Role of Nondiagnostic Exercise-Induced ST-Segment Abnormalities in Predicting Future Coronary Events in Asymptomatic Volunteers

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Background—Whether exercise-induced ST-segment depression < 1 mm is an independent predictor of future coronary events (CEs) in asymptomatic subjects is unknown.

Methods and Results—We performed maximal treadmill exercise tests on 1083 volunteers from the Baltimore Longitudinal Study of Aging who were free from clinical coronary heart disease. Exercise ST-segment changes were stratified by Minnesota code criteria: 11:1 (n=213), flat or downsloping ST depression ≥ 1 mm; 11:2 (n=66), flat or downsloping ST depression ≥ 0.5 mm and < 1 mm; 11:4 (n=124), ST-J depression ≥ 1 mm with slowly rising ST segments; and 11:5 (n=69), minor ST depression (< 0.5 mm) before exercise that worsened to flat or downsloping ST depression ≥ 1 mm during or after exercise. Risk of CE was compared with subjects with normal exercise ECG (n=611). Over a mean follow-up of 7.9 years, 76 subjects developed CEs (angina pectoris, myocardial infarction, or coronary death). On univariate analysis, age (relative risk [RR]=1.07/year, P<0.0001), male sex (RR=1.98, P=0.009), plasma cholesterol (RR=1.02/mg per dL, P<0.0001), hypertension (RR=2.23, P=0.002), duration of exercise (RR=0.71/min, P=0.0001), and systolic blood pressure at peak effort (RR=1.02/mm Hg, P=0.002) were associated with CE. By Cox proportional hazards analysis, age (RR=1.06/year, P<0.0001), male sex (RR=2.76, P=0.0002), plasma cholesterol (RR=1.02 per 1 mg/dL, P<0.0001), duration of exercise (RR=0.87/min, P=0.004), and ST-segment changes coded as either 11:1 (RR=2.70, P=0.0005) or 11:5 (RR=2.73, P=0.04) were independent predictors of CE.

Conclusions—Both a classic ischemic ST-segment exercise response and intensification of minor preexercise ST-segment depression to levels ≥ 1 mm independently predicted future CE in this asymptomatic population. Neither slowly rising ST depression nor horizontal ST depression < 1 mm was prognostic. (Circulation. 2002;106:2787-2792.)

Key Words: exercise • coronary disease • prognosis

The electrocardiographic response to treadmill exercise occupies a major role in the diagnosis and prognostic assessment of individuals with suspected coronary heart disease (CHD). Despite the availability of newer methods, it remains a first-line diagnostic test for CHD. Numerous studies,1-13 including two from our laboratory,1,2 have shown that a horizontal or downsloping ST-segment depression ≥ 1 mm in response to exercise is a powerful harbinger for future coronary events (CE), ie, angina pectoris, myocardial infarction (MI), or sudden cardiac death, in an apparently healthy population, independent of conventional risk factors. In symptomatic populations, lesser ST-segment shifts defined by horizontal depression < 1 mm or slowly upsloping ST segments have also demonstrated diagnostic14,15,16 and prognostic significance.17 However, the prognostic utility of such lesser ST-segment shifts in asymptomatic individuals has not been systematically addressed. This lack of specific information and the need to avoid affixing a false diagnosis of CHD has led to the dismissal of such modest exercise-induced ST shifts as unimportant. Thus, it remains unknown if any prognostic significance is carried by these lesser exercise-induced ST-segment changes in this setting.

The present study was therefore designed to determine whether ST-segment depression responses to treadmill exercise not meeting the standard 1.0-mm criterion for ischemia have prognostic significance for future CE in apparently healthy volunteers across a broad age range. All subjects were volunteers from the Baltimore Longitudinal Study of Aging (BLSA)18 and were free from CHD by history, physical examination, and resting ECG.

Methods
The BLSA is a prospective study of the aging process.18 Volunteers are generally well educated, financially comfortable, health con-
sicious, and free of major illness. They underwent 2 to 2.5 days of medical, physiological, and psychological testing at the Gerontology Research Center in Baltimore, Maryland, approximately every 2 years. Although motivation to join the study varies among individuals, they are typically motivated by a desire to learn about their own aging process and to help others. Treadmill exercise testing is offered to all individuals without clinical CHD or major noncardiac diseases that would limit the ability to perform aerobic exercise. A family history of CHD before age 55 years was reported by only 9.4% of the sample eligible for exercise testing in this study.

Between January 1978 and December 1993, 1448 subjects underwent maximal exercise treadmill testing using a modified Balke protocol, during which the treadmill grade was increased 3% every 2 minutes, starting from a horizontal position; women walked at an initial speed of 3.0 mph and men at 3.5 mph. In more aerobically fit subjects, speed was increased by 0.5 mph one to three times during the test. Before exercise, a routine 12-lead ECG was recorded with the subject in the supine and seated positions after 30 seconds of forced hyperventilation and after 30 seconds of standing. A 12-lead ECG and brachial artery cuff blood pressure were recorded every 2 minutes during exercise, at maximal effort, immediately after exercise cessation, and every 2 minutes for at least 6 minutes into recovery. Collection of expired gases was performed throughout exercise after June 1980 and analyzed at 30-second intervals for oxygen and carbon dioxide content by dedicated analyzers or a medical mass spectrometer for determination of peak oxygen consumption (Vo2 peak). Testing was terminated because of fatigue, dyspnea, or leg discomfort. All postexercise ECGs were taken in the seated position. Individuals who developed anginal pain during the test were excluded from the present analysis.

Electrocardiographic changes were assessed by Minnesota Code criteria19 by a single observer (I.L.F.). A positive or ischemic response was defined as ≥1 mm J point depression with flat or downsloping ST segment in most complexes in any lead except aVR (Minnesota code 11:1). Lesser ST-segment changes were coded as follows: horizontal or downsloping ST-segment depression between 0.5 and 1.0 mm (Minnesota code 11:2), J point depression <0.5 mm but ST segment downward sloping and ST-segment or T nadir <0.5 mm below baseline (Minnesota code 11:3), J point depression of 1.0 mm and ST segment sloping upward at ≤5 mm/s or U-shaped (Minnesota code 11:4), and ST-segment depression <0.5 mm at rest or induced by postural shift or hyperventilation, which worsened to type 11:1 response during or after exercise (Minnesota code11:5). The ECG response was not an indication for test modification or termination.

Of the 1448 subjects who underwent treadmill exercise testing, 711 subjects demonstrated some codable exercise-induced ST-segment changes. Of these, 172 subjects were excluded for the following reasons: exercise-induced angina pectoris before or on the index visit (n=49), pathological Q waves (Minnesota code 1:1 or 1:2) present on any ECG before the index visit (n=39), known valvular heart disease (n=39), the presence of cardiac glycosides or other antiarrhythmic drugs (n=40), or prior heart failure (n=5). After eliminating an additional 28 subjects from groups without a definite ischemic exercise ECG response who did not achieve ≥85% of predicted maximal heart rate (defined by 220−age), 511 of the original subjects met the inclusion criteria for this analysis. Because there were only 39 individuals in group 11:3, none of whom developed a coronary event on follow-up, we did not include this group in the analysis, leaving 472 individuals. After these exclusion criteria were applied to the 737 subjects with a normal exercise ECG response (group 11:0), 611 individuals constituted the control group.

All participants were evaluated for the development of new CE during subsequent biennial visits to the Gerontology Research Center and by hospital and outpatient records, death certificates, and autopsy reports, as available. Coronary events were defined as angina pectoris, myocardial infarction, or coronary death (fatal myocardial infarction or sudden death), as previously described.1,2 Myocardial infarction was diagnosed by conventional clinical criteria during a subsequent hospitalization or by the development of diagnostic Q waves on the resting ECG (Minnesota codes, 1:1 or 1:2). Follow-up time for individuals who experienced a CE was calculated to the event date. When subjects developed more than one CE, only the first event was used, and the follow-up analysis was censored after this time, unless otherwise described. For event-free subjects, follow-up time was calculated to their last biennial visit or their death from a noncoronary cause.

Subjects were divided into 5 groups: 11:0, 11:1, 11:2, 11:4, or 11:5, on the basis of their ST-segment responses to exercise, as described above. The following baseline characteristics were compared among the groups: age, sex, body mass index defined by weight in kilograms divided by height in meters squared (kg/m2), present smoking status (smoker defined by 10 or more cigarettes per day), prevalence of hypertension (BP ≥160/95 mm Hg or currently taking antihypertensive medication), and family history of CHD (clinical CHD or sudden death in a first degree relative <55 years old), diabetes requiring insulin or oral hypoglycemic agents, and serum cholesterol. Duration of exercise, peak oxygen consumption (available in 77% of participants), follow-up duration, and incidence rates of CE were also compared. Comparisons were made among the 5 groups using χ2, ANOVA, or Kruskal-Wallis test with adjustments for multiple comparisons by the method of Tukey or Bonferroni. To adjust for differences in follow-up time, CE rates were calculated per person-year of observation. Simple logistic regression and Cox proportional hazard were used to determine the independent predictors of CE in the entire sample. Indicator variables were used to identify differences between groups with ST-segment changes (11:1, 11:2, 11:4, 11:5) and group 11:0. Event-free survival was compared in the 5 groups by Kaplan-Meier survival analysis, using the log-rank statistic. The Statistical Analysis System (SAS) was used for all analyses; a two-tailed probability value ≤0.05 was required for statistical significance.

**Results**

Of the 1083 subjects who met the inclusion criteria, 472 individuals demonstrated exercise-induced ST-segment changes and 611 did not. Of the 472 with ST changes, 213 developed ischemic ST-segment depression (group 11:1), 75 showed ST depression of 0.5 to 0.9 mm (group 11:2), 124 presented with slowly upsloping ST-segment changes (group 11:4), and 60 experienced worsening of preexercise ST depression to ≥1.0 mm (group 11:5). Baseline characteristics for the 5 groups are presented in Table 1. Group 11:0 was significantly younger than all of the others, whereas group 11:1 was the oldest. Groups 11:1 and 11:0 had a greater proportion of men than groups 11:1 and 11:5. Smoking prevalence was lowest in group 11:1 and highest in group 11:0. Conversely, hypertension prevalence was lowest in group 11:0 and highest in groups 11:1 and 11:5. Total serum cholesterol was highest in groups 11:1 and 11:4 and lowest in group 11:0. Fasting plasma glucose levels and body mass index were similar among the groups.

Comparing exercise test variables (Table 2), exercise duration, peak Vo2, and maximal heart rate were highest in individuals with a normal exercise ECG, who differed significantly from groups 11:1, 11:4, and 11:5. Systolic blood pressure at peak effort was lowest in group 11:0 and highest in groups 11:1 and 11:5. The observed dissimilarities between group 11:0 and the other groups are explicable by the younger age of group 11:0. (Table 1). Conversely, group 11:1 was the oldest and displayed the lowest exercise duration and maximal heart rate and highest exercise systolic blood pressure. Rate pressure product at peak exercise was similar among the groups.
Table 3 compares the incidence of CE among the 5 ST-segment response groups. During a median follow-up of 7.9 years, 76 subjects (54 men and 22 women) experienced CE, comprising 31 cases of angina pectoris, 27 nonfatal myocardial infarctions, and 18 coronary deaths; 10 of these deaths were sudden. The incidence of future CE was highest in group 11:1 (15%) and lowest in group 11:0 (3%). When events were expressed per person-year, to adjust for group differences in follow-up time, groups 11:1 and 11:5, but not groups 11:2 or 11:4, experienced significantly higher event rates than group 11:0 in both men and women. Within group 11:5, CE developed in 4 of 35 individuals (11%) who developed <1.0 mm additional ST depression, or downsloping ST-segment depression with exercise versus 3 of 25 (12%) who developed ≥1.0 mm additional ST depression, P = NS.

In groups 11:1, 11:2, 11:5, and 11:0, there were 4, 1, 1, and 1 individuals, respectively, who experienced more than one end point; ie, after developing angina pectoris or MI as the initial manifestation of CHD, they later developed MI or coronary death. Coronary revascularization was performed after the initial event in 5 subjects from group 11:0 (3 with angina pectoris and 2 with MI), 11 subjects from group 11:1 (8 with initial angina and 3 with MI), and no subjects from other groups.

Univariate non–ST segment predictors of CE included older age (OR = 1.07/year, P < 0.0001), male sex (OR = 1.98, P < 0.01), higher serum cholesterol (OR = 1.02/mg per dL, P < 0.0001) and plasma glucose levels (OR = 1.01/mg per dL, P = 0.03), hypertension (OR = 2.23, P = 0.002), and higher systolic blood pressure at peak exercise (OR = 1.02/mm Hg, P < 0.001) and were all associated with unfavorable prognosis, whereas longer duration of exercise (OR = 0.71/min, P < 0.0001), higher maximal heart rate (OR = 0.96/bpm, P < 0.0001), and greater peak VO₂ (OR = 0.92/mL per kg.min, P < 0.0001) were protective. LDL-cholesterol (OR = 1.02, P = 0.0001) available in <50% of subjects was also an unfavorable marker, whereas HDL-cholesterol, also available in <50% of subjects, did not influence prognosis. Current smoking (OR = 0.89, P = 0.74) was not a prognostic factor in this analysis, perhaps because of its relatively low prevalence and intensity.

To determine the independent predictors of future CE, we constructed a Cox proportional hazards model that included those variables significant on univariate analysis plus the exercise ST-segment response, with group 11:0 (controls) as a reference. The full model was strongly predictive of CE (χ² = 130.1, P = 0.0001). As shown in Table 4, older age, male

Table 2. Exercise Test Variables Stratified by Exercise ST-Segment Response

<table>
<thead>
<tr>
<th></th>
<th>11:1 (n = 213)</th>
<th>11:2 (n = 75)</th>
<th>11:4 (n = 124)</th>
<th>11:5 (n = 60)</th>
<th>Negative (n = 611)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration, min*</td>
<td>10±2</td>
<td>11±3</td>
<td>10±2</td>
<td>10±3</td>
<td>12±3</td>
<td>0.0001</td>
</tr>
<tr>
<td>VO₂ peak, mL/kg per min†</td>
<td>29±7</td>
<td>30±8</td>
<td>29±8</td>
<td>27±7</td>
<td>33±9</td>
<td>0.0001</td>
</tr>
<tr>
<td>MHR, bpm‡</td>
<td>162±19</td>
<td>166±15</td>
<td>166±19</td>
<td>165±22</td>
<td>175±18</td>
<td>0.0001</td>
</tr>
<tr>
<td>SBP peak, mm Hg§</td>
<td>185±28</td>
<td>177±24</td>
<td>178±31</td>
<td>183±35</td>
<td>171±29</td>
<td>0.0001</td>
</tr>
<tr>
<td>RPP peak, x10⁶</td>
<td>30±5</td>
<td>29±5</td>
<td>29±6</td>
<td>30±6</td>
<td>29±5</td>
<td>0.9</td>
</tr>
</tbody>
</table>

*P = 0.0001 between negatives and groups 11:1, 11:4, 11:5 (significant adjusted P at level 0.005).
†Adjusted P = 0.0005 between negatives and all other groups.
‡P = 0.0005 between negatives and other groups (significant adjusted P at level 0.005).
§Adjusted P = 0.05 between negatives and groups 11:1 and 11:5.

VO₂ data available in 77% of subjects. MHR indicates maximal heart rate; SBP, systolic blood pressure; and RPP, rate pressure product.
sex, higher cholesterol, and shorter exercise duration were strongly predictive of future CE. With regard to ST-segment shift, only groups 11:1 (OR = 2.70) and 11:5 (OR = 2.73) were at increased risk for an event relative to group 11:0. Neither group 11:2 nor group 11:4 demonstrated significantly increased event risk. The survival analysis (Figure) confirmed the unfavorable prognosis of both groups 11:1 and 11:5. Survival curves for group 11:2 and 11:4 lay between that for group 11:0 and those for groups 11:1 and 11:5.

**Discussion**

Prior studies from our laboratory in apparently healthy BLSA volunteers demonstrated that an ischemic ST-segment response to treadmill exercise, whether developing during exercise or in recovery, was associated with nearly a 3-fold relative risk of future coronary events, independent of conventional risk factors. The present study, encompassing a larger sample of the same asymptomatic BLSA population, confirms previous findings and clarifies the prognostic significance of lesser ST-segment shifts. By Cox proportional hazards analysis, minor preexercise ST-segment abnormalities that intensify to ≥1 mm of flat or downsloping ST depression with exercise (type 11:5) carry the same adverse prognostic significance as a classic ischemic response, (type 11:1), whereas lesser degrees of ST shift do not significantly influence prognosis.

The concept of exercise screening for the prediction of future CE in apparently healthy middle-aged and older populations has been applied for many years, especially to those with a high coronary risk profile.

Numerous studies have demonstrated that asymptomatic subjects with exercise-induced ischemic ST-segment depression, defined by ≥1 mm horizontal or downsloping ST depression, have a several-fold higher risk of future CE than those with negative exercise ECGs.

For many years, exercise-induced ST-segment depression <1 mm has generally been considered negative or nondiagnostic for ischemia, on the basis of the observation that these lesser ST-segment shifts increase sensitivity for angiographic CHD, but with substantial drops in specificity. In 100

<table>
<thead>
<tr>
<th>Group</th>
<th>Incidence of Coronary Events by Exercise ST-Segment Response and Sex</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>11:1</td>
</tr>
<tr>
<td>Men (n=612)</td>
<td>(n=137)</td>
</tr>
<tr>
<td>Follow-up, y</td>
<td>6.9±4.6</td>
</tr>
<tr>
<td>Events, n (%)</td>
<td>23 (17)</td>
</tr>
<tr>
<td>Events per person-year</td>
<td>0.024</td>
</tr>
<tr>
<td>Event type*</td>
<td>12/7/4</td>
</tr>
<tr>
<td>Women (n=471)</td>
<td>(n=76)</td>
</tr>
<tr>
<td>Follow-up, y</td>
<td>8.0±5.0</td>
</tr>
<tr>
<td>Events, n (%)</td>
<td>8 (11)</td>
</tr>
<tr>
<td>Events per person-year</td>
<td>0.013</td>
</tr>
<tr>
<td>Event type*</td>
<td>4/2/2</td>
</tr>
</tbody>
</table>

*Numbers represent number of cases of angina pectoris, myocardial infarction, or coronary death, respectively.

**Table 4. Cox Proportional Hazards Predictors of Coronary Events**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>1.06</td>
<td>1.03 to 1.08</td>
<td>0.0001</td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
<td>1.02</td>
<td>1.01 to 1.02</td>
<td>0.0001</td>
</tr>
<tr>
<td>Sex, male</td>
<td>2.76</td>
<td>1.61 to 4.71</td>
<td>0.0002</td>
</tr>
<tr>
<td>Duration, min</td>
<td>0.87</td>
<td>0.79 to 0.96</td>
<td>0.004</td>
</tr>
<tr>
<td>11:1*</td>
<td>2.7</td>
<td>1.55 to 4.73</td>
<td>0.0005</td>
</tr>
<tr>
<td>11:2*</td>
<td>1.79</td>
<td>0.60 to 5.39</td>
<td>0.30</td>
</tr>
<tr>
<td>11:4*</td>
<td>1.34</td>
<td>0.62 to 2.89</td>
<td>0.46</td>
</tr>
<tr>
<td>11:5*</td>
<td>2.73</td>
<td>1.05 to 7.10</td>
<td>0.04</td>
</tr>
</tbody>
</table>

* Group 11:0 (negatives) is the reference. Modex χ²=130.1; P<0.0001.
consecutive symptomatic patients referred for angiography, Martin and McConahay\textsuperscript{16} demonstrated that a criterion of 0.5-mm ST-segment depression increased the false-positive diagnosis rate from 11% to 43% compared with 1-mm ST depression, with an increase in sensitivity from 62% to 84%. Another study in symptomatic patients who underwent angiography found that the specificity and sensitivity for 0.5-mm ST depression were 83% and 63% compared with 100% and 35%, respectively, for 1-mm horizontal or downsloping ST-segment depression.\textsuperscript{23} Our findings extend this concept to the prediction of CE in asymptomatic subjects.

The diagnostic and prognostic value of exercise-induced slowly upsloping ST-segment depression has received considerable attention in the last few decades.\textsuperscript{7,8,14,15,24,25} Most of these studies have been performed in symptomatic populations. Goldschlager et al\textsuperscript{24} reported that >30% of patients with upsloping ST-segment responses \( \geq 1.5 \) mm or \( \geq 1 \) mm with slope less than 1 mv/s were false-positive; however, this group was more likely to have triple-vessel disease and less likely to have normal coronary arteries than those with a normal ST-segment response. Stuart and Ellestad\textsuperscript{25} observed that individuals with \( \geq 2 \) mm of upsloping ST-segment depression had the same incidence of major 2- or 3-vessel disease as those with \( \geq 1 \) mm horizontal ST-segment depression. However, Sansoy et al\textsuperscript{14} showed that including slowly rising ST-segment depression as an ischemic response decreased the positive predictive value of the exercise ECG to 49% from 64% when only horizontal ST-segment depression was used, with a drop in specificity from 84% to 56%.

In asymptomatic populations, the prognostic value of upsloping ST-segment depression is controversial. Bruce et al\textsuperscript{8} observed that subjects with at least 1 mm of upsloping ST-segment depression had the same risk ratio of developing subsequent symptomatic CHD as subjects with horizontal ST changes. Conversely, Allen et al\textsuperscript{17} found that slowly rising ST depression \( \geq 1.5 \) mm yielded only 6% positive predictive value for future events compared with 14% in those with horizontal or downsloping depression, consistent with the nonsignificance of the type 11:4 response in the present study.

Whether horizontal ST-segment depression \( \geq 1 \) mm on the exercise ECG resulting from exercise-induced ST shifts superimposed on minor resting ST abnormalities has prognostic significance in an asymptomatic population is unknown. In the only prior study to examine this issue, McHenry et al\textsuperscript{10} could not demonstrate any prognostic value of such additional ST-segment depression for future CE in 27 asymptomatic men aged 27 to 55 years. However, the youth and small size of their sample limit the generalizability of their findings. In patients with suspected CHD and resting ST depression, Miranda et al\textsuperscript{26} reported that \( \geq 1 \) mm additional ST-segment depression during exercise had 56% positive predictive value for 3-vessel CHD compared with 27% in subjects with a normal resting ECG who developed \( \geq 1 \) mm horizontal or downsloping ST-segment shift. Other studies in symptomatic patients have also documented increases in diagnostic yield by including individuals with exercise-induced ST-segment depression \( \geq 1 \) mm superimposed on resting ST depression.\textsuperscript{27,28} Meta-analysis by Detrano et al\textsuperscript{29} showed that excluding patients with ST-segment alterations at rest did not significantly change either sensitivity or specificity for angiographic CHD. Our results extend these previous findings in symptomatic populations by showing adverse prognostic significance for additional ST depression in apparently healthy volunteers. We observed a similar adverse prognosis in those who developed <1 mm versus \( \geq 1 \) mm additional flat or downsloping ST-segment depression, as long as the absolute magnitude of ST depression reached or exceeded 1 mm.

Although the present results in this asymptomatic lower risk sample may not necessarily apply to the general population, this and prior studies in the BLSA\textsuperscript{1,2,20} have identified coronary risk factors similar to those in less highly selected population samples. Angina pectoris, which is generally regarded as a soft event, constituted approximately half of initial events. However, many of these subjects subsequently developed a “hard” end point or underwent coronary revascularization, confirming the presence of significant CHD.

Thus, asymptomatic subjects with minor preexercise ST-segment abnormalities that intensify to \( \geq 1 \) mm ischemic ST-segment depression during or after exercise were at similarly increased risk for future CE as those who developed a classic ischemic ST response from a normal resting ECG. This expanded definition of an ischemic exercise ECG response may identify additional asymptomatic higher risk individuals who could benefit from early identification and aggressive control of modifiable coronary risk factors.

**Acknowledgments**

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**References**


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