Heart Rate Adjustment of ST Segment Depression for Improved Detection of Coronary Artery Disease

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Normal values for heart rate–adjusted indexes of ST segment depression during treadmill exercise electrocardiography (the ST segment/heart rate slope and the ΔST segment/heart rate index) were derived from evaluation of 150 subjects with a low likelihood of coronary artery disease, including 100 normal subjects and 50 subjects with nonaninal chest pain. Partitions chosen by the method of percentile estimation to include 95% of normal subjects remained highly specific in subjects with nonaninal pain syndromes. Sensitivities of the derived partitions for detection of myocardial ischemia were tested in an additional 150 patients with a high likelihood of coronary disease, including 100 patients with angiographically demonstrated coronary obstruction and 50 patients with stable angina. In contrast to the 68% (102 of 150 subjects) sensitivity of standard exercise electrocardiographic criteria for the detection of disease in this population, the sensitivity of an ST segment/heart rate slope partition of 2.4 μV/beats/min was 95% (142 of 150 subjects, \( p < 0.001 \)), and the sensitivity of a ΔST segment/heart rate index partition of 1.6 μV/beats/min was 91% (137 of 150 subjects, \( p < 0.001 \)). Analysis of receiver-operating curves confirmed the superior performance of the heart rate–adjusted indexes throughout a wide range of test specificities. These findings suggest that heart rate adjustment of ST segment depression can markedly improve the clinical usefulness of the treadmill exercise electrocardiogram. (Circulation 1989;79:245–255)

The exercise electrocardiogram remains the most widely accessible method for evaluating suspected coronary artery disease in asymptomatic subjects and in patients with chest pain syndromes. However, test accuracy and usefulness have been limited by poor sensitivity for the detection of myocardial ischemia, by frequent indeterminate test responses, and by poor positive predictive value in populations with a low prevalence of disease. Improved test performance remains an important goal.

By normalizing ST segment depression for corresponding changes in myocardial workload at peak exercise, the ST segment/heart rate (ST/HR) slope has been shown to markedly improve the accuracy of bicycle exercise testing for identifying and quantifying coronary disease. Indeed, several retrospective studies have confirmed that even abbreviated forms of the ST/HR slope method can improve the ability of treadmill exercise electrocardiography to detect the presence and to assess the severity of coronary obstruction. However, further application of this physiologic approach to treadmill exercise testing requires definition of normal test values by standardized methods because ST/HR slope outcome is highly dependent on the type of exercise performed, the number and location of monitoring electrodes, the method of measuring ST segment depression, and the clinical characteristics of the study population.

Therefore, the purpose of this study was to establish normal limits during treadmill exercise for the ST/HR slope and for an extreme simplification of the original method, the ΔST/HR index. These findings were then used to test the ability of heart rate adjustment of ST segment depression to improve the electrocardiographic detection of coronary artery disease.

Methods

Study Population

Three hundred consecutively studied subjects and patients who met criteria outlined below were
entered into one of four clinical groups, which included two groups with a low likelihood of coronary disease and two with a high (or certain) likelihood of disease. ST/HR slope and ΔST/HR index partitions defining the upper 95th percentile limits of normal were determined in normal subjects and were further tested in subjects with non anginal chest pain. The sensitivity of each partition for the detection of coronary disease was then compared with standard exercise test criteria in patients with coronary obstruction as demonstrated by angiography and was tested further in a separate group of patients with clinical angina who were not referred for catheterization. All subjects and patients were assigned to one of the clinical groups before examination of the exercise electrocardiogram, and no study was excluded after group assignment.

**Normal subjects.** There were 100 normal subjects (group 1), which included 81 men and 19 women, whose mean age was 47±13 (SD) years. There were no volunteer subjects in this group, and each was referred by a physician for a routine exercise electrocardiogram. In each subject, exercise testing was performed in the absence of symptoms or abnormal signs suggestive of disease, usually as part of a comprehensive screening evaluation or as a precautionary evaluation before beginning a program of regular exercise. All subjects were free of chest pain, had no history of cardiac disease, were not taking medications; also, all had normal resting electrocardiograms, normal blood pressure, and normal cardiac physical examinations. In addition, all subjects were free of chest pain during treadmill exercise. Based on the data of Diamond et al.,22 and Diamond and Forrester,23 the age- and sex-adjusted likelihood of coronary disease in this asymptomatic group can be estimated as no more than 0.05.

**Subjects with nonanginal chest pain.** There were 50 subjects who had nonanginal chest pain (group 2), which included 33 men and 17 women, whose mean age was 46±13 years. Each was referred by a physician because of chest pain that was not caused by physical exertion, not relieved by rest, and not retrosternal in location. None of the subjects was taking medications, and all had normal resting electrocardiograms, normal blood pressure, and normal cardiac physical examinations. In addition, all subjects were free of chest pain during treadmill exercise. The age- and sex-adjusted likelihood of coronary disease in this group that had nonanginal chest pain can be estimated as no more than 0.10,22,23

**Patients with clinical angina.** There were 50 patients that had clinical angina (group 3), which included 31 men and 19 women, whose mean age was 61±10 years. Each was referred by a physician for exercise electrocardiography to evaluate clinically stable retrosternal chest pain or discomfort that was consistently caused by exertion and relieved by rest. In addition, all patients in this group developed typical chest pain during treadmill exercise. However, the decision to include patients in this group, as in all other groups, was made without knowledge of the electrocardiographic response to exercise. In no patient was coronary angiography a pretest consideration by the referring physician. No patient was included in this group if a bundle branch block pattern or nonspecific intraventricular block pattern (QRS > 110 msec) was present on the resting electrocardiogram. Two patients had a history of remote myocardial infarction, and five patients were known to have had resting electrocardiographic evidence of previous Q wave infarction. There were 37 patients in this group who were not taking medications; among the remaining 13 patients, 11 were taking β-blocking drugs, and seven were taking nitrates at the time of exercise testing. The age- and sex-adjusted likelihood of coronary disease in this group can be estimated as no less than 0.93,22,23

**Patients with catheterization-proved coronary disease.** There were 100 patients that had coronary disease proved by catheterization (group 4), which included 84 men and 16 women, whose mean age was 58±9 years. Each patient was referred by a physician for coronary angiography and underwent exercise testing and were admitted to the hospital for this procedure.

Included are the first 100 patients with stable angina and coronary disease who were entered into our prospective trial of the ability of an ST/HR slope partition of 6.0 μV/beats/min to recognize anatomically and functionally extensive coronary obstruction. Accuracy of this test partition for the identification of severe disease, selected from previous reports5,8 and from our own retrospective studies of the method,13–16 has recently been reported in detail.24 Though no data on test partitions for detecting the presence or absence of disease in this population have been previously presented, this group of patients has been used before to evaluate heart rate–adjusted indexes of ST depression for determining severity of disease.24

All patients in this group had stable, effort-related chest pain that was relieved by rest. In no patient was the ST/HR slope a pretest consideration in referral for catheterization, but many patients in this group had undergone diagnosis by standard exercise electrocardiography or by radionuclide cineangiography before entering this study. Patients with bundle branch block or nonspecific intraventricular block patterns on the resting electrocardiogram were excluded. Patients with recent myocardial infarction (<8 weeks) were not included in this group. There were 32 patients in this group with a history of remote myocardial infarction, and 17 patients had resting electrocardiographic evidence of previous Q wave infarction. There were 13 patients in this group who were unmedicated; among the remaining 87 patients, 71 were taking β-blocking drugs, 57 were taking nitrates, and 56 were taking calcium channel blocking drugs at the time of exercise evaluation. By definition, the likelihood of coronary disease in this group is 1.00.
Patients With Stable Angina and Normal Coronary Arteries

In addition to the 300 patients forming the primary population of this report, exercise electrocardiographic data were examined in 18 consecutive patients with stable angina who were referred for coronary angiography but who were found to have no significant extramural coronary obstruction as defined below. There were nine men and nine women in this group, whose mean age was $54 \pm 10$ years. $\beta$-Blocking drugs were used by six, nitrates by six, and calcium-blocking drugs by five of these patients; none was taking digitalis. In no patient was the ST/HR slope a pretest consideration in referral for angiography.

Exercise Electrocardiography

While the patients were on a treadmill, exercise electrocardiograms were performed with a Computer Assisted System for Exercise (CASE II) (Marquette Electronics, Milwaukee, Wisconsin) modified by the addition of a bipolar CM5 lead to the standard 12-lead recording system. All patients exercised according to our recently reported modification of the standard Bruce protocol that produces small heart rate increments between stages, which allows more accurate calculation of the ST/HR slope\textsuperscript{17,18}; at the same time, alternate stages of the new protocol are directly comparable with standard Bruce stage workloads.\textsuperscript{17} Age-adjusted target heart rates were sought as the exercise endpoint for all studies, but tests were terminated when necessary because of limiting chest pain, dyspnea, or fatigue. Exercise double products were calculated by multiplying systolic blood pressure and heart rate at the end of exercise.

Exercise tests were evaluated with standard electrocardiographic criteria measured from the raw intraexercise tracings in each study.\textsuperscript{4} The test was considered positive in the presence of a type 1 response, defined as $0.1 \text{ mV}$ or more of additional downsloping or horizontal ST segment depression, measured between 60 and 80 msec after the J point, at the end of exercise. The test was considered equivocal in the presence of a type 2 response, defined as $0.1 \text{ mV}$ or greater of additional upsloping ST segment depression. When additional ST segment depression was less than $0.1 \text{ mV}$, the test was considered negative.

$\Delta$ST Segment/Heart Rate Slope Method

In addition to providing standard electrocardiographic output during exercise, the CASE II system provides continuously updated, computer-based measurement of ST segment levels in each lead based on incremental averaging of normal complexes during exercise. Computer-calculated ST segment amplitudes measured to the nearest 10 $\mu\text{V}$ at a point 60 msec after the J point, in which the end of the PR segment was used as reference, were obtained in each lead after each minute of exercise and at peak effort. Accuracy of this measurement has been previously validated in our laboratory.\textsuperscript{17}

Calculation of the maximal ST/HR slope in $\mu\text{V}$/beats/min was performed by linear regression analysis, which related the measured amount of ST segment depression in each lead except $aV_R$, $aV_L$, and $V_2$ to the heart rate at the end of each stage of exercise according to methods previously reported in detail.\textsuperscript{7,17,18} Because the maximal rather than the average ST/HR slope was sought in each patient, linear regression analysis was performed from the end of exercise to earlier intermediate stage points with heart rate as the independent variable and the magnitude of ST segment depression as the dependent variable. The slope derived from linear regression analysis of the final three data points was then compared with slopes obtained by including progressively earlier data points. The highest ST/HR slope with a statistically significant coefficient of correlation was then taken as the test finding for that lead. After calculation of the maximal ST/HR slope in each lead, the highest ST/HR slope from among all the leads was taken as the final test result.

$\Delta$ST Segment/Heart Rate Index Calculation

The $\Delta$ST/HR index represents the average change of ST segment depression with heart rate throughout the entire course of exercise and may differ markedly in magnitude from the ST/HR slope, which represents the peak rate of ST segment change with heart rate during higher exercise workloads.\textsuperscript{17} The $\Delta$ST/HR index in $\mu\text{V}$/beats/min was calculated by dividing the maximal additional computer-measured ST segment depression at the end of exercise, which was corrected for any resting ST segment depression in that lead on the upright preexercise control electrocardiogram, by the exercise-induced change in heart rate from upright control. Computer measurements used for the $\Delta$ST/HR index were identical with simultaneous data recorded for calculation of the ST/HR slope, but only preexercise and peak-exercise data points were required. All recorded leads, including CM5, were examined, and ST segment depression was measured by computer at 60 msec after the J point, irrespective of the upsloping, horizontal, or downsloping direction of the ST segment.\textsuperscript{17,21}

Coronary Angiography

In the group with catheterization-proved coronary disease, selective coronary cineangiography was performed with the Judkins technique. Multiple views were obtained in all patients, and the left anterior descending and left circumflex coronary arteries were visualized in at least four views and the right coronary artery in at least two views. The results were interpreted separately from the original clinical report, specifically for the purpose of our exercise test studies, by a single experienced angiographer using calipers without knowledge of clinical or exercise test data as previously reported in detail.\textsuperscript{24}
Degree of stenosis was defined as the greatest percent reduction of luminal diameter in any view compared with the nearest normal segment. For classification of the number of obstructed coronary arteries, disease was considered significant when 50% luminal obstruction was present in the left anterior descending artery or a major diagonal branch, in the left circumflex artery, or in the right coronary artery or a major marginal branch. Left main narrowing of 50% or greater was scored as the equivalent of two-vessel disease. According to these criteria, there were 28 patients with one-vessel disease, 31 with two-vessel disease, and 41 with three-vessel coronary disease. Nine patients had left main coronary disease, including three with additional two-vessel disease and six with additional three-vessel disease.

Patients were also graded according to the presence or absence of 75% luminal obstruction criteria (rather than 50%) for determining significant disease. By this definition, 96 of the 100 catheterized patients had important coronary obstruction, and primary analysis of the data was performed on the group defined by 50% luminal obstruction criteria. All clinical catheterization reports were subsequently reviewed for additional confirmation of the presence of coronary disease; in each patient, at least 50% luminal obstruction of one or more vessels was also noted in the original report.

Data Analysis and Statistical Methods

Definitions of test sensitivity, specificity, and predictive value conform to standard use.25 ST/HR slope and ΔST/HR index partitions defining upper limits of normal under the present experimental conditions were calculated from data in the group of 100 normal subjects by the method of percentile estimation,26,27 which requires no assumption regarding the normal distribution of individual test values. With this method, the partition value that includes X% of patients is calculated by ranking test results in ascending order and determining an interpolated value for the X%(n+1) rank. The test partitions were selected to incorporate 95% of ST/HR slope and ΔST/HR index values in clinically normal subjects. Specificity of the derived partition values were subsequently examined in the group of subjects with nonanginal chest pain. Test sensitivities of these partitions, as indicators of underlying coronary artery disease, were then separately examined in the patients with catheterization-proved coronary obstruction and in the patients with clinical angina.

The performance of standard exercise electrocardiographic criteria4 was calculated separately in these groups. Specificity was tested in the two subject groups with a low likelihood of coronary artery disease, and sensitivity was tested in the two patient groups with a high likelihood of disease. Sensitivity of the standard test was calculated with only type 1 responses considered positive; equivocal (type 2) responses were considered negative. Specificity was calculated with only the absence of significant ST segment depression that was considered indicative of absence of disease. As a consequence, and similar to test outcome in clinical practice, the occurrence of equivocal responses in all groups served to reduce the calculated sensitivity and specificity of the standard exercise test. This effect was explored by separate calculation of standard test sensitivity with type 2 responses considered positive. Occurrence of equivocal responses was further examined by receiver-operating curves28 that were used in comparing the sensitivities of a range of partitions for calculated ST/HR slope, ΔST/HR index, and ST segment depression in patients with catheterization-proved coronary disease according to matched levels of test specificities determined by percentile estimation in normal subjects. In addition, the predictive values of the ST/HR slope and the ΔST/HR index were separately examined in subjects and patients with type 2 standard test responses.

Comparison of sensitivity and specificity of the standard exercise test with outcome based on the heart rate–adjusted methods was performed in each group by McNemar’s modification of the χ² method for paired proportions. In addition, sensitivity of each method was compared for the total patient populations that had a high risk of coronary disease (combined clinical angina and catheterization-proved coronary disease groups) and for patients that had demonstrated coronary disease subgrouped according to the number of obstructed arteries. Comparison of subgroup proportions was performed by χ² analysis with correction for continuity. Mean values for all findings are reported with the standard deviation as the index of dispersion. Comparison of mean values for normally distributed variables among groups was performed by one-way analysis of variance and posthoc testing of individual group differences by Scheffe’s method. For tests of proportion and for posthoc testing of mean values of normally distributed variables, a p value less than 0.05 was required for rejection of the null hypothesis. Because ST/HR slopes and ΔST/HR index values were not normally distributed within groups, the significance of differences among groups for these findings was examined by the nonparametric Kruskal-Wallis rank method. Because six posthoc Kruskal-Wallis tests between pairs were performed among the four groups for each method, a p value less than 0.0083 (Bonferroni’s correction) was required for rejection of the null hypothesis.

Results

Group Characteristics and Exercise Performance

Group characteristics and exercise performance are shown in Table 1. Normal subjects were similar to subjects with nonanginal chest pain, and patients with clinical angina were similar to patients with
Table 1. Group Characteristics and Exercise Performance

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1 Clinical normal (n=100)</th>
<th>Group 2 Nonanginal chest pain (n=50)</th>
<th>Group 3 Clinical angina (n=50)</th>
<th>Group 4 Catheterized coronary artery disease (n=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>47±12</td>
<td>46±13</td>
<td>61±10</td>
<td>58±9*</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>81/19</td>
<td>33/17</td>
<td>31/19</td>
<td>84/16</td>
</tr>
<tr>
<td>Exercise duration (min)</td>
<td>18±3</td>
<td>16±4</td>
<td>9±4</td>
<td>9±4*</td>
</tr>
<tr>
<td>Target rate achieved (%)</td>
<td>93±7</td>
<td>93±9</td>
<td>72±12</td>
<td>65±10†</td>
</tr>
<tr>
<td>Maximum heart rate (beats/min)</td>
<td>164±16</td>
<td>164±19</td>
<td>123±21</td>
<td>111±18†</td>
</tr>
<tr>
<td>Maximum systolic pressure (mm Hg)</td>
<td>177±21</td>
<td>167±23</td>
<td>160±21</td>
<td>157±21‡</td>
</tr>
<tr>
<td>Maximum double product (x 10^-3) (mm Hg x beats/min)</td>
<td>29±5</td>
<td>28±5</td>
<td>20±5</td>
<td>18±4*</td>
</tr>
</tbody>
</table>

Data are mean±SD.

*Groups 1 and 2 each different from groups 3 and 4 each (p<0.0001); †groups 1 and 2 each different from groups 3 and 4 each (p<0.0001) and group 3 different from group 4 (p<0.005); ‡group 1 different from groups 3 and 4 each (p<0.0001).

catheterization-proved coronary disease with respect to age, exercise duration, and maximum double product achieved. Each patient group with a high likelihood of disease was older, exercised for a shorter duration, and achieved lower percentage of target heart rates, maximum heart rates, and maximum double products than did either group of subjects with a low likelihood of disease. Maximum predicted heart rate achieved and peak exercise heart rate achieved were higher in each group of subjects with a low likelihood of disease than in patients with clinical angina and were higher in patients with clinical angina than in patients with proved coronary disease. A greater proportion of patients with clinical angina compared with patients with proved coronary disease were female (p<0.01). However, sex distribution was similar in normal subjects and in patients with proved coronary disease, and it was nearly identical in groups combined according to high and low likelihoods of disease.

ST Segment/Heart Rate Slope in Study Groups and Derivation of Normal Limits

Calculated ST/HR slope values in the 300 subjects and patients, grouped according to low and high likelihoods of coronary artery disease, are shown in Figure 1. Mean ST/HR slope was 0.64 μV/beats/min (range, 0.0–3.9) in the normal group, 0.93 (range, 0.0–4.9) in the nonanginal chest pain group, 6.42 (range, 0.0–15.9) in the clinical angina group, and 10.05 (range, 0.5–97.1) in the catheterization-proved coronary artery disease group. ST/HR slopes were not significantly different between subjects in the normal and nonanginal chest pain groups or between patients in the clinical angina and proved coronary disease groups. However, ST/HR slopes in each subject group with a low likelihood of disease were significantly lower than test values in either patient group with a high likelihood of disease (p<0.001 for each comparison).

The 95th percentile value of the ST/HR slope in normal subjects was 2.395 μV/beats/min during

![Figure 1. Plot of ST segment/heart rate (ST/HR) slope in subgroups with low and high likelihoods of coronary artery disease (CAD). Line at 2.4 μV/beats/min represents the 95% partition determined by percentile estimation in normal subjects. CATH, catheterized.](http://circ.ahajournals.org/figure/1)
treadmill testing with our modified protocol. Accordingly, for the further evaluation of test performance, ST/HR slopes less than 2.4 μV/beats/min were defined as normal, and values 2.4 or greater were defined as abnormal; this ST/HR slope partition is shown as the dashed line in Figure 1.

Normal Limits of the ΔST Segment/Heart Rate Index

Mean ΔST/HR index was 0.50 μV/beats/min (range, 0.0–2.2) in the clinically normal group, 0.72 (range, 0.0–2.6) in the nonanginal chest pain group, 4.11 (range, 0.67–11.43) in the clinical angina group, and 4.78 (range, 0.33–14.17) in the catheterization-proved coronary disease group. Test values were not significantly different between subject groups with a low likelihood of disease or between patient groups with a high likelihood of disease, but values in each subject group with a low likelihood of disease were significantly lower than values in each patient group with a high likelihood of coronary disease ($p < 0.001$ for each comparison).

The 95th percentile value of the ΔST/HR index in normal subjects was 1.604 μV/beats/min. For the evaluation of test performance, ΔST/HR indexes 1.6 or less were defined as normal, and values greater than 1.6 were defined as abnormal.

Specificity and Sensitivity of ST Segment/Heart Rate Slope, ΔST Segment/Heart Rate Index, and Standard Test Criteria

Test outcome for all studies, specificity of the ST/HR slope and ΔST/HR index in subjects with a low likelihood of disease, and sensitivity of the ST/HR slope and ΔST/HR index in patients with a high likelihood of disease are compared with test outcome, specificity, and sensitivity of standard exercise test criteria in these groups in Table 2.

By definition, the ST/HR slope partition value of 2.4 μV/beats/min and the ΔST/HR index partition value of 1.6 μV/beats/min each resulted in a specificity of 95% in the normal subjects. Although only one subject in this group had a positive standard test response, there were 15 equivocal test responses, resulting in a significantly lower specificity (84%) for standard test criteria ($p < 0.01$). Among subjects with nonanginal chest pain, the 90% specificity of the ST/HR slope and 88% specificity of the ΔST/HR index were not significantly different from the 82% specificity of standard test criteria. However, the strong dependence of test specificity on population characteristics and group selection was apparent in the 18 patients with stable angina who had normal coronary arteries at angiography. In this group, specificity of the ST/HR slope was only 72% (13 of 18 patients), whereas specificity of the ΔST/HR index was 61% (11 of 18 patients) and that of standard test criteria was 56% (10 of 18 patients).

In patients with catheterization-proved coronary disease, 95% had ST/HR slopes 2.4 μV/beats/min or greater and 93% had ΔST/HR index values greater than 1.6 μV/beats/min; in contrast, sensitivity of the standard test was only 68% ($p < 0.001$ for each comparison). Similarly, significant differences

### Table 2. Specificity and Sensitivity of the Standard Exercise Test and ST Segment/Heart Rate Slope

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n=100)</th>
<th>Group 2 (n=50)</th>
<th>Group 3 (n=50)</th>
<th>Group 4 (n=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ST/HR slope criteria</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST/HR slope &lt;2.4</td>
<td>95</td>
<td>45</td>
<td>3</td>
<td>5</td>
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<tr>
<td>ST/HR slope ≥2.4</td>
<td>5</td>
<td>5</td>
<td>47</td>
<td>95</td>
</tr>
<tr>
<td>Specificity</td>
<td>95% (95/100)</td>
<td>90% (45/50)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>...</td>
<td>...</td>
<td>94% (47/50)</td>
<td>95% (95/100)</td>
</tr>
<tr>
<td>p value*</td>
<td>$p &lt; 0.01$</td>
<td>$p = NS$</td>
<td>$p &lt; 0.001$</td>
<td>$p &lt; 0.001$</td>
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<tr>
<td>Standard test criteria</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Negative</td>
<td>84</td>
<td>41</td>
<td>7</td>
<td>13</td>
</tr>
<tr>
<td>Equivocal</td>
<td>15</td>
<td>9</td>
<td>9</td>
<td>19</td>
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<tr>
<td>Positive</td>
<td>1</td>
<td>0</td>
<td>34</td>
<td>68</td>
</tr>
<tr>
<td>Specificity</td>
<td>84% (84/100)</td>
<td>82% (41/50)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>...</td>
<td>...</td>
<td>68% (34/50)</td>
<td>68% (68/100)</td>
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<tr>
<td>p value†</td>
<td>$p &lt; 0.01$</td>
<td>$p = NS$</td>
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<td>$p &lt; 0.001$</td>
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<tr>
<td>ΔST/HR index criteria</td>
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<tr>
<td>ΔST/HR index ≤1.6</td>
<td>95</td>
<td>44</td>
<td>6</td>
<td>7</td>
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<tr>
<td>ΔST/HR index &gt;1.6</td>
<td>5</td>
<td>6</td>
<td>44</td>
<td>93</td>
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<tr>
<td>Specificity</td>
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<td>88% (44/50)</td>
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</tr>
<tr>
<td>Sensitivity</td>
<td>...</td>
<td>...</td>
<td>93% (93/100)</td>
<td></td>
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</table>

*ST/HR, ST segment/heart rate.
†ΔST/HR index vs. standard exercise test.
were found between test sensitivities in patients with clinical angina (Table 2). When patient groups with a high likelihood of disease were combined, sensitivity of the ST/HR slope partition of 2.4 μV/beats/min was 95% (142 of 150 patients), markedly greater than the 68% (102 of 150 patients) sensitivity of standard exercise test criteria \( (p < 0.001) \). Sensitivity of the ST/HR slope was also significantly greater than the potential identification of 87% (130 of 150) of patients with a high likelihood of disease that would result if equivocal electrocardiographic responses were considered positive tests \( (p < 0.01) \). The 91% (137 of 150 patients) sensitivity of the ΔST/HR index partition of 1.6 μV/beats/min in combined patient groups with a high likelihood of disease was also significantly greater than the sensitivity of standard test criteria \( (p < 0.001) \) and was not significantly different from the 95% sensitivity found for the ST/HR slope \( (\chi^2 = 2.3) \).

**Comparison of Test Performance by Receiver-Operating Curves**

Receiver-operating curves were used to compare the sensitivity of different partitions of the ST/HR slope, the ΔST/HR index, and ST segment depression in patients with catheterization-proved coronary disease at matched levels of test specificity determined by percentile estimation in normal subjects (Figure 2). At partition values corresponding to any specificity, sensitivity of the ST/HR slope was slightly higher than that for the ΔST/HR index, and each heart rate–adjusted method exceeded the sensitivity of maximum ST segment depression for the detection of coronary artery disease. Thus, improved performance of the ST/HR slope and the ΔST/HR index was not a consequence of partition value definition or criteria selection.

**Heart Rate–Adjusted Criteria in Equivocal Standard Exercise Tests**

The proportion of equivocal (type 2) standard exercise test responses was similar in each study group (Table 2). Equivocal tests occurred in 16% (24 of 150) of subjects with a low likelihood of disease and in 19% (28 of 150) of patients with a high likelihood of disease \( (p = NS) \). The calculated ST/HR slopes in these studies are shown in Figure 3 in relation to the magnitude of upsloping ST segment depression and the likelihood of disease. Although measured ST segment depression was similar in these populations, patients with a high likelihood of disease had significantly higher ST/HR slopes than did subjects with a low likelihood of disease. Among patients with a high likelihood of disease, 96% (27 of 28 patients) had ST/HR slopes above 2.4 μV/beats/min, whereas among subjects with a low likelihood of disease, 71% (17 of 24 subjects) had ST/HR slopes below 2.4 μV/beats/min. Thus, based on pretest clinical assessment of the study population, the ST/HR slope correctly classified 85% (44 of 52) of unequivocal standard exercise test responses. By similar analysis, the ΔST/HR index partition of 1.6 μV/beats/min correctly classified 83% (43 of 52) of equivocal standard test responses.

**Test Sensitivity in Relation to Extent of Coronary Artery Disease**

Test sensitivities of the ST/HR slope, the ΔST/HR index, and standard test criteria are shown in Table 3 in relation to the anatomic extent of coronary disease in the 100 patients with catheterization-proved coronary obstruction. For each test, sensitivity increased with increasing numbers of obstructed arteries. Within each subgroup defined by extent of obstruction, detection of disease by the
ST/HR slope was significantly greater than by the standard test. Of note, the ST/HR slope identified all patients with three-vessel coronary disease, and 97% (70 of 72) of patients with multivessel disease. The ΔST/HR index identified 95% of patients with three-vessel disease and 94% (68 of 72) of patients with multivessel disease. In contrast, standard test criteria identified only 83% (60 of 72) of patients with three-vessel disease and only 76% (55 of 72) of patients with multivessel disease.

Discussion

These data demonstrate that heart rate–adjusted ST segment partition criteria with high specificity in normal subjects can markedly improve the sensitivity of treadmill exercise electrocardiography for the detection of coronary artery disease in patients with angina pectoris. In contrast is the significantly lower test sensitivity of standard test criteria for the detection of myocardial ischemia and the high prevalence of equivocal test findings in these groups. As shown by the receiver-operating curves, improved test performance of the ST/HR slope and the ΔST/HR index is a function of heart rate correction of ST depression and is not an artifact of selection of partition criteria. Thus, our findings confirm the value, if not the near-perfect accuracy, of the ST/HR slope in evaluating suspected coronary disease as reported from Leeds, England.7–10 Further support is found in other early studies that used bicycle testing.11,12 In our own retrospective studies of abbreviated ST/HR slope methodology during treadmill testing,13–18 and in other retrospective approximations of the method,19,20

**TABLE 3. Sensitivity of Standard Test Criteria and the ST Segment/Heart Rate Slope According to the Extent of Coronary Disease in Catheterized Patients**

<table>
<thead>
<tr>
<th>Extent of coronary artery disease</th>
<th>One-vessel</th>
<th>Two-vessel</th>
<th>Three-vessel</th>
<th>Total coronary artery disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>ST/HR slope ≥2.4</td>
<td>89% (25/28)</td>
<td>94% (29/31)</td>
<td>100% (41/41)</td>
<td>95% (95/100)</td>
</tr>
<tr>
<td>p value*</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.05</td>
<td>p &lt; 0.05</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Standard exercise test</td>
<td>46% (13/28)</td>
<td>68% (21/31)</td>
<td>83% (34/41)</td>
<td>68% (68/100)</td>
</tr>
<tr>
<td>p value†</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.05</td>
<td>p = NS</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>ΔST/HR index &gt; 1.6</td>
<td>89% (25/28)</td>
<td>94% (29/31)</td>
<td>95% (39/41)</td>
<td>93% (93/100)</td>
</tr>
</tbody>
</table>

ST/HR, ST segment/heart rate.

*ST/HR slope vs. standard exercise test; †ΔST/HR index vs. standard exercise test.
Methodologic Considerations

Our data establish criteria that extend the diagnostic applicability of the ST/HR slope, originally developed during upright bicycle exercise,7,8 to more widely used treadmill exercise electrocardiography. The present findings are based on a number of clinical observations and technical modifications, derived from our retrospective experience with the method13-17 and recently reviewed in detail,18 that are important for accurate calculation of the ST/HR slope during treadmill exercise. These include pretest exclusion of patients with clinically evident recent infarction16 and valvular disease,15 use of a modified treadmill protocol with smaller workload increments between stages to allow linear regression of peak exercise data,17 and incorporation of bipolar precordial lead CMS.17,18 Although the regression method is time consuming, analysis has been greatly simplified by the use of computer-assisted ST segment measurement that has previously been validated in our laboratory.17

Our ST/HR slope partition of 2.4 µV/beat/min is considerably higher than the 1.1 µV/beat/min found by Elamin et al18 as an upper limit in normal subjects during bicycle testing, and this difference highlights the extreme dependence of test findings on methodology.18 Although varying physiologic responses to treadmill and bicycle exercise may account for part of this difference, an additional factor is likely to be our measurement of ST segment depression at 60 msec, rather than at 80 msec, after the J point. Particularly in subjects with rapidly upsloping ST segments, earlier measurement results in greater magnitude of ST segment change and a consequent increase in calculated values. On the other hand, our partition compares closely with the 2.2 µV/beat/min value selected from retrospectively derived receiver-operating curves by Finkelhor et al19 for optimal identification of coronary disease among catheterized patients.

Normal Limits of Heart Rate–Adjusted ST Segment Indexes and Test Specificity

A major purpose of our study was to prospectively establish normal limits of the heart rate–corrected ST segment indexes in a clinically relevant reference population. However, unbiased definition of a normal population for such evaluation, short of random examination and catheterization, is difficult and imperfect.29-32 Specificity of a new test is often overestimated when normal limits are derived from normal volunteers who are generally not representative of the population in whom the criteria will be applied.30,31 Conversely, specificity is clearly underestimated when test partition values are derived from patients with normal coronary angiograms, who are usually highly symptomatic and often have other cardiac abnormalities that may cause abnormal test results in the absence of coronary disease.30

Although coronary disease cannot be excluded with certainty in our normal population, age- and sex-adjusted symptom-based risk assessment,22,23 taken together with normal cardiac examinations and normal resting electrocardiograms required for entry to this group, suggest that considerably less than 5% of these subjects are likely to have important coronary obstruction. In addition to avoiding bias introduced by alternate reference standards for subject selection, derivation of normal limits for the new exercise electrocardiographic criteria in this population has clinical relevance that outweighs the diagnostic uncertainty. This group is representative of a large proportion of people currently referred for screening exercise electrocardiography, and it is precisely in this population that highly specific test criteria are required in practice. Given the 15% prevalence of equivocal standard test findings in these subjects (Table 2), the improved predictive accuracy of the ST/HR slope and the ΔST/HR index in this subset suggest that the advantage of these methods for accurate diagnosis may extend beyond improved sensitivity for coronary disease alone.

It must be recognized that the selected nature of our clinically normal subjects limits the extent to which test performance can be generalized to other groups. The high specificity of test partitions derived from our reference populations should remain comparably high in similarly selected subjects with a low likelihood of coronary disease. However, as suggested by our retrospective experience with patients with aortic regurgitation,15 specificity of these methods should decline in symptomatic or asymptomatic populations with a high prevalence of additional nonischemic diseases that are characterized by abnormal loading conditions. Further, specificity of any imperfect test will be lower in patients subject to post-test referral bias because the test itself becomes an important determinant of subsequent clinical management30,31 and because individuals with both true-positive and false-positive tests are selected for coronary angiography. This is well illustrated by our findings in patients with stable angina who had normal coronary arteries at angiography, in whom specificity of the ST/HR slope was only 72% and specificity of the ΔST/HR index was only 61%. Although in no patient were heart rate–adjusted ST segment indexes themselves a consideration in referral for catheterization, each method is partially covariate with the absolute magnitude of ST depression, which in turn was a contributing factor in the clinical decision to recommend angiography in this group.

Thus, test specificity can be expected to decline as these methods are applied to heterogenous populations.31 Using a limited number of electrocardiographic leads in a retrospective evaluation of catheterized patients with only a 46% prevalence of coronary disease, Detrano et al20 found a modified ΔST/HR index to have a specificity of approximately 80%, when interpolated data from their
report are examined at an estimated partition value of 1.6 μV/ beats/min. This result falls between the high specificity found in our subjects with a low likelihood of disease and the lesser specificity found in our highly preselected patients with angina but normal coronary angiograms. Similar variability should affect future test performance with our methods in different populations and should not be equated with test error.

Improved Sensitivity of the Exercise Electrocardiogram

In addition to establishing normal test values, the second major goal of our study was to prospectively compare the sensitivity of the ST/HR slope and the ΔST/HR index with standard exercise electrocardiographic criteria for the detection of myocardial ischemia in patients with stable angina pectoris due to coronary artery disease. Confirmation of this diagnosis requires angiography, but because the extent of coronary obstruction may differ in patients with angina who are referred for invasive evaluation, these patients may not be representative of the general stable angina population.26,32 Accordingly, we also examined test sensitivity in a group of patients with stable angina who were not referred for catheterization but had a high pretest likelihood of coronary disease based on age- and sex-adjusted symptoms. In each of the angina groups, the heart rate–adjusted ST depression indexes significantly increased the sensitivity of the exercise electrocardiogram for coronary disease, and interestingly, the sensitivity of each test was similar in catheterized and noncatheterized patients with angina.

It must be emphasized that neither of these symptomatic groups should be considered representative of the general population of asymptomatic subjects with coronary disease, and no conclusions should be drawn about test performance in this important group, which requires carefully designed prospective evaluation. Our data do not address the performance of either of the heart rate–adjusted ST segment indexes in patients with intermediate pretest probabilities of coronary artery disease, such as atypical angina, which also require future evaluation. However, it is reasonable to postulate that improved sensitivity for occult coronary obstruction will only occur with a test that can improve the poor ability of standard exercise electrocardiographic criteria to detect overt myocardial ischemia. The poor sensitivity of standard test criteria for coronary disease in our patients is consistent with findings in previous studies,1–5 and despite the relatively low exercise heart rates achieved in our angina groups, this performance cannot be attributed to the effect of drugs or to the absence of exercise-induced ischemia at peak effort. All treadmill tests were symptom limited, and all patients in the noncatheterized stable angina group were limited by chest pain during exercise testing. Among catheterized patients with angina, most were limited by chest pain, and only a few were limited by fatigue alone.

Test sensitivity is also affected by other clinical characteristics of the study population, and it is not appropriate to extend our findings beyond our stable angina groups without further evaluation. We have previously demonstrated in retrospective studies that the ST/HR slope is poorly sensitive for the detection of coronary disease shortly after Q wave myocardial infarction. Admixture of such patients may explain discordant test findings in two studies that have been critical of the method,33,34 but because recent infarction is ordinarily easily detected in practice, recognition of this limitation should be considered a guideline for test applicability rather than generalized as evidence for test failure.18,35

It is also clear that test sensitivity is highly dependent on the severity of disease in the study population.2–4 As demonstrated in Table 3, not only standard test criteria but each of the heart rate–adjusted ST segment indexes detect a lower proportion of patients with one-vessel coronary disease than with multivessel disease. Indeed, recent studies have confirmed that an important clinical role for these indexes is the identification of patients with anatomically severe obstruction within the stable angina population.24 It is therefore evident that in addition to variable performance related to pretest selection factors, sensitivity of our partition values for the detection of coronary obstruction in future studies will vary with the distribution of disease. However, although these limitations require consideration, the markedly improved sensitivities of the ST/HR slope and the ΔST/HR index for one-vessel and multivessel coronary disease remain striking evidence for the merit of these methods.

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References


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