Accuracy of Exercise Electrocardiography in Detecting Physiologically Significant Coronary Arterial Lesions

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The accuracy of exercise electrocardiography in detecting a physiologically significant coronary artery stenosis has been assessed previously by comparing the exercise test with a coronary arteriogram. The inherent inaccuracy of visually determined percent diameter stenosis measurements might have lead to the conclusion that the exercise electrocardiogram was less accurate than it truly was. To determine the accuracy of the exercise electrocardiography in detecting a physiologically significant coronary stenosis, we studied 40 patients with one-vessel, one-lesion coronary artery disease, a normal resting electrocardiogram, and no hypertrophy or prior infarction. Each patient underwent exercise electrocardiography (Bruce protocol) that was interpreted as abnormal if the ST segment developed 0.1-mV or greater depression 80 msec after the J point. The physiological significance of each coronary stenosis was assessed by measuring of coronary flow reserve (peak divided by resting blood flow velocity) in the stenotic artery using a Doppler catheter and intracoronary papaverine (normal, 3.5 or greater peak/resting velocity). The percent diameter and percent area stenosis produced by each lesion were determined using quantitative angiography (Brown/Dodge method). Of the 17 patients with reduced coronary flow reserve (3.5 or greater peak/resting blood flow velocity) in the stenotic artery, 14 had an abnormal exercise electrocardiogram (sensitivity, 0.82; 95% confidence interval, 0.70–0.94). Conversely, 20 of 23 patients with normal coronary flow reserves had normal exercise tests (specificity, 0.87; 95% confidence interval, 0.77–0.97). The exercise electrocardiogram was abnormal in each of 11 patients with markedly reduced coronary flow reserve (less than 2.5 peak/resting velocity) and in three of six patients with moderately reduced reserve (2.5–3.4 peak/resting velocity). The products of systolic blood pressure and heart rate at peak exercise were significantly correlated with coronary reserve in patients with truly abnormal exercise tests. In comparison, the sensitivity (0.61; 95% confidence interval, 0.46–0.76) and specificity (0.73; 95% confidence interval, 0.60–0.86) of exercise electrocardiography in detecting a 60% or greater diameter stenosis may be significantly lower ($p < 0.05$). Exercise electrocardiography, therefore, was a good predictor of the physiological significance (assessed by coronary flow reserve) of a coronary stenosis in patients with a normal resting electrocardiogram and no hypertrophy or prior infarction. Its value in a broader and larger patient population will require further study. These results, however, underscore the importance of a physiological gold standard in assessing the accuracy of noninvasive studies for detecting coronary artery disease. (*Circulation* 1991;83:412–421)

Since its introduction more than 50 years ago, exercise electrocardiography has become a widely used test for detecting coronary artery disease.\(^1\)\(^-\)\(^5\) However, despite its use in nearly every major hospital and hundreds of clinical investigations, the accuracy of exercise electrocardiography in detecting the presence of a significant coronary stenosis is still controversial. The sensitivity of the exercise electrocardiogram has been reported to be as low as 25% in patients with one-vessel coronary

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artery disease to as high as 99% in patients with advanced disease.16 Similarly, estimates of its specificity in detecting significant coronary artery disease have varied widely.

One important explanation for these divergent findings might be that the accuracy of the exercise electrocardiogram was previously determined by comparing it with an inaccurate standard, visual interpretation of the coronary arteriogram. Several recent studies have demonstrated that the arteriographic assessment of coronary artery disease may not reflect accurately the anatomical distribution of coronary atherosclerosis as observed in postmortem pathological examinations or using in vivo echocardiographic coronary imaging.17,18 More important, in patients with advanced coronary artery disease, arteriographic assessments of individual coronary lesions often fail to predict the physiological impact of the lesion, as assessed by direct measurements of coronary flow reserve.19,20 Hence, use of a visual interpretation of the coronary arteriogram as the gold standard may have prevented prior investigators from determining the accuracy of exercise electrocardiography in assessing the presence of physiologically significant coronary artery disease.

The recent development of a coronary Doppler catheter has made it possible to assess the physiological significance of an isolated coronary arterial lesion at the time of coronary arteriography.21-24 In this study, we compared the results of exercise electrocardiography with measurements of coronary flow reserve to determine the accuracy of standard exercise electrocardiography in predicting the physiological significance of an individual coronary arterial lesion.

Methods

Patient Selection

Forty patients with one-vessel, one-lesion coronary artery disease were selected for study. These were consecutive patients studied in our laboratory, meeting the criteria described below, in whom an exercise electrocardiogram could be obtained within 1 month of coronary arteriography for a chest pain syndrome. The exercise study was obtained before catheterization in 31 patients, and after catheterization in the remaining nine. In addition, an M-mode and cross-sectional echocardiogram and an estimate of left ventricular global and regional function (contrast or radionuclide equilibrium ventriculogram) were obtained in each patient as part of the study protocol.

Patients were prospectively excluded from the study if they were unable to perform treadmill exercise (e.g., claudication, amputation, severe lung disease), if they were unable to discontinue digoxin use for 1 week before the exercise study, or if the resting electrocardiogram was significantly abnormal, precluding accurate analysis of the exercise electrocardiogram. These abnormalities included bundle branch block, ventricular preexcitation, resting ST segment depression of 0.1 mV or greater, deep T wave inversion, and a rhythm other than sinus.1,25,26

Patients with conditions that might independently alter coronary flow reserve were also excluded, including left ventricular hypertension (septal or posterior wall thickness of more than 1.1 cm), prior myocardial infarction, decreased left ventricular systemic function (global ejection fraction of less than 50% or regional wall motion abnormality), anemia (hemoglobin of 11 g/dl), collagen vascular diseases, and the presence of intracoronary thrombus.27-29

Exercise Electrocardiography

All cardioactive medications, except sublingual nitroglycerin, were withdrawn at least 24 hours before exercise electrocardiography (2-7 days for long-acting β-receptor antagonists). A modified Bruce (Sheffield) treadmill exercise protocol with standard 12-lead electrocardiographic monitoring was used.30 Exercise was continued until one or more of the following end points was reached: 1) one or more electrocardiographic leads demonstrated 0.1-mV or greater flat or downsloping ST segment depression consistent with ischemia, 2) achievement of 85% of the predicted maximal heart rate, or 3) inability of the patient to exercise further (fatigue, dyspnea). An electrocardiogram and a measurement of arterial blood pressure (arm cuff) were obtained at 1-minute intervals from the beginning of exercise until 5 minutes after completion of exercise. A final electrocardiogram was obtained after 10 minutes of recovery from exercise. If the patient developed chest pain during the test, the time of its onset and relief were recorded.

The duration of exercise, heart rate, systolic blood pressure, and double product (heart rate multiplied by systolic blood pressure) were recorded at the development of 0.1- and 0.2-mV ST segment depression (where present) and peak exercise and when ST segments returned to their basal state.

The electrocardiogram obtained during exercise was interpreted by three cardiologists blinded to the clinical history and other experimental data. An abnormal test was defined as the development of 0.1-mV or greater ST segment depression 0.08 seconds from the J point. Each reader recorded the time at which 0.1- and 0.2-mV ST segment depression, where present, first occurred. Differences in individual interpretation were resolved by consensus.

Catheterization Protocol and Measurement of Coronary Flow Reserve

Patients were brought to the catheterization laboratory in a fasting state. Cardioactive medications were continued, but no patient received atropine. After administration of nitroglycerin (200-400 μg) and heparin (130 units/kg), arteriograms of the vessel containing the coronary lesion were obtained in orthogonal projections (e.g., right anterior oblique 60° and left anterior oblique 30°). Coronary flow reserve was then measured in the artery with the
stenotic lesion. The technique has been described in detail.21-24 Briefly, the coronary artery containing the stenosis was cannulated with a 3F coronary Doppler catheter (NuMed, Hopkinton, N.Y.). Phasic and mean coronary blood flow velocities, mean arterial pressure (obtained via the coronary guiding catheter), mean heart rate, and electrocardiogram were continuously recorded. Sequentially greater boluses of papaverine hydrochloride (2 mg/ml, 0.9% saline) were injected into the coronary ostium until a maximal increase in coronary blood flow velocity was achieved. The minimum dose of papaverine that caused maximal coronary hyperemia was 9±1 mg (mean±SEM; range, 6–12 mg) in the left coronary artery and 4±1 mg (range, 2–8 mg) in the right coronary. Since we used a dose–response curve in each patient, the maximum dose was 11±1 mg (range, 8–14 mg) in the left coronary and 6±1 mg (range, 4–10 mg) in the right coronary. Coronary flow reserve was calculated as the quotient of the peak blood flow velocity and the resting blood flow velocity.

In a previous study of 20 patients with normal coronary arteries, coronary flow reserve measured using this technique averaged 4.8±0.6 peak/resting velocity and ranged from 3.5 to 8.2 peak/resting velocity.31 In this study, coronary flow reserve was defined as abnormally low if it was found to be less than 3.5 peak/resting velocity.

Quantitative Coronary Arteriography

Arteriograms of each lesion were analyzed by an arteriographer (blinded to the results of the exercise test) using the Brown/Dodge method of quantitative coronary angiography. The technique has been described in detail elsewhere.32 Briefly, each arteriogram was projected onto a rectilinear grid at ×5 magnification. The outline of each coronary lesion was traced from two orthogonal projections during three portions of the cardiac cycle. The traced lesion was outlined, digitized, and computer corrected for radiographic pin-cushion and magnification distortion. The maximal percent area stenosis, most severe percent diameter stenosis, and minimum lesion cross-sectional area were then calculated by averaging the values obtained from each portion of the cardiac cycle.

Statistical Analysis

Except where noted, all data are expressed as mean±SEM. Differences between group means were analyzed using an analysis of variance. Differences in paired nonparametric data were analyzed by McNemar's test. Nonpaired data were analyzed by Fisher's exact test for nonpaired data. Sensitivity and specificity were assessed by previously described methods.8 Confidence intervals were calculated by the method described by Simon.33 The overall accuracy was defined as the quotient of (true-positives plus true-negatives) and the total number of studies performed. Linear correlation was measured using Pearson's correlation coefficient. Statistical significance was defined as a probability value of 0.05 or less.

### Table 1. Clinical Characteristics and Exercise Hemodynamics

<table>
<thead>
<tr>
<th>Exercise test</th>
<th>Normal</th>
<th>Abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>23</td>
<td>17</td>
</tr>
<tr>
<td>Female (n)</td>
<td>3 (13)</td>
<td>4 (24)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>55±2</td>
<td>57±2</td>
</tr>
<tr>
<td>Stenosed coronary artery (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left anterior descending</td>
<td>11 (48)</td>
<td>9 (53)</td>
</tr>
<tr>
<td>Circumflex</td>
<td>4 (17)</td>
<td>3 (18)</td>
</tr>
<tr>
<td>Right</td>
<td>8 (35)</td>
<td>5 (29)</td>
</tr>
<tr>
<td>Drug therapy (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Receptor antagonist</td>
<td>1 (4)</td>
<td>7 (41)†</td>
</tr>
<tr>
<td>Nitrates</td>
<td>7 (30)</td>
<td>5 (29)</td>
</tr>
<tr>
<td>Calcium channel antagonist</td>
<td>11 (48)</td>
<td>12 (70)†</td>
</tr>
<tr>
<td>Exercise hemodynamics at 1-mV or greater ST depression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>112±5</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>156±5</td>
<td></td>
</tr>
<tr>
<td>Heart rate×systolic blood pressure (beats/min·mm Hg·10⁵)</td>
<td>17.7±0.2</td>
<td></td>
</tr>
<tr>
<td>Duration of exercise (min)</td>
<td>8.9±1.1</td>
<td></td>
</tr>
<tr>
<td>Exercise hemodynamics at peak exercise</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>137±4</td>
<td>124±5†</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>173±5</td>
<td>164±5</td>
</tr>
<tr>
<td>Heart rate×systolic blood pressure (beats/min·mm Hg·10⁵)</td>
<td>23.2±0.9</td>
<td>20.6±1.1</td>
</tr>
<tr>
<td>Duration of exercise (min)</td>
<td>14.3±0.6</td>
<td>11.7±1.0†</td>
</tr>
<tr>
<td>Chest pain during exercise test (n)</td>
<td>5 (22)</td>
<td>10 (59)</td>
</tr>
</tbody>
</table>

Values in parentheses indicate percentages.
*Taken at the time of catheterization.
†p≤0.05 versus normal exercise test.

### Results

#### Exercise Electrocardiography

Twenty-three patients had a normal exercise electrocardiogram, and 17 developed 0.1-mV or greater ST segment depression. Nine of the patients with an abnormal exercise electrocardiogram developed 0.2-mV or greater ST segment depression during the test. There was a high degree of concordance among the three blinded readers. Thirty-five of 40 tests were interpreted unanimously by the readers. Four normal tests and one abnormal study were decided by consensus.

The characteristics of patients with normal and abnormal exercise electrocardiograms are shown in Table 1. There were no significant differences between groups with respect to these factors. The duration of exercise and exercise hemodynamics are also shown in Table 1. As expected, the duration of exercise and peak heart rate were significantly less in patients who developed 0.1-mV or greater ST segment depression than in those with a normal study. Seventeen normal tests were terminated because the patients reached 85% of the predicted maximal heart
rate, and six were stopped because the patients were unable to continue. Ten abnormal tests were stopped because the electrocardiogram demonstrated 0.1-mV or greater ST depression, six because of fatigue or dyspnea, and one because of severe chest pain. Patients who developed chest pain during exercise were not significantly more likely to have an abnormal exercise test (p =0.09, Table 1).

Coronary Flow Reserve

Of the 17 patients with reduced coronary flow reserve (less than 3.5 peak/resting velocity) in the stenotic coronary artery, 14 developed 0.1-mV or greater ST segment depression during exercise (Figure 1 and Table 2). Conversely, 20 of 23 patients with normal coronary flow reserves (3.5 or greater peak/resting velocity) in the stenotic vessels had normal exercise studies (Figures 1 and 2). The sensitivity and specificity of the exercise electrocardiogram in detecting a physiologically significant lesion (coronary flow reserve less than 3.5 peak/resting velocity) were 82% and 87%, respectively.

The likelihood of the exercise electrocardiogram being abnormal was directly related to the flow

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**TABLE 2. Relation of Coronary Flow Reserve to Exercise Electrocardiography and Arteriographic Stenosis Geometry**

<table>
<thead>
<tr>
<th>Exercise electrocardiography</th>
<th>Coronary flow reserve (peak/resting velocity)</th>
<th>&lt;3.5</th>
<th>≥3.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td></td>
<td>17</td>
<td>23</td>
</tr>
<tr>
<td>Exercise electrocardiography</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;0.1-mV ST depression</td>
<td></td>
<td>3</td>
<td>20</td>
</tr>
<tr>
<td>0.1–&lt;2.0-mV ST depression</td>
<td></td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>≥0.2-mV ST depression</td>
<td></td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Chest pain</td>
<td></td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Quantitative lesion geometry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diameter stenosis (%) (range)</td>
<td></td>
<td>71±4 (45–95)</td>
<td>53±3* (38–71)</td>
</tr>
<tr>
<td>Area stenosis (%) (range)</td>
<td></td>
<td>85±3 (69–99)</td>
<td>63±2* (36–74)</td>
</tr>
<tr>
<td>Minimum lesion cross-sectional area (mm²) (range)</td>
<td></td>
<td>1.1±0.2 (0.1–2.7)</td>
<td>3.1±0.3* (1.3–4.1)</td>
</tr>
</tbody>
</table>

*p<0.05 versus <3.5 peak/resting velocity coronary flow reserve.
reserves present in the stenotic artery (Figure 3). Each of the 11 patients with severely depressed coronary reserve (less than 2.5 peak/resting velocity) developed significant ST segment depression with exercise. Three of six patients with mildly to moderately depressed coronary flow reserve (2.5–3.4 peak/resting velocity) developed significant ST segment depression.

To the converse, severe ST depression with exercise (≥ 0.2 mV) was not significantly related to the degree of flow reserve impairment. Three of 23 patients with normal flow reserve had 0.2-mV or greater ST depression. One of six patients with a moderate reduction in reserve (2.5 peak/resting velocity ratio) had 0.2-mV or greater ST depression. Five of 11 patients with a severe reduction in reserve (less than 2.5 peak/resting velocity) exhibited 0.2-mV or greater ST depression. The incidence of chest pain with exercise was not significantly different in patients with normal and abnormal coronary reserves.
The heart rate during the flow reserve measurement was 66±1 beats/min and ranged from 54 to 76 beats/min. The heart rate of patients with normal coronary reserve (65±2 beats/min) was not significantly different from that measured in patients with reduced reserve (66±2 beats/min), and the heart rate of patients with an abnormal exercise test (66±2 beats/min) was not different from patients with a normal test (66±2 beats/min). Moreover, the heart rate of patients with a normal exercise test but reduced coronary reserve (false-negative exercise test; 62±3 beats/min) was similar to patients with a normal exercise test and normal coronary reserve (true negative; 67±2 beats/min), suggesting that differences in heart rate did not importantly affect the comparison of flow reserve measurements between patients.

Relation of Exercise Hemodynamics to Coronary Flow Reserve
In patients with an abnormal exercise test, coronary flow reserve measured in the stenotic coronary artery was inversely correlated with the double product (heart rate multiplied by systolic blood pressure) at the onset of 0.1-mV or greater ST segment depression (r=0.58, Figure 4) and with the heart rate at the onset of 0.1-mV ST segment depression (r=0.61). In addition, the ratio of the modified double product (mean blood pressure multiplied by heart rate) during the flow reserve measurement and the double product at the onset of 0.1-mV or greater ST segment depression during exercise was directly correlated with the flow reserve (r=0.59, p=0.04).

Quantitative Coronary Arteriography
The percent diameter and percent area stenosis produced by each coronary arterial lesion are shown in Figures 5 and 6. The average percent diameter stenosis of lesions in vessels with normal coronary reserve (53±3%) was less than that found in patients with a reduced reserve (71±4%, p<0.01); however, using either criterion for lesion significance (less than 50% or more than 60% stenosis), there was a great deal of overlap in the range of percent diameter stenosis in arteries with normal and abnormal flow reserve (Table 3 and Figure 5).

In contrast to percent diameter stenosis, the sensitivity and specificity of the exercise test in predicting a coronary lesion producing 75% or greater area stenosis were 79% and 81%, respectively (Tables 3 and 4 and Figure 6). Of importance, the average percent area stenosis of lesions in patients with a normal coronary reserve was 63±2% and ranged widely from 36% and 74%.

Comparative Accuracy of Exercise Electrocardiography in Predicting Physiological and Arteriographic Measurements of Lesion Severity
A comparison of the sensitivity, specificity, and overall accuracy of exercise electrocardiography in predicting the presence of a significant coronary lesion, defined by different physiological and arteriographic criteria, is shown in Table 4. The exercise test was a much better predictor of lesions that reduced coronary flow reserve to less than 3.5 peak/resting.
TABLE 3. Relation of Arteriographic Stenosis Geometry to Exercise Electrocardiography

<table>
<thead>
<tr>
<th>Diameter stenosis (%)</th>
<th>Area stenosis (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤60</td>
<td>&gt;60</td>
</tr>
<tr>
<td>n</td>
<td>22</td>
</tr>
</tbody>
</table>

Exercise electrocardiography

- No significant ST depression: 16, 7, 20, 3
- ≥0.1-mV ST depression: 6, 11, 5, 12
- ≥0.2-mV ST depression: 5, 4, 3, 6
- Chest pain: 8, 7, 6, 9

velocity than in predicting any level of diameter stenosis. Although coronary flow reserve and diameter stenosis were related, the correlation was not strong (r=0.66). The exercise electrocardiogram was a much better predictor of the area stenosis, but this is not surprising because coronary flow reserve and area stenosis were correlated in these patients with one-vessel coronary artery disease (r=0.77, p<0.01).

Discussion

These data demonstrate that the exercise electrocardiogram is a good predictor of the physiological significance (assessed by coronary flow reserve) of an individual coronary arterial stenosis in patients with one-vessel coronary artery disease, a normal resting electrocardiogram, and no evidence of infarction or hypertrophy. The test was universally sensitive to moderate-to-severe coronary stenoses (i.e., stenoses reducing coronary flow reserve to less than 2.5 peak divided by resting velocity). Coronary lesions that resulted in a mild reduction in coronary flow reserve, however, frequently did not result in an abnormal exercise test. Conversely, coronary lesions that did not reduce coronary flow reserve were very infrequently associated with an abnormal exercise electrocardiogram.

These findings contrast sharply with many prior studies showing strikingly lower specificity and sensitivity of exercise electrocardiography in patients with coronary artery disease limited to a single vessel.6–15 The differences are particularly remarkable because we studied a group of patients who had at least a moderate coronary lesion (percent area stenosis, 36–38%), whereas some prior studies included patients with a wider range of stenoses, including totally occluded and normal coronary arteries.

One explanation for these differences is that the "significance" of a coronary arterial lesion was measured by looking at the arteriographic outline of the coronary artery. Instead, we measured directly the capacity of the stenosed coronary artery to conduct hyperemic blood flow (a physiological measurement of stenosis severity). Because visual assessment of the anatomical severity of a coronary lesion poorly predicts the physiological significance of the lesion, one would anticipate that the exercise electrocardiogram (a physiological study) would produce results that are often discordant with the arteriographic findings (an anatomical study).19,20 Our study suggests that the exercise electrocardiogram may have been truly normal or abnormal in many cases in which the arteriographic assessment suggested otherwise.

It should be noted that exercise electrocardiography was nearly as accurate in predicting percent area stenosis (quantitatively determined) as coronary flow reserve. This presumably is because flow reserve and precise quantitative arteriographic measurements of percent area stenosis are highly correlated in patients with limited coronary artery disease.34 When more disease is present, however, the two parameters unlink, and area stenosis is not predictive of coronary hemodynamics.35

Potential Limitations

There are several potential pitfalls in the measurement of coronary flow reserve using a Doppler catheter and intracoronary papaverine (e.g., changes in vascular cross-sectional area at the site of velocity measurement, guide or Doppler catheter obstruction, abnormal velocity profiles). These factors have been discussed in detail elsewhere.25–29 Importantly, maximal coronary dilation was produced by nitroglycerin immediately before arteriography and flow reserve measurements. Pretreatment with nitroglycerin was intended to keep the epicardial coronary artery containing the Doppler catheter in a maximally dilated state, hence "freezing" the cross-sectional area of the artery at the point where blood flow velocity

TABLE 4. Accuracy of Exercise Electrocardiography in Predicting Physiological and Arteriographic Measurements of Stenosis Severity

<table>
<thead>
<tr>
<th>Gold standard</th>
<th>Sensitivity</th>
<th>95% CI</th>
<th>Specificity</th>
<th>95% CI</th>
<th>Overall accuracy</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary flow reserve</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3.5*</td>
<td>0.82</td>
<td>(0.70–0.94)</td>
<td>0.87</td>
<td>(0.77–0.97)</td>
<td>0.85</td>
<td>(0.74–0.96)</td>
</tr>
<tr>
<td>Diameter stenosis (%)</td>
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<tr>
<td>&gt;50</td>
<td>0.50</td>
<td>(0.35–0.65)</td>
<td>0.71</td>
<td>(0.57–0.85)</td>
<td>0.58</td>
<td>(0.43–0.73)</td>
</tr>
<tr>
<td>&gt;60</td>
<td>0.61</td>
<td>(0.46–0.76)</td>
<td>0.73</td>
<td>(0.60–0.86)</td>
<td>0.63</td>
<td>(0.48–0.78)</td>
</tr>
<tr>
<td>Area stenosis (%)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;70</td>
<td>0.57</td>
<td>(0.42–0.72)</td>
<td>0.76</td>
<td>(0.63–0.89)</td>
<td>0.65</td>
<td>(0.50–0.80)</td>
</tr>
<tr>
<td>&gt;75</td>
<td>0.80</td>
<td>(0.68–0.92)</td>
<td>0.80</td>
<td>(0.68–0.92)</td>
<td>0.80</td>
<td>(0.68–0.92)</td>
</tr>
</tbody>
</table>

CI, confidence interval.
*Peak divided by resting velocity.
was measured. However, nitroglycerin also may have caused maximal dilation of the stenosis and might thereby have decreased the obstruction to blood flow produced by the lesion.36

A second potential limitation is that we studied a highly selected group of patients—those with one-vessel coronary artery disease, a normal resting electrocardiogram, and absence of a variety of factors that might independently alter the exercise electrocardiogram (e.g., hypertrophy, infarction, drug therapy). Although our study demonstrates that the exercise test is remarkably accurate in this group, coronary lesions in vessels perfusing small amounts of myocardium might not result in significant abnormalities in the surface electrocardiogram during exercise.

Caution should also be applied to the extrapolation of these data to patients with other factors known to independently alter the exercise electrocardiogram (e.g., electrolyte abnormalities, bundle branch block, drug treatment, hypertrophy, infarction).21–25 Some of these abnormalities can be associated with reduced coronary flow reserve (e.g., hypertrophy and infarction) due to abnormalities in the microcirculation. Although they may significantly alter the accuracy of the exercise electrocardiogram in predicting reduced coronary flow reserve due to epicardial coronary obstruction, an abnormal exercise test might still signify exercise-induced ischemia. Other factors that alter myocardial repolarization (e.g., serum electrolyte abnormalities, bundle branch block, drugs), however, might reduce the accuracy of any electrocardiographic test for coronary artery disease, independent of abnormalities in coronary blood flow. Additionally, drug treatment might prevent exercise-induced myocardial ischemia by limiting metabolic demand or improving myocardial perfusion (e.g., by epicardial coronary vasodilation, improvement of collateral blood flow, or by improving the ratio of epicardial to endocardial blood flow). It should be emphasized that we studied patients without these other confounding abnormalities. The accuracy of exercise electrocardiography in detecting the physiological significance of individual coronary lesions in a broader population will require further study.

We recently found that changes in heart rate or ventricular preload can change measurements of coronary flow reserve (peak divided by resting method) by increasing resting blood flow without changing hyperemic blood flow.37 Differences in hemodynamics among patients at the time of catheterization could have obscured the relation between our assessment of physiological significance and the results of the exercise test. We found, however, that the range of heart rates in our patient group was small and that patients with a normal test had heart rates similar to those with an abnormal test. Similarly, patients with normal coronary reserve had heart rates nearly identical to patients with reduced reserve. Finally, the patients with reduced reserve and a normal exercise test had heart rates similar to those of patients with normal reserve and a normal exercise test. These findings suggest that differences in resting heart rate did not importantly alter our assessment of the exercise electrocardiogram. Moreover, alterations in measured coronary reserve would have tended to cloud the relation of the exercise test to flow reserve measurements, making it appear that the exercise test was less valuable than was true.

Although a normal maximal exercise electrocardiogram implies that a moderate-to-severe coronary stenosis is not present when the test is performed, vasospasm or intracoronary thrombus might later result in transient myocardial ischemia. These data should not be extended to patients with suspected vasospastic or new unstable angina. It is also possible that some of the tests conventionally labeled as “false-positive” (based on a flow reserve measurement in the catheterization laboratory) were truly positive for exercise-induced ischemia because atherosclerotic coronary stenoses, in contrast to normal coronary arteries, constrict during exercise.38

Finally, two factors might have reduced the sensitivity of exercise electrocardiography. First, ischemia in the posterior myocardial wall can be electrocardiographically “silent.”39 Second, a well-developed collateral circulation could also “hide” the presence of a significant coronary lesion.40 Stenotic coronary vessels often have a significant potential collateral source of perfusion from surrounding arteries, and these pathways are not accounted for by pharmacological measurements of coronary flow reserve.41

Implications

Many clinical studies have demonstrated a relation between exercise electrocardiography and the subsequent incidence of a cardiac event (e.g., myocardial infarction, death).42–45 Our data suggest that these exercise tests mark the presence or absence of a physiologically significant coronary arterial stenosis. Taken together, these studies imply that physiologically significant lesions are associated with higher event rates. The concept is supported by data from the Coronary Artery Surgery Study demonstrating a higher incidence of infarction and death in patients with a 90% or greater stenosis of the left anterior descending coronary artery (nearly always physiologically significant) compared with patients with a similarly located stenosis of lesser severity (50% or less, usually not physiologically significant).46 Furthermore, a preliminary study from our laboratory suggests that patients with chest pain and a single, physiologically insignificant lesion (similar to 23 of the patients reported here) have a low incidence of a cardiac event and a high incidence of spontaneous improvement in symptoms over time.47

These data also suggest that the exercise electrocardiogram may be a very cost-effective method of detecting a significant coronary stenosis. The cost of thallium scintigraphy in our hospitals averages 3.1-fold the cost of exercise electrocardiography alone. In addition, although thallium-201 scintigraphy has
been widely used as an adjunct to exercise electrocardiography, its additional contribution in detecting a physiologically significant lesion may be limited in patients without conditions that, independent of coronary atherosclerosis, often lead to exercise-induced ST segment deviations (e.g., infarction, hypertrophy, digoxin therapy). 48

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