Diagnostic Value of the Recovery Time-Course of ST Slope on Exercise ECG in Discriminating False-From True-Positive ST-Segment Depressions

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Background Using the exercise ECG for diagnosing coronary artery disease (CAD) is hampered by the occurrence of false-positive (FP) ST-segment depression. Because it is known that the recovery ST-T time-course in CAD differs from that in FP subjects, the ST slope may help discriminate FP from true-positive (TP) results.

Methods and Results Treadmill digitized ECG from patients with significant ST-segment depressions and normal resting ECG were analyzed in 134 patients with CAD on angiography (>50% narrowing) and reversible perfusion defects (TP group), and 64 subjects with normal perfusion (FP group) on exercise single photon emission computed tomography. The ST slope between the J-point and J80 was measured every minute up to 6-min postexercise. The ST slope was significantly higher in FP than in TP at peak exercise, and at postexercise 1-, 2- and 3-min (p<0.01, all). Thereafter, it gradually increased in TP, while monotonically decreasing in FP. Its decrease from 3- to 6-min could correctly diagnose 88% of FP subjects, whereas it was found in only 19% of TP patients (total accuracy 83%).

Conclusions The ST slope change from early to late recovery is a simple yet reliable marker for discriminating FP from TP ST-segment responses in subjects with a normal resting ECG. (Circ J 2004; 68: 915–922)

Key Words: Coronary disease; Electrocardiography; Exercise; Ischemia

Gender and several anatomical and functional characteristics are associated with an increased incidence of abnormal ST-segment responses to exercise in the absence of coronary artery disease (CAD). Subsets with an increased incidence of false-positive (FP) exercise ECG responses with respect to ischemia include middle-aged women,1–3 and patients with mitral valve prolapse.1,4,5 Patients with left ventricular hypertrophy (LVH) form a separate subset with the potential for inadequate myocardial perfusion in the absence of significant CAD.6,8 Advanced ECG analysis approaches applicable to the clinical evaluation of the standard exercise ECG in these subjects are currently unavailable and need to be developed.

The ST slope, usually computed as the slope between the J-point and the J80, has been mainly used for differentiating the configuration of ST-segment depression (ie, upsloping, horizontal, and downsloping). The latter two are considered more specific for myocardial ischemia than the upsloping shape.1,7 However, in CAD, the shape often changes with time during the test and a relatively characteristic time-course can be seen. ST-segment depression during exercise changes from upsloping (or horizontal) to downsloping in the early recovery at 2–4 min; that is, the ST slope decreases in early recovery (Fig 1A).7,8 Subsequently, both ST-segment depression and the ST slope return gradually toward the baseline; that is, the ST slope increases in late recovery. On the other hand, in many subjects with FP ST-segment depression (FPD) (Fig 1B), the downsloping shape appears, not in the early, but in the late recovery. Unlike in CAD, the ST slope monotonically decreases from early to late recovery, possibly serving as the differentiating characteristic.5,8

We thus hypothesized that the temporal changes in the ST slope from early to late recovery are capable of differentiating these 2 groups and we performed high-resolution computer analysis of the ST slope in the recovery in a relatively large population with normal resting ECGs. Because the majority of subjects with normal exercise single-photon emission computed tomography (SPECT) results are no longer referred for coronary angiography in the clinical practice, we used this technique for the selection of FPD subjects. True-positive (TP) results were defined when both angiographic and exercise SPECT images were abnormal.

Methods

Study Population

From the digitized ECG recordings consecutively obtained during routine treadmill testing for the evaluation of CAD, the 198 patients (62±9 years) with an exercise-induced significant ST-segment depression were recruited. Patients were excluded if they had resting ECG abnormal...
malities such as prior myocardial infarction, ST-segment depression, T-wave inversion, LVH, or bundle branch block. We also excluded patients with atrial fibrillation or frequent extrasystole (>10 beats/min) and those with exercise-induced ST-segment elevation (≥0.1 mV). All subjects gave informed consent.

Patients were divided into the 2 groups according to the results of coronary angiography and exercise SPECT performed within 3 months after treadmill testing. The TP group comprised 134 patients (62±9 years) who had angiographical coronary artery stenosis (>50% luminal narrowing). Inducible ischemia was confirmed by the presence of reversible defects corresponding to coronary lesions. The FP group included 64 subjects (63±10 years) with normal exercise SPECT images. Of them, 19 (30%) had undergone coronary angiography and none had significant CAD.

We investigated the presence of a history of hypertension, which may be associated with a high incidence of FPD in patients with mild LVH only discernible by echocardiographic study.9,10

Treadmill Exercise ECG

Exercise testing was performed according to our protocol, which was similar to the modified Bruce protocol.11 We performed the test using a treadmill system (Formula, Esaote, Italy), while simultaneously digitizing the ECG data at 500 Hz (12-bit resolution) from rest, during exercise, and into recovery for at least 6 min. A hard copy of the standard 12-lead ECG at a paper speed of 25 mm/s at rest, at the end of each stage, at peak exercise, and every minute into recovery was produced. Termination of exercise was decided by the occurrence of exhaustion, ST-segment depression >0.3 mV, significant arrhythmias, moderately severe angina, inadequate blood pressure response, or the attainment of 90% predicted maximal heart rate.
Table 1 Clinical Characteristics of the Study Population

<table>
<thead>
<tr>
<th></th>
<th>FP (n=64)</th>
<th>TP (n=134)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>M/F (n, %)</td>
<td>34/30 (53/47)</td>
<td>118/16 (88/12)</td>
<td>**</td>
</tr>
<tr>
<td>Age (years)</td>
<td>63±10</td>
<td>62±9</td>
<td></td>
</tr>
<tr>
<td>Coronary risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>44</td>
<td>60*</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>14</td>
<td>40*</td>
<td></td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitrates (%)</td>
<td>11</td>
<td>60**</td>
<td></td>
</tr>
<tr>
<td>ß-blockers (%)</td>
<td>16</td>
<td>57**</td>
<td></td>
</tr>
<tr>
<td>Calcium-antagonists (%)</td>
<td>27</td>
<td>68**</td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMT (%)</td>
<td>–</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>SVD (%)</td>
<td>–</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>DVD (%)</td>
<td>–</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>TVD (%)</td>
<td>–</td>
<td>20</td>
<td></td>
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Values are mean±SD or numbers (percentage). **p<0.01 vs FP group. *p<0.05 vs FP group. FP , fales-positive; TP , true-positive; LMT, left main trunk disease; SVD, single vessel disease; DVD, double vessel disease; TVD, triple vessel disease.

On the ECG hard copies, we identified a significant ST-segment depression according to the following criteria: (1) horizontal or downsloping ST-segment displacement at the J-point ≥0.1 mV; and (2) upsloping ST-segment displacement at Jso ≥0.15 mV in at least 3 consecutive beats at peak exercise. Arterial blood pressure was measured by a sphygmomanometer at the end of each stage, peak exercise and recovery.

ECG Analysis

For the standard 12-lead ECG, only 2 of 6 limb leads are actually recorded, and the other 4 leads are derived mathematically from these 2 leads.12 Our stress system capable of reproducing the 12-lead ECG actually records 2 unique limb leads (leads I and II) and 6 precordial leads in a similar manner. We performed the following analysis using the digitized ECG data set of 8 leads (I, II, and V1–6; Fig 2A).

To determine the ST slope, we found the peak of each R wave in lead V5, with which the QRS-T complex was averaged over 5 beats to improve the signal-to-noise ratio. On the QRS-T complex, we measured ST-segment displacement at peak exercise and at every minute during the first 6 min postexercise, in a lead with a greater ST-segment depression of either lead V5 or V6. Because the J-point determination is occasionally difficult, we used the algebraic sum (|V|) of the absolute value of voltage relative to the isoelectric Q-Q baseline from all 8 leads (Fig 2B). With reference to this curve, we determined the J-point by detecting the point at which the curve most closely approached the baseline (the lowest point of the trough). If the curve did not have a distinct trough, the J-point was assumed to be the inflection point at which a steep descent of the curve was terminated. Once the J-point was determined, ST-segment displacement from the Q-Q baseline at the J-point and Jso was measured automatically (Fig 2C). From these 2 values, we calculated the ST slope (mV/s). The ST slope, treated as a continuous variable ranging from negative to positive values, was used for the later intra- and intergroup comparisons. The time-courses of ST-segment depression and ST slope from peak exercise to the 6-min recovery (every minute, 7 time points) were assessed.

Table 2 Exercise Test Results

<table>
<thead>
<tr>
<th></th>
<th>FP (n=64)</th>
<th>TP (n=134)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest HR (beats/min)</td>
<td>72±11</td>
<td>67±11</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Rest SBP (mmHg)</td>
<td>139±22</td>
<td>132±19</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Peak HR (beats/min)</td>
<td>149±19</td>
<td>127±21</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Peak SBP (mmHg)</td>
<td>178±27</td>
<td>160±24</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Exercise time (s)</td>
<td>526±150</td>
<td>480±136</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Exercise-induced chest pain (%)</td>
<td>9</td>
<td>46</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ST-segment depression (mV)</td>
<td>–0.20±0.11</td>
<td>–0.22±0.12</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

FP, fales-positive; TP, true-positive; HR, heart rate; SBP, systolic blood pressure.

Exercise Thallium-201 Scintigraphy

All subjects underwent bicycle exercise testing according to the same end points as defined earlier. At near-maximal exercise, thallium-201 was intravenously injected and the patient was encouraged to exercise for another 1 min. SPECT images were obtained at 15 min (initial images) and 4 h (delayed images). The images were reconstructed into transaxial tomograms, which were assessed by 2 experienced physicians unaware of the coronary anatomy. Thallium uptake in myocardial segments was classified as normal, mildly, moderately or severely reduced, or absent. A reversible defect was defined when the classification of uptake improved by at least one category from the initial to the delayed image.

Statistical Analysis

All data are presented as mean±SD. Unpaired t-test was used for comparisons between 2 groups. Differences in categorical variables were analyzed by chi-square analysis. The time-course of ST-segment depression and the ST slope were compared by analysis of variance for repeated measurement. When this test was significant, the Newman-Keuls post-hoc multiple comparison was performed.

For convenience in presentation, the term ‘sensitivity’ is used to measure the percentage of subjects who met the criteria for identifying FP results in the FP group. The term ‘specificity’ is used to measure the percentage of subjects who did not fulfill the criteria in the TP group.

Performance of diagnostic criteria was evaluated using receiver operating characteristic (ROC) curve analysis.13,14 The area under the curve (AUC), which is a measure of the discriminatory power of the index, was calculated for each variable and these areas were compared statistically.15 A p-value <0.05 was considered significant.

Results

Patient Characteristics

Although age was similar between the groups, the FP group included more females than the TP group (p<0.01, Table 1). Hypertension, common to both groups, was found more frequently in the TP (60%) group than in the FP group (44%, p<0.05). Approximately half of the TP patients (46%) had single-vessel disease.

Treadmill Exercise Test

Resting heart rate and systolic blood pressure were higher in the FP group than in the TP group (p<0.01 and p<0.05, respectively; Table 2). Exercise time, peak heart rate and peak systolic blood pressure were also higher in the FP group (p<0.05, p<0.01, and p<0.01, respectively). Chest
pain, including atypical, equivocal, or typical features for angina, occurred in 46% of the TP group and 9% of the FP group (p<0.01) during the test. Maximal ST-segment depression (J80) was marginally but significantly greater in the TP (–0.23±0.15 mV) than in the FP group (–0.20±0.11 mV, p=0.002, unpaired t-test).

**Time-Course of ST-Segment Depression**

Fig 3 shows the time-course of the recovery of ST-segment depression (J80). At peak exercise and in early recovery (at 1 and 2 min), ST-segment depression was significantly greater in the TP group (p<0.01, all) than in the FP group. No difference was observed at 3, 4, and 5 min. In the late recovery, ST-segment depression gradually recovered toward the baseline in the TP group, but remained unchanged in the FP group. Consequently, it was greater in the FP group than in the TP group at 6 min postexercise (p<0.01). Despite these differences, ST-segment depression at any time point hardly differed between the 2 groups because of a considerable overlap, evidenced by the large standard deviation.

**Time-Course of the ST Slope**

Fig 4 shows the time-course of the recovery of the ST slope. It decreased with time up to 3 min postexercise in each group. During this period, the ST slope was significantly lower in the TP group than in the FP group (all p<0.01). Thereafter it continued to decrease in the FP group, whereas it gradually recovered toward the baseline in the TP group. Thus, in the late recovery, the ST slope in the FP group changed in the opposite direction to that in the TP group.

Fig 5 shows the changes in the ST slope for each subject. In the FP group, the ST slope decreased between 3 and 6 min (0.12±0.55 to –0.28±0.50 mV/s, p<0.001), whereas it increased in the TP group (–0.25±0.77 to 0.06±0.52 mV/s, p<0.001). Most FP subjects (56/64, 88%) showed a decrease during this period, which was observed in only 19% of TP patients (25/134).

The time-course difference in the ST slope (∆ST Slope,
ST slope at 6 min minus that at 3 min) is plotted for each subject in Fig 5. When a decrease in the ST slope (∆ST Slope <0 mV/s) was set as the criterion for FPD, we could discriminate FP from TP patients with a sensitivity of 88% and a specificity of 81%. Conversely, its increase was highly predictive for TP patients; ∆ST slope ≥0.4 mV/s was 100% predictive for TP patients (FP n=0, TP n=49) and ∆ST slope ≥0.0 mV/s was 93% predictive for TP patients (FP n=8, TP n=109).

Because coronary angiography was not performed in 70% of the FP group, we performed separate subgroup analysis of subjects with (n=19) and without (n=44) angiography. As a result, the ST slope significantly decreased from postexercise 3- to 6-min in each group (p<0.001, for both groups). ∆ST slope was very similar between the 2 groups (−0.36±0.43 mV/s with vs −0.42±0.35 mV/s without angiography, NS).

Comparison of Test Performance by ROC

Fig 7 shows the ROC curves describing the ability for the discrimination using the ST slope for 1, 3 and 6 min after exercise and ∆ST slope. The AUC for ∆ST slope was significantly greater than that of the ST slope obtained at any of the 3 time points (p<0.01, all).
Discussion

We have demonstrated that computer analysis of the recovery time-course of the ST slope is a simple, reliable method of discriminating FP from TP ST-segment responses. The accuracy using $\Delta ST$ slope $<0.0$ mV/s as the criterion for FP response is considered to substantially improve the diagnostic value of exercise ECG. Furthermore, the finding that $\Delta ST$ slope $\geq 0.4$ mV/s could correctly identify TP responses without exception is important for the interpretation of the exercise ECG. One can consider that an exercise-induced ST-segment depression followed by an ST slope increase from post-exercise 3 to 6 min would credibly strengthen the diagnosis of CAD. To our best knowledge, there have been few studies conducted specifically to differentiate FP from TP ST-segment responses using a simple ECG marker in a relatively large population.

Diagnostic Value of ST Slope

To improve the accuracy of the exercise ECG, various indices have been proposed, including the degree of ST-segment depression, R wave amplitude changes, ST/HR slope, ST index, QT dispersion, ST slope, and concomitant changes in hemodynamic parameters. Each has been reported to improve accuracy; however, only a few are in clinical use, presumably because there has not been a dramatic increase in accuracy, the method is complicated or time-consuming, or both.

Downsloping or horizontal ST-segment depression is more specific for CAD than upsloping depression. Furthermore, the downsloping pattern has been reported as a marker for severe ischemia. Thus, the ST slope offers some useful diagnostic information. Also, in CAD patients, exercise-induced ST-segment depression often changes from an upsloping or horizontal pattern during exercise to a downsloping pattern in recovery. Therefore, because the ST-segment usually returns to baseline between 6 to 10 min postexercise, the ST-T time-course of CAD patients can be characterized by a transient decrease in the ST slope soon after exercise with a gradual increase toward baseline in late recovery.

Unlike the characteristic time-course of the ST slope in CAD patients, individuals with FPD often show several patterns, one of which was observed in the present FP subjects. In it, the magnitude of ST-segment depression remained almost constant and the ST slope rather decreased from postexercise 3- to 6-min, whereas, in TP patients, both ST-segment depression and ST slope recovered toward baseline during this period. The directionally opposite ST slope changes emphasized the intergroup difference, contributing to accurate differentiation of the FPs from the TPs.
Different Recovery Time-Courses of the ST Slope in the TP and FP Groups

Despite the potential usefulness of ST-T time-course for diagnosis, few studies have focused on this possibility, especially in conjunction with the ST slope. In our analysis, the postexercise ST slope in TP patients progressively decreased up to 3 min, at which time it reached the lowest value of less than zero (downsloping) and gradually increased until 6 min. The mechanism(s) for this postexercise transient ST slope decrease in CAD is uncertain, but it could be, at least partially, explained by the effect of heart rate dependent J-point depression. In many CAD patients, tachycardia-induced J-point depression would lower the initial portion of ST-segment (ie, draw the ST-segment upward) during exercise, thereby obscuring or masking the downsloping depression, and the slowing of the heart rate following exercise would readily unmask the downsloping configuration. The subsequent progressive increase in ST slope from 3- to 6-min postexercise reflects the recovery process of the ischemia-induced electrophysiological impairment.

On the other hand, we observed a progressive decrease in the ST slope from 1- to 6-min postexercise in the FP subjects. After becoming negative at 4 min, the ST slope further decreased until 6 min, at which time the FP group eventually had a lower ST slope with a greater ST-segment depression than the TP group. This recovery time-course in FP subjects, characterized by the inappropriately late aggravation of ST-T abnormalities, has also been reported by Malcom et al who examined patients with mitral valve prolapse, a condition prone to FP. The mechanism for this late aggravation is unknown. Although the FP group included many females (47%), in agreement with previous reports, it is noteworthy that the prevalence of hypertension was considerably high (44%) compared with that in the general population. In the presence of hypertension, complicated as one potential cause of FPD, strenuous exercise may acutely induce electrophysiological changes with late ST-segment aggravation by a mechanism such as the reduction of coronary flow reserve documented in those patients.

Advantages of Computer Analysis

Our computer analysis method using an 8-lead ECG ensures high-resolution analysis as well as objective and reproducible measurements; in particular, in terms of the J-point determination. Because it is difficult to precisely determine the J-point in a single lead with ST-segment depression, which may seriously affect the ST slope, we incorporated the QRS information of all 8 leads in a single complex (algebraic sum). Like other available systems, our stress system yields the ST slope in mV/s to one decimal place (eg, 0.3 mV/s). However, those values were not used for the analysis in the present study because the resolution was considered insufficient. More importantly, the measured values are occasionally inaccurate because of erroneous determination of the Q-Q baseline or J-point. Although ΔST slope could accurately differentiate FP from TP patients (Fig 6), the absolute values were very small in most subjects. We believe that high-resolution analysis can contribute to accurate diagnosis of the presence or absence of inducible ischemia by detecting the subtle ECG changes that are otherwise undetectable by conventional methods such as by a simple categorical judgement of the ST-segment shape.

Potential Limitations

First, FPD are frequently seen in patients with abnormal resting ECGs such as those with LVH, valvular disease, or cardiomyopathy. Because we examined subjects with a normal resting ECG, our findings cannot be extrapolated to those other categories of patients. Second, only patients with both angiographically and scintigraphically documented abnormalities were enrolled into the TP group because the diagnostic accuracy of SPECT is not perfect. This is probably the reason why the positive predictive value (68% = 134/198) for our entire population seems to be slightly lower than that previously reported. Furthermore, FPD was based on the normal exercise SPECT imaging, and 70% of FP subjects did not undergo angiography. Although the changes in ST slope from postexercise 3- to 6-min were similar in FP subjects with and without angiographic results, we cannot completely exclude the possibility that a number of FP subjects might have angiographical CAD.

Conclusion

Our study has demonstrated that a simple observation of the ST slope recovery time-course is very useful for discriminating FP from TP ST-segment depressions. Although our findings are currently confined to subjects with a normal resting ECG, they should enhance the diagnostic value of the exercise ECG and serve to reduce the number of more costly, time-consuming and invasive procedures.

Acknowledgments

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