Can Serial Exercise Testing Improve the Prediction of Coronary Events in Asymptomatic Individuals?

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An abnormal ST segment response to treadmill exercise has a low predictive value for future coronary events (angina pectoris, nonfatal myocardial infarction, or cardiac death) in apparently healthy individuals. To determine whether the conversion from a normal to an abnormal ST segment response might identify individuals at high risk for a future coronary event, we analyzed the results of serial exercise tests performed at 2–4-year intervals in 726 male and female volunteers, aged 22–84 years (mean, 55.1 years), from the Baltimore Longitudinal Study of Aging (BLSA). All subjects were free of cardiovascular disease at entry by history, physical examination, and resting 12-lead electrocardiogram. Over a mean overall follow-up of 7.4 years, coronary events occurred in 34 of 178 (19.1%) of those with an abnormal ST response to exercise versus 30 of 548 (5.5%) in those with a normal response (p=0.001). Angina pectoris was the most common presenting coronary event regardless of ST segment exercise response. Among individuals with an abnormal ST segment response, the incidence of events was virtually identical between those with an initially abnormal response (group 1) and those who converted from a normal to an abnormal response (group 2), 19.8% versus 18.5%. After adjustment for standard coronary risk factors by proportional hazards regression analysis, the risk of a coronary event relative to subjects with persistently normal ST segment responses (group 3) remained nearly identical in the two groups, 2.72 in group 1 (p<0.003) and 2.80 in group 2 (p<0.002). Thus, in asymptomatic individuals, conversion from a normal to an abnormal exercise ST segment response portends a prognosis similar to an initially abnormal response and cannot be considered a more specific marker for future coronary events. (Circulation 1990;81:20–24)

For three decades, investigators have attempted to use exercise electrocardiography to predict the development of clinical coronary artery disease in asymptomatic individuals. Although numerous studies of this type have documented a higher subsequent incidence of clinically significant coronary events (angina pectoris, nonfatal myocardial infarction, or cardiac death) in those individuals demonstrating exercise-induced ST segment depression than in those without such depression, the predictive value of this electrocardiographic finding has generally been low.1–14 Thus, the percentage of asymptomatic individuals with exercise-induced ST segment depression who subsequently developed angina pectoris, myocardial infarction, or experienced cardiac death averaged only 21% in a pooled series of eight studies comprising over 7,000 subjects.15

Given the high percentage of false-positive exercise electrocardiographic responses in apparently healthy populations, it has been postulated that conversion from a normal to an abnormal ST segment response during serial testing might improve the predictive value of the exercise electrocardiogram for a future coronary event.3,16 The present study was designed to test this hypothesis in the Baltimore Longitudinal Study of Aging (BLSA), a volunteer community-dwelling population of men and women representing a broad age range.17 The BLSA has used serial treadmill exercise testing since 1969 as part of the overall effort to separate the effects of aging from those of disease on the cardiovascular system. The longitudinal character of this study allows for the assessment of the effect of exercise ST segment response at a particular time.
point on subsequent cardiovascular morbidity and mortality as well as the effect of a change in ST segment response on these end points. In addition, we sought to confirm and perhaps generalize the recent observation that in asymptomatic men with an abnormal ST segment response to exercise, the first clinical manifestation of coronary artery disease is usually angina pectoris, whereas in those with a normal ST segment response, the presenting coronary event is more often myocardial infarction or sudden cardiac death.13

Methods
Since its inception in 1958, the BLSA has enrolled approximately 2,000 community-dwelling volunteers, aged 21–92 years, who return biennially to the Gerontology Research Center in Baltimore, Maryland, for 2½ days of extensive testing.17 Included among the tests are a thorough history and physical examination by an internist, a resting 12-lead electrocardiogram, and, in those without clinical heart disease who are able to exercise (>80% of population), a maximal treadmill exercise test. Exercise tests are performed on alternate visits in subjects less than 60 years old and every visit after this age. Between 1969 and 1985, 726 individuals (560 men and 166 women) who were free of cardiac disease by history, physical examination, and resting 12-lead electrocardiogram underwent maximal treadmill exercise testing on at least two visits. These 726 individuals form the basis for this study.

Exercise Testing Protocol
Before exercise testing, a routine 12-lead electrocardiogram was recorded with the patient supine and erect, and after 30 seconds of forced hyperventilation. Those subjects who exhibited labile ST segment shifts in response to postural change or hyperventilation were excluded from this study (n=33). After giving informed consent, all subjects exercised to exhaustion according to a modified Balke protocol, that is, the treadmill grade was increased 3% every 2 minutes, starting from a horizontal position; women walked at a constant speed of 3.0 mph, and men at 3.5 mph. A 12-lead electrocardiogram and cuff blood pressure were recorded every 2 minutes during exercise, at maximal effort, immediately after exercise, every 2 minutes for at least 6 minutes into recovery, and whenever the monitor tracing suggested ST segment changes. Testing was terminated because of fatigue, dyspnea, or leg discomfort. Individuals who developed anginal pain or those without ischemic ST segment responses who failed to achieve 85% of age-predicted maximal heart rate were excluded. Electrocardiographic changes were assessed according to Minnesota Code criteria by a single observer (J.L.F.).18 A positive or ischemic response was defined as 1 mm or more of flat or downsloping ST segment depression 0.08 seconds after the J-point in the majority of complexes in any electrocardiographic lead except aVR (code, 4:1). The electrocardiographic response was not an indication for test modification or termination.

Follow-up
The status of study subjects was assessed during subsequent biennial longitudinal visits to the Gerontology Research Center. Follow-up information on subjects who failed to return was obtained by telephone interview, contact with the subject's family, or contact with the subject's personal physician. Follow-up data were complete in 97% of the subjects. The subsequent development of angina pectoris was determined from the subjects’ response to a standard questionnaire and individual clinical assessment by a specially trained cardiopulmonary technologist and a cardiologist, and was made independent of exercise test results. Myocardial infarction was diagnosed by conventional clinical criteria during a subsequent hospitalization or by the development of diagnostic Q waves on the resting electrocardiogram (codes, 1:1 or 1:2). For deceased individuals, the cause of death was determined by the consensus of three BLSA physicians after review of the death certificate, hospital records, autopsy data, and communications with the subject's family and personal physician. In those subjects who developed more than one cardiac event (n=6), only the initial event was used for analysis.

Groups
For each individual who demonstrated an ischemic ST segment response to treadmill exercise, whether on initial testing (group 1) or on repeat testing after an initially negative test (group 2), a control subject was selected from among the 548 subjects who manifested only negative exercise electrocardiographic responses to at least 85% of age-predicted maximum heart rate without the development of anginal pain (group 3). These age- and sex-matched controls constituted group 3A. All group 3A subjects were successfully matched to within 2 years of subjects in groups 1 and 2. Follow-up duration for individuals in groups 1 and 2 was calculated from the time of the first positive exercise test; follow-up duration for subjects in groups 3 and 3A was calculated from the time of their second normal exercise test.

Statistical Analysis
The following baseline characteristics of individuals with initially positive exercise electrocardiograms (group 1) were compared with those of converters (group 2): age, gender, current smoking status (smokers were defined as those smoking at least five cigarettes daily), presence of hypertension (defined as a resting blood pressure ≥160/95 mm Hg or treatment with antihypertensive drug therapy), and total serum cholesterol. The rates and distribution of coronary events (angina, nonfatal myocardial infarction, and cardiac death) and the latency from the first positive exercise electrocardiogram to the time of the event were compared in subjects with a positive exercise electrocardiogram (groups 1 and 2 com-
TABLE 1. Risk Factor Profile

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)*</td>
<td>64±15</td>
<td>63±11</td>
<td>53±14</td>
<td>0.01</td>
</tr>
<tr>
<td>Sex (% men)†</td>
<td>63</td>
<td>87</td>
<td>78</td>
<td>0.05</td>
</tr>
<tr>
<td>Current smokers (%)‡</td>
<td>9.6</td>
<td>13.7</td>
<td>20.7</td>
<td>0.05</td>
</tr>
<tr>
<td>Hypertensives (%)§</td>
<td>18.0</td>
<td>31.4</td>
<td>21.3</td>
<td>0.05</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>214±43</td>
<td>208±41</td>
<td>208±40</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values for smokers, hypertensives and serum cholesterol have been adjusted for age and gender by multiple logistic regression analysis.

* p<0.01, between group 3 and groups 1 and 2; † p<0.01, between group 1 and groups 2 and 3; ‡ p<0.05, between groups 1 and 3.

Table 2. Characterization of Initial Cardiac Events

<table>
<thead>
<tr>
<th></th>
<th>Combined groups 1 and 2</th>
<th>Group 3A</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angina pectoris</td>
<td>20</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>6</td>
<td>4</td>
<td>NS*</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>8</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>34 (19%)</td>
<td>18 (10%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Events/100 person-years</td>
<td>2.99</td>
<td>1.30</td>
<td>0.005</td>
</tr>
<tr>
<td>Age at event (yr)</td>
<td>72±8</td>
<td>69±8</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (% men)</td>
<td>91</td>
<td>94</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Compares the relative frequency of angina pectoris, myocardial infarction, and cardiac death as a proportion of all events within a group.

Group I, Initially positive exercise electrocardiogram; group II, conversion from a negative to a positive exercise electrocardiogram; group IIIA, persistently negative exercise electrocardiogram, matched for age and gender with combined groups I and II.

RESULTS

Overall, 178 of the 726 subjects manifested a positive exercise ST segment response. In 86 of these subjects, the initial test was positive (group 1), whereas 92 subjects converted from an initial negative response to a positive one (group 2) over a mean interval of 3.0±2.0 years. A comparison of the risk factor profiles of the three groups is shown in Table 1. Groups 1 and 2 were significantly older than group 3 subjects. Converters (group 2) were more likely to be male, hypertensive, or both. Smoking was more prevalent in group 3 than in the other groups. Groups 1 and 2 were quite similar with respect to age, smoking status, and total serum cholesterol.

During a mean follow-up period of 6.4 years, 34 of the 178 (19.1%) individuals with an abnormal ST segment response (groups 1 and 2) experienced a cardiac event compared with 30 of 548 subjects in group 3 (5.5%) over a 7.7-year follow-up (p<0.001).

"Hard events" (myocardial infarction or cardiac death) occurred in 14 group 1 and 2 individuals (7.9%) versus 15 subjects (2.7%) in group 3 (p<0.01). The follow-up period was slightly longer in group 1 than in group 2 (group 1, 6.9±4.1 years; group 2, 5.9±2.4 years; p<0.05), and was longer in group 3A than in combined groups 1 and 2 (7.8±3.9 vs. 6.4±3.3 years, p<0.01). The coronary event frequency (19.8% vs. 18.5%), age at event (74±8 vs. 70±8 years), and distribution of events (11 cases of angina, four nonfatal infarctions, and two cardiac deaths vs. nine cases of angina, two nonfatal infarctions, and six cardiac deaths) were nearly identical between groups 1 and 2, respectively. In particular, angina pectoris comprised 59% of the initial events among all individuals with a positive exercise electrocardiogram and did not differ significantly between group 1 (65%) and group 2 (53%).

Age- and sex-matched individuals who demonstrated only negative exercise electrocardiograms (group 3A) were approximately one half as likely to experience a coronary event as individuals in groups 1 and 2 (Table 2). Although the overall event rate of group 3A subjects was lower than in groups 1 and 2, their mean age at event, gender distribution, and mode of presentation were similar, with angina pectoris comprising 44% of all initial events. Among the entire set of 548 subjects with persistently negative ST segment responses (group 3), a total of 30 events occurred: 15 cases of angina pectoris, seven nonfatal myocardial infarctions, and eight cardiac deaths. The latency period to an event in group 3 subjects was 6.4±3.9 years after their second exercise test and 3.4±2.7 years after their most recent test, with 26 of 30 events occurring within 5 years of the most recent test.

The results of the proportional hazards regression analyses for the entire population are shown in Table 3. Most noteworthy is the nearly identical augmented risk of a coronary event in groups 1 and 2, relative to group 3 controls. As anticipated, older age, male sex, cigarette smoking, hypertension, and elevated total cholesterol were also significant independent risk factors for a future cardiac event in this asymptomatic population. Although only four of the 64 total coronary events occurred in women, such events developed in three of the 32 women in group 1, none of the 2 women in group 2, and only one of the 123 women in group 3 (p<0.02).
### Table 3. Association Between Risk Factors and Cardiac Events

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Relative risk*</th>
<th>95% Confidence interval</th>
<th>Significance (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1/group 3</td>
<td>2.72</td>
<td>(1.40, 5.27)</td>
<td>0.003</td>
</tr>
<tr>
<td>Group 2/group 3</td>
<td>2.80</td>
<td>(1.45, 5.41)</td>
<td>0.002</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male/female</td>
<td>3.40</td>
<td>(1.18, 9.81)</td>
<td>0.02</td>
</tr>
<tr>
<td>Cigarette smoker</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current/other</td>
<td>2.54</td>
<td>(1.35, 4.80)</td>
<td>0.004</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes/no</td>
<td>1.99</td>
<td>(1.14, 3.49)</td>
<td>0.01</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>1.28†</td>
<td>(1.13, 1.46)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Age</td>
<td>1.08‡</td>
<td>(1.05, 1.10)</td>
<td>0.00001</td>
</tr>
</tbody>
</table>

*Relative risk of cardiac event from Cox’s proportional hazards regression; †relative risk per 20 mg/dl difference; ‡relative risk per 1-year difference.

Survival analysis for groups 1, 2, and 3 after adjustment for standard coronary risk factors is shown in Figure 1. As anticipated from Table 3, an abnormal ST segment response to exercise (groups 1 and 2) portends a diminished event-free survival. Furthermore, the survival curves for groups 1 and 2 are quite similar, confirming the results in Tables 2 and 3.

### Discussion

In asymptomatic populations, an abnormal ST segment response to exercise has generally proven disappointing as a predictor of future coronary events. The positive predictive value of such an ST segment response in this study was 19%, which is within the range previously reported.1–13,15 The positive predictive value for a "hard end point" (myocardial infarction or cardiac death) as the presenting event was even lower (7.9%), consistent with a recent analysis of several large studies.21 Such low predictive value is in accord with Bayes’ theorem when a test of less than 100% specificity is used in a population with a low prevalence of significant coronary artery disease. Thus, this study confirms previous investigations that indicated a positive exercise treadmill test was usually not predictive of clinical coronary artery disease in an asymptomatic individual. Although a positive ST segment response, whether on initial or serial testing, was associated with a doubling of the risk for a future coronary event, 81% of such subjects did not experience an event during the mean follow-up interval of 6.4 years.

It has been postulated that in an asymptomatic individual, conversion from a normal to an abnormal ST segment exercise response might be more predictive of significant coronary artery disease or a future cardiac event than an initially abnormal test.3,11,16 According to this hypothesis, a serial change in the ST segment response is presumed to represent an interim reduction in coronary artery luminal diameter sufficient to produce silent myocardial ischemia. Such a distinction between true positive and false positive tests based on a change from previous test results is theoretically attractive. Unfortunately, our longitudinal data do not support such an assumption.

In this study, the incidence of subsequent coronary events (i.e., angina pectoris, nonfatal myocardial infarction, or cardiac death) was nearly identical between the 86 asymptomatic group 1 subjects whose initial exercise test was abnormal and the 92 group 2 subjects who converted from a negative (normal) to a positive test. This was true whether the results are expressed as the percentage of individuals experiencing an event or after adjustment for standard coronary risk factors by proportional hazards regression. Our findings also suggest that in women as in men, an initially abnormal exercise ST segment response is associated with increased cardiovascular risk, as three of 32 women with such a response subsequently experienced a cardiac event as compared with only one of 123 women with only normal tests.

The few previous studies that have examined the predictive value of serial exercise tests in asymptomatic individuals have been limited to younger and middle-aged men. In male New York State employees who underwent submaximal single-stage treadmill exercise, Doyle and Kinch9 noted that clinical coronary artery disease developed in 34 of 75 (45%) of those who converted from a normal to an abnormal test as compared with 17 of 28 (61%) with an initially abnormal test. This difference is not statistically significant. More recently, McHenry et al11,13 have analyzed the results of multistage maximal treadmill exercise testing longitudinally administered to Indiana State policemen, aged 27–55 years, as well as to a smaller group of men referred because of a previous abnormal exercise electrocardiogram. In neither group was serial conversion from a normal to an abnormal ST segment response found to be more predictive of future coronary events than an initially abnormal test.

The distribution of coronary events (angina pectoris, nonfatal myocardial infarction, or cardiac death) in the present investigation was similar among the three groups. In accord with previous studies,12 angina pectoris was the most common initial event in those
with a positive exercise electrocardiogram (groups 1 and 2) as well as in those with a persistently negative response (group 3). Our findings differ from those of McHenry et al., who noted over a 12.7-year mean follow-up period that individuals with abnormal ST segment responses were more likely to present with angina pectoris, whereas initial coronary events in those with normal ST responses were more frequently myocardial infarction or sudden death. This difference might relate to the younger age or longer follow-up of their subjects, or to differences in lifestyle variables or cardiovascular risk factors.

The results of this study do not exclude the possibility that serial exercise testing in specific subsets of asymptomatic subjects such as those with multiple coronary risk factors or serial testing using more sophisticated techniques such as radionuclide imaging can be valuable in identifying those at high risk for experiencing a future cardiac event. Even if enhanced diagnostic accuracy is demonstrated in these settings, however, the cost-effectiveness of such an approach remains to be proved. It is also possible that a longer follow-up period than the 6.4-year mean in our groups 1 and 2 might demonstrate enhanced sensitivity of serial exercise testing for predicting coronary events, both in the converters and in those with initially abnormal tests. It seems unlikely, however, that an improvement in specificity or overall predictive value would occur in either group.

In summary, the present study in a community-dwelling population of men and women of a broad age range, coupled with previous observations in relatively homogeneous male cohorts suggest that serial exercise treadmill testing in apparently healthy subjects does not facilitate the identification of a subset of individuals at high risk for future coronary events. Those who demonstrate a positive ST segment response have a modestly greater (although still relatively low) risk for a future event than those with a negative response, but conversion from a negative to a positive ST segment response does not appear to confer any greater risk than an initially positive response. Thus, vigorous pursuit of “silent ischemia” with serial exercise testing in asymptomatic individuals with low coronary risk profiles, whether as part of an executive physical examination or for monitoring individuals in high-risk occupations, is probably unwarranted.

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References

2. Robb GP, Marks HH: Postexercise electrocardiogram in arteriosclerotic heart disease. JAMA 1967;200:918
15. Froelicher VF: Exercise Testing & Training. Chicago, Year Book Medical Publisher’s Inc, 1983, p 94

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