Accurate Detection of Coronary Artery Disease by Integrated Analysis of the ST-Segment Depression/Heart Rate Patterns During the Exercise and Recovery Phases of the Exercise Electrocardiography Test

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The diagnostic accuracy of the standard end-exercise ST-segment criterion of the exercise electrocardiography (ECG) test is limited to only about 70% in detection of coronary artery disease in clinical populations.1-7 Recently, the ST-segment depression/heart rate (ST/HR) slope, the ST/HR index, and multivariate ST/HR analysis have markedly improved the diagnostic performance of the exercise ECG test.3-10 However, none of the above methods quantify evidence favoring the clinical utility of the ST/HR criterion. Therefore, the objective of this study was to evaluate whether a novel continuous diagnostic variable, the HR-adjusted ST depression pattern during the exercise phase, integrated with the HR-adjusted ST depression pattern during the recovery phase after exercise, can significantly improve the diagnostic performance and clinical utility of the exercise ECG test for the detection of coronary artery disease. ©1996 by Excerpta Medica, Inc.

index, all of which variables use either the exercise or recovery phase alone.

**METHODS**

**Study population:** The computerized exercise ECG measurements of 1,507 consecutive patients were digitally stored for later analysis in Tampere University Hospital, Finland. Each patient was referred by a physician for a routine clinical exercise ECG test because of symptoms or abnormal signs suggesting disease. All patients with either a left or right bundle branch block pattern on the resting electrocardiogram were excluded.

After the exclusion of patients with bundle branch block, there were 180 patients who were also investigated by coronary angiography within 180 days of the exercise test and were not treated by coronary angioplasty or surgery between the exercise test and coronary angiography. In addition, there were 18 patients who had no perfusion defect according to technetium-99m sestamibi single-photon emission computed tomography (MIBI SPECT) myocardial imaging and 189 patients who were clinically normal with respect to cardiac diseases (no history of any cardiac disease, normal resting electrocardiogram, and no anginal chest pain or cardiac medication).

Of the 180 angiographically examined patients, 162 had a significant (≥50%) stenosis at least in 1 of the major coronary arteries. Nine of these 162 patients were also examined by MIBI SPECT myocardial imaging, which showed no perfusion defect in 1 case. This controversial case was excluded, together with all 30 patients who had a recent (<8 weeks) myocardial infarction and all 4 patients without a recorded electrocardiogram up to 3 minutes of recovery. Thus, 127 patients were selected for the group of angiographically proven coronary artery disease (Table I).

Of the 18 patients without significant coronary artery disease according to angiography, 4 with a previous myocardial infarction and 1 without a recorded electrocardiogram up to 3 minutes of recovery were excluded. Thus, the clinical reference group comprised 220 patients, consisting of 13 patients without coronary artery disease according to angiography, 18 patients without myocardial ischemia according to MIBI SPECT, and 189 clinically normal patients with respect to cardiac diseases (Table I).

**Exercise electrocardiography test:** All subjects were tested on a bicycle ergometer. The exercise protocols were individualized to some extent depending on the patient’s physical condition. The protocol followed a standard clinical routine, with an initial workload of 40 W for women and 50 W for men, and an increment of 40 W or 50 W every 4 minutes for women and men, respectively.

The ECG recordings were made with a commercial ECG recording system (SYSTEM II EXES; Siemens-Elema, Solna, Sweden). The ST-segment and HR data were stored for further processing and analysis. The ECG lead system used in the exercise test was the Mason-Likar modification of the standard 12-lead system. Exercise tests were sign-or symptom-limited maximal tests using recommended criteria for termination; exhaustion or chest pain was the most common reason for termination.

**Exercise electrocardiographic variables:** Using computer analysis of the stored ST-segment and HR data, the maximum values of the ST/HR hysteresis, end-exercise ST depression (STend), ST depression at 3 minutes of recovery (STrec), and ST/HR index were determined from the 12-lead system (leads aVL, aVR, and V1 excluded) for each patient without knowledge of his or her status. In addition, by analyzing the same set of leads, we determined the HR recovery loop from the lead with the most pronounced end-exercise ST-segment depression, as described by Okin et al. The ST-segment amplitudes used in constructing all these diagnostic variables were measured to the nearest 10 μV at 60 ms after the QRS offset.

For the ST/HR diagram, the pairs of ST depression and HR were measured immediately before starting the exercise with the patient sitting on the bicycle, at the end of each minute of exercise, at the end of exercise, and at the end of each of the first 3 consecutive minutes of recovery after exercise. Determination of the ST/HR hysteresis from a single-lead ST/HR diagram in different cases is illustrated.

**TABLE I** Study Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Angiographically Proven CAD (n = 127)</th>
<th>Total (n = 220)</th>
<th>No CAD by Angiography (n = 13)</th>
<th>No Ischemia by MIBI SPECT (n = 18)</th>
<th>Clinically Normal (n = 189)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>55 ± 8</td>
<td>48 ± 12</td>
<td>52 ± 5</td>
<td>50 ± 9</td>
<td>47 ± 12</td>
</tr>
<tr>
<td>Sex (men/women)</td>
<td>101/26</td>
<td>113/107</td>
<td>4/9</td>
<td>0/0</td>
<td>100/89</td>
</tr>
<tr>
<td>Medication (+)</td>
<td></td>
<td></td>
<td>4/9</td>
<td>0/0</td>
<td>100/89</td>
</tr>
<tr>
<td>β blockers</td>
<td>104/23</td>
<td>12/208</td>
<td>9/4</td>
<td>3/15</td>
<td>0/189</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>46/01</td>
<td>4/216</td>
<td>4/9</td>
<td>0/10</td>
<td>0/109</td>
</tr>
<tr>
<td>Nitrates</td>
<td>86/41</td>
<td>5/215</td>
<td>5/8</td>
<td>0/18</td>
<td>0/189</td>
</tr>
<tr>
<td>Anginal chest pain (+)</td>
<td>30/67</td>
<td>3/217</td>
<td>3/10</td>
<td>0/18</td>
<td>0/189</td>
</tr>
<tr>
<td>MaxHR (beats/min)*</td>
<td>125 ± 21</td>
<td>102 ± 19</td>
<td>143 ± 23</td>
<td>102 ± 17</td>
<td>104 ± 19</td>
</tr>
</tbody>
</table>

*Continuous data are expressed as mean ± SD.

CAD = coronary artery disease, MaxHR = maximal heart rate achieved, MIBI SPECT = technetium-99m sestamibi single-photon emission computed tomography.
in Figure 1. It is emphasized that ST depression is plotted in an upward direction on the vertical axis, and the negative values represent ST elevation. A continuous piecewise linear function between ST depression and HR for the exercise phase ($F_{ex}$) was obtained by connecting the consecutive ST/HR data pairs of the exercise phase with lines (solid lines, Figure 1). Similarly, a continuous piecewise linear function for the recovery phase after exercise ($F_{rec}$) was constructed by connecting the consecutive ST/HR data pairs of the first 3 minutes of the recovery phase, starting from the ST/HR data pair at the end of exercise (dashed lines, Figure 1). Then the difference between the $F_{rec}$ and $F_{ex}$ was integrated over the HR from the minimum HR of recovery ($HR_{rec}$) to the maximum HR ($HR_{ex}$). Finally, the integrated net difference was divided by the HR difference of the integration interval ($\Delta HR_{rec}$) to normalize the ST/HR hysteresis with respect to the HR decrease after exercise. Consequently, the dimension of the ST/HR hysteresis is in millivolts, representing the average difference of ST depression between the $F_{rec}$ (i.e., recovery phase) and the $F_{ex}$ (i.e., exercise phase).

The ST/HR index was calculated as the gradient between the ST/HR pairs at the start of exercise and at the end of exercise, as suggested by Detrano et al. The HR recovery loop was determined exactly as described by Okin et al. When the ST depression at 1 minute of recovery was less than the ST depression at matched HR during exercise, the direction of the HR recovery loop was considered to be clockwise (i.e., nonischemic direction). If the ST depression at 1 minute of recovery was greater than or equal to the ST depression at matched HR during exercise, the direction of the loop was considered to be counterclockwise (i.e., ischemic direction).

**Coronary angiography:** Selective coronary angiography was performed using the Judkins technique. Each coronary artery was imaged in multiple views in all cases. Degree of stenosis was defined as the greatest percent reduction of luminal diameter in any view compared with the nearest normal segment, without knowledge of the exercise ECG data. Coronary artery disease was considered significant when $\geq 50\%$ luminal narrowing was observed at least in 1 major coronary artery (left main, left anterior descending, left circumflex, or right coronary).

**Technetium-99m-sestamibi myocardial imaging:** MIBI myocardial perfusion imaging followed the standard clinical routine. Abnormalities in myocardial perfusion were identified as abnormal distribution images. Distribution images were determined by computer analysis of the results obtained from SPECT. Visual interpretation of regional perfusion defects was determined in the septal, anterior, lateral, posterior, inferior, and apical regions of the left ventricle. Perfusion defects were classified into 4 categories: (1) reversible, (2) persistent but partially reversible, (3) normal, and (4) fixed, which corresponded with (1) myocardial ischemia, (2) a combination of myocardial ischemia and infarction, (3) no perfusion defects, and (4) myocardial infarction.

![Figure 1. Plots of ST-segment depression against heart rate (HR) during both the exercise phase and the first 3 minutes of recovery after exercise (i.e., ST/HR diagrams) illustrating the computerized determination of the ST/HR hysteresis from a single lead. In these diagrams, ST depression is plotted on an upward direction on the vertical axis, and the negative values represent ST elevation. Typical ST/HR diagrams are shown for a clinically normal subject (upper left) with an unambiguously negative hysteresis in ST depression against HR (i.e., clockwise hysteresis loop in recovery) and for a patient with coronary artery disease (upper right) with an unambiguously positive hysteresis in ST depression against HR (i.e., counterclockwise hysteresis loop in recovery). More complex ST/HR diagrams are shown for a normal patient (lower left) and for a patient with coronary artery disease (lower right), in which cases the direction of the hysteresis in ST depression against HR was changed during the recovery phase. In a graphic sense, the ST/HR hysteresis was obtained by subtracting the area of negative hysteresis from the area of positive hysteresis and dividing the resulting net area by the $\Delta HR_{rec}$. 1v-CAD = 1-vessel coronary artery disease; 3v-CAD = 3-vessel coronary artery disease; $HR_{max}$ = maximum HR; $HR_{min}$ = minimum heart rate of recovery; $\Delta HR_{rec}$ = $HR_{max}$ - $HR_{min}$; MIBI SPECT = technetium-99m sestamibi single-photon emission computed tomography.](image-url)
Patients with all regions of the left ventricle classified in category 3 were considered to have no perfusion defect according to MIBI SPECT myocardial imaging.

Data analysis and statistical methods: Mean values of the descriptive variables are reported with SDs. The overall diagnostic performance of the continuous diagnostic variables, the ST/HR hysteresis, STend, STrec, and ST/HR index was compared independently of the operating point (i.e., partition value) selection by means of receiver-operating characteristic analysis. The area under the receiver-operating characteristic curve represents the overall diagnostic performance, i.e., the probability that a random pair of patients with and without coronary artery disease will be correctly diagnosed. The differences between the areas under the receiver-operating characteristic curves of the ST/HR hysteresis and those of the other diagnostic variables were compared using a computer program for nonparametric receiver-operating characteristic analysis (version 2.5, McGill University, Montreal, Canada) of correlated curves. Because of 3 comparisons, the alpha level of 0.017 was used for statistical significance.

RESULTS

The receiver-operating characteristic curves of the ST/HR hysteresis, STend, STrec, and ST/HR index, as well as the operating point of the HR recovery loop in the study population, are given in Figure 2. The area under the receiver-operating characteristic curve of the ST/HR hysteresis was 89%, which was significantly larger than that of the other continuous diagnostic variables. This result showed that the diagnostic performance of the ST/HR hysteresis in terms of coronary artery disease was the best regardless of the partition value selection. Furthermore, the sensitivity of the ST/HR hysteresis was higher than that of the other diagnostic variables at high specificities of >80%. This is the most important portion of the receiver-operating characteristic curve for diagnostic tests, such as the exercise ECG test, applied to populations with a relatively low prevalence of disease. The area under the receiver-operating characteristic curve of the STend was the smallest, at 76% (p < 0.0001 vs ST/HR hysteresis), whereas the 84% area of the STrec (p = 0.0063 vs ST/HR hysteresis) and the 83% area of the ST/HR index (p = 0.0023 vs ST/HR hysteresis) indicated mutually compatible overall diagnostic performance. The HR recovery loop resulted in 85% specificity and 72% sensitivity in the study population.

DISCUSSION

The initial observation by Bruce and McDonough of the diagnostic value of the hysteresis in ST-segment depression against HR in the detection of coronary artery disease was quantitatively proven by Okin et al. In their recent clinical study, Okin et al showed that the dichotomous HR recovery loop provided a significantly better diagnostic accuracy than the standard end-exercise ST depression criterion. The present results confirmed these findings with bicycle ergometry. Further, the diagnostic performance of the continuous ST/HR hysteresis was shown to be significantly better than the end-exercise ST depression, ST depression at 3 minutes of recovery, or ST/HR index regardless of the partition value selection in the clinical population of 347 patients.

Okin et al determined the HR recovery loop simply as a vector whereby the difference between the ST depression at 1 minute after peak exercise and the ST depression at matched HR during exercise determined the direction of the given vector. Thus, the HR recovery loop conveys information only on the direction of this difference and not about its magnitude, which may have independent diagnostic potential. In line with the notion by Okin et al., a refined continuous diagnostic variable is needed because a method using only 1 ST/HR data pair from the recovery phase may occasionally be unstable.

In this study, we refined further this useful approach and developed a continuous diagnostic vari-
able, the ST/HR hystersis, which extracts the prevailing direction and average magnitude of the hysteresis in ST depression against HR. It is obvious that this analysis is not straightforward, as even the direction of the hysteresis may change during the recovery period, as was illustrated in Figure 1 and by Bruce and McDonough. However, the ST/HR hysteresis attempts to take into account the complex pattern of the ST/HR diagram by allocating the ST-depression pattern of the first 3 consecutive minutes of the recovery phase after exercise to the ST depression pattern of the exercise phase in an HR-adjusted manner (Figure 1). Through this adjustment, the ST/HR hysteresis actually represents the average difference in the HR-adjusted ST-segment depressions between the exercise and recovery phases regardless of the magnitude of HR decrease during the recovery phase.

The relatively complex determination of the ST/HR hysteresis required computerized measurement and offline analysis of the ECG data; these features may be well integrated to commercial exercise ECG systems and thus accessible to clinical users. Furthermore, we believe that the ST/HR hysteresis reflects more accurately the actual pattern of the ST/IIR diagram and is likely more reproducible and stable than a simple vector analysis based on only a single recovery ST/HR data pair. When compared with the dichotomous HR recovery loop, the continuous nature of the ST/HR hysteresis is an obvious advantage allowing free selection of the partition value. This property would facilitate effective use of pretest probability according to Bayes' theorem when applied individually in diagnostic decision making.20

The major limitation of this study was the influence of referral bias; i.e., the conventional interpretation of the exercise ECG probably affected the decision to proceed with coronary angiography. In practice, this limitation is unavoidable in exercise ECG studies using coronary angiography as the gold standard because it is impossible to investigate all patients with coronary angiography regardless of the outcome of the preceding exercise ECG. It is obvious that the referral bias affects the sensitivity and specificity of the ECG test.21 However, we emphasize that the entire areas under the receiver-operating characteristic curves were compared to be able to analyze the performance characteristics of the exercise ECG variables independently of the partition value selection (i.e., without fixing the sensitivity or specificity of the diagnostic variable).22 Furthermore, all these exercise ECG variables were determined from the same study population, thus minimizing the differences between the variables induced by selection bias. This may not be the case if the variables were evaluated in different populations.

Another limitation of this study was the scanty sample rate of the ST/HR data pairs during recovery after exercise. The relation between ST depression and HR during exercise is mostly linear, but during recovery is apparently not, and thus more ST/HR pairs from the recovery phase might be useful for more accurate construction of the ST/HR diagram. This especially applies to the very beginning of the recovery, when the HR decreases most rapidly. However, the present calculation algorithm of the ST/HR hysteresis sets no limit to the sampling frequency of the ST/HR pairs and would apply even to the beat-to-beat ST/HR sampling.

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