PATHOPHYSIOLOGY AND NATURAL HISTORY
CORONARY ARTERY DISEASE

The abnormal exercise electrocardiogram in apparently healthy men: a predictor of angina pectoris as an initial coronary event during long-term follow-up

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ABSTRACT  A group of 916 apparently healthy men between the ages of 27 and 55 years (mean 37) were followed up with serial medical and exercise test evaluations for a period of 8 to 15 years (mean 12.7) to determine (1) the prevalence and specific types of new coronary events observed in subjects with and without abnormal ST segment responses to exercise and (2) the predictive value of a serial conversion to an abnormal ST segment response to exercise for new coronary events. During the initial evaluation there were 23 subjects (2.5%) with an abnormal ST segment response to exercise. During follow-up there were nine (39%) coronary events in this group: eight cases of angina and one of sudden death. With serial testing, an additional 38 subjects (5.1%) experienced conversion to an abnormal ST segment response to exercise. During follow-up there were 12 (32%) coronary events in this group: 10 cases of angina, one of myocardial infarction, and one other. There were 833 subjects with normal ST segment responses to exercise with all tests. In this group there were 44 (5.3%) coronary events: 25 cases of myocardial infarction, seven of sudden death, and 12 of angina. We conclude that in apparently healthy middle-aged men an abnormal ST segment response to exercise is predictive of angina pectoris but not of myocardial infarction or sudden cardiac death as an initial coronary event.

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THERE HAVE BEEN ample studies to document that an abnormal ST segment response to exercise in an otherwise apparently healthy subject represents a significant, independent risk factor for the future development of symptomatic coronary heart disease. However, considerable controversy exists as to how an abnormal test result should be approached clinically in light of the known, low predictive value of the test for underlying coronary artery disease. A review of the literature reveals a paucity of data on the specific types of new coronary events one might expect in those apparently healthy subjects who do go on to develop symptomatic coronary artery disease after first manifesting an abnormal ST segment response to exercise. This information is of considerable importance since it may have an impact on how the physician elects to deal with an abnormal test result once it is identified.

The purpose of this report is to review our experience with the prevalence and types of new coronary events observed during the course of long-term, serial exercise and follow-up studies of asymptomatic male employees of the Indiana State Police Department. We have collated the specific types of new coronary events recorded in subjects with abnormal ST segment responses to exercise and compared these with the initial coronary events recorded in subjects who had consistently normal ST segment responses before an event. We have also reviewed our experience with the predictive value of a conversion to an abnormal ST segment response during serial exercise testing for new coronary events, another area in which there is a paucity of available data.

Materials and methods

In 1968 the Indiana University School of Medicine and the Department of Medicine entered into an agreement with the Indiana State Police Department to provide employees with periodic medical evaluations, including symptom-limited treadmill exercise tests. Participation in the program by employees
was voluntary. This report covers our experience with the first 950 male employees who underwent initial medical evaluations between July 1, 1968, and June 30, 1975, and includes our follow-up experience for all subjects through June 30, 1983.

Initial medical evaluation. Initial medical evaluations were offered to all employees of the Indiana State Police Department who were 30 years of age or over, although a few younger subjects were scheduled by special request from the department. The participants reported to our exercise laboratory in the fasting state in the early morning. A complete history and physical examination was performed at that time. Routine laboratory tests included posteroanterior and lateral roentgenograms of the chest, resting 12-lead electrocardiogram, fasting blood sugar level, and serum cholesterol and triglyceride levels. Echocardiographic evaluations were obtained if there was clinical evidence of enlargement of the cardiac chamber, valvular disease, or previous myocardial ischemic events.

Treadmill exercise testing. After the medical examination, the subjects were prepared for treadmill exercise testing unless there was a medical contraindication. The purpose of the test was explained in detail and the subjects signed an appropriate consent form. Before 1974 a single modified bipolar CC5 lead was used to record the exercise electrocardiogram.11 Starting in 1974 a vertically oriented bipolar lead system was added. Before the exercise test, the CC5 electrocardiogram was recorded during and after 20 sec of voluntary hyperventilation in the standing position. During exercise the electrocardiogram was recorded at the end of each 3 min stage of exercise or whenever abnormal ST segment depression was observed on the monitor, and at peak exercise. Recordings were obtained routinely immediately after exercise and at 1, 3, and 6 min.

A modified Balke protocol was used for all exercise tests.11 The subjects were encouraged to continue until they reached a symptom-limited maximal effort. The exercise test was terminated short of a maximal effort if three consecutive ventricular premature complexes were observed. No tests were terminated because of abnormal ST segment depression during exercise.

Criteria for abnormal ST segment response. The exercise electrocardiogram was considered abnormal if there was 1.0 mm or more of horizontal or downsloping ST segment depression on the CC5 lead during or after exercise. All interpretations were made initially by visual analysis but all were subsequently confirmed by previously described computer-averaging and quantitation techniques.10, 11 If a subject demonstrated transient T wave inversion or horizontal ST segment depression of 0.5 mm or more with standing or hyperventilation and an abnormal ST segment response with exercise, the response was classified as a probable false positive.

Medical follow-up and serial exercise testing. Serial medical evaluations and exercise testing were originally planned at 5 year intervals for those subjects under the age of 40 years, at 3 year intervals for subjects between 40 and 49 years of age, and at 1 to 2 year intervals for subjects 50 years of age and older. The Indiana State Police Department has a mandatory retirement age of 55 years, but subjects were invited to continue in the program after their retirement. Attempts were made to reevaluate all subjects with an abnormal ST segment response to exercise at 1 to 2 year intervals irrespective of age. In general our serial evaluations proceeded as planned but the voluntary nature of the program resulted in considerable variations in the timing of follow-up studies. About 15% of subjects elected not to return after their initial evaluation. Another 20% of the subjects missed one or more of their scheduled follow-up evaluations but continued in the program and were examined at some later date.

Continuous medical surveillance was maintained on all subjects irrespective of their continued participation in our program by means of the Insurance and Benefits Section of the Indiana State Police Department. All new illnesses in current or former participants that led to sick leave or hospitalization were reported to the investigators and medical information was then obtained from the patient, the private physician, and, when appropriate, hospital records. Once a new cardiovascular event was identified, every effort was made to schedule the patient for examination at our facility as soon as possible. Finally, those subjects with abnormal ST segment responses to exercise who dropped out of the program were contacted at least yearly to update their medical histories.

Classification of new cardiac events. For the purpose of this study the new coronary events were classified according to initial clinical manifestations as either typical angina pectoris, acute myocardial infarction, or sudden cardiac death. If a subject experienced angina initially but went on to develop an acute myocardial infarction within 7 days of the initial event, the event was classified as acute myocardial infarction. Sudden cardiac death was defined as witnessed death within 2 hr of onset of symptoms.

Counseling of subjects with abnormal clinical or exercise test results. Once a subject was identified as having an abnormal ST segment response to exercise he was informed of the finding and advised that he was perhaps at increased risk of developing cardiac symptoms in the future. He was counseled in appropriate risk factor control, instructed as to the types of symptoms he should be aware of, and urged to promptly report new symptoms to our examining physician and his family physician. The family physician was also made aware of all abnormal clinical or laboratory test results at the time of each evaluation. Abnormal clinical or test results were not reported to the Indiana State Police Department unless requested by the study subject. The subjects participated in the study with a full understanding that their jobs would not be placed in jeopardy for reasons arising from the study.

Results

Initial evaluations. Between July 1, 1968, and June 30, 1975, we completed the initial evaluations on 950 male subjects between the ages of 25 and 55 years. From this group, 916 subjects were determined to be free of cardiovascular disease and they form the basis for this report. The mean age of these subjects was 37 years (range 27 to 55). All subjects had a normal resting electrocardiogram. Subjects with an abnormal ST segment response to exercise were not excluded if they were deemed to be otherwise free of cardiovascular disease. Subjects with mild hypertension defined as resting blood pressures of 140/90 mm Hg or more but less than 160/100 mm Hg were not excluded if they were not being treated with antihypertensive medications. There were 37 subjects (4%) who were diagnosed as having mild hypertension during the initial evaluation.

A total of 23 subjects (2.5%) had abnormal ST segment responses during the initial evaluation. The mean age of the subgroup was 43.2 years (range 30 to 55). An additional 14 subjects (1.5%) had labile ST or T wave changes with standing or hyperventilation and an
abnormal ST segment response to exercise. The mean age of this subgroup was 39.8 years (range 29 to 50).

**Serial evaluations.** Serial medical and exercise evaluations were initiated in July 1969 and, for the purposes of this report, continued through June 1983. Of the 879 subjects who initially had a normal ST segment response to exercise, 740 returned for one or more serial evaluations (range one to 10). From this group there were 38 subjects (5.1%) who demonstrated conversion to an abnormal ST segment response with exercise. The mean age at the time of conversion was 46 years (range 35 to 63). In addition there were eight subjects demonstrating conversion (1.1%) who also demonstrated labile ST segment or T wave changes with standing or hyperventilation. The mean age of this subgroup at the time of conversion was 41.6 years (range 33 to 50).

**New coronary events during follow-up.** Follow-up for new coronary events by means of serial evaluations and other established mechanisms was continued through June 1983 and follow-up data were available for all subjects. The maximal follow-up period for the 916 subjects was 15 years, the minimum was 8 years. The mean follow-up period from the time of the initial evaluation was 12.7 years.

Of the 23 subjects who demonstrated an abnormal ST segment response to exercise without labile ST-T wave changes during their initial evaluation, nine (39%) developed a new coronary event during the follow-up period. The initial symptomatic event was angina pectoris in eight of the nine subjects (table 1). The presence of significant coronary artery disease (stenosis of ≥75% in one or more major coronary vessels) was subsequently confirmed by coronary arteriographic studies in five of these eight subjects, while one additional subject went on to develop a nonfatal inferior or myocardial infarction 57 months after the onset of angina. The ninth subject died suddenly 57 months after his first abnormal exercise test and 3 months after his last asymptomatic test. An autopsy revealed advanced triple-vessel coronary artery disease. None of the 14 subjects with labile ST-T wave changes and an abnormal ST segment response during initial testing experienced a new coronary event.

The mean duration of follow-up of the 38 subjects who demonstrated a serial conversion to an abnormal ST segment response to exercise was 5.5 years (range 1.0 to 12.5). During this follow-up period there were 12 new coronary events (table 1). The initial symptomatic event was angina pectoris in 10 of the 12 subjects. Significant coronary artery disease was sub-

### TABLE 1

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of subjects</th>
<th>No. with an event</th>
<th>Mean duration (mo) from first abnormal or last normal exercise ECG to event (range)</th>
<th>Mean age at event (yr)</th>
<th>Type of event</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ang.</td>
</tr>
<tr>
<td>Abnormal exercise ST segment response during initial test, no labile ST-T wave changes</td>
<td>23</td>
<td>9 (39%)</td>
<td>34.9 (10–88)</td>
<td>45.0</td>
<td>8</td>
</tr>
<tr>
<td>Abnormal exercise ST segment response during initial test, labile ST-T wave changes present</td>
<td>14</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serial conversion to abnormal exercise ST segment response, no labile ST-T wave changes</td>
<td>38</td>
<td>12 (32%)</td>
<td>24.6 (6–48)</td>
<td>50.6</td>
<td>10</td>
</tr>
<tr>
<td>Serial conversion to abnormal exercise ST segment response, labile ST-T wave changes present</td>
<td>8</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined initial and serial abnormal ST segment response without labile ST-T wave changes</td>
<td>61</td>
<td>21 (34.4%)</td>
<td>29.0 (6–88)</td>
<td>48.2</td>
<td>18</td>
</tr>
<tr>
<td>Normal ST segment responses to exercise</td>
<td>833</td>
<td>44 (5.3%)</td>
<td>35.4 (5–120)</td>
<td>46.4</td>
<td>12</td>
</tr>
</tbody>
</table>

Ang. = angina; MI = myocardial infarction; SD = sudden death.

^AOne asymptomatic patient with coronary angiography and coronary bypass surgery.
sequently documented by coronary arteriographic studies in seven of these 10 subjects. One of the two subjects who experienced a new coronary event other than angina pectoris had a nonfatal inferior myocardial infarction 48 months after he demonstrated conversion to an abnormal exercise test. The other underwent coronary arteriographic studies at another institution while he was still asymptomatic. He was found to have severe triple-vessel disease as well as a 75% stenosis of the left main coronary artery and he underwent coronary bypass surgery. There were no new coronary events in the eight subjects who converted to an abnormal ST segment response to exercise in the face of labile ST segment or T wave changes.

The prevalence rate of new coronary events in the combined group of initial and serial abnormal ST segment responders without labile ST-T wave changes was 21 of 61 or 34.4%. The initial event was angina pectoris in 18 of the 21 subjects (85.7%), while one had a myocardial infarction (4.8%), one had sudden death (4.8%), and one underwent coronary bypass surgery while still asymptomatic (4.8%) (table 1).

There were 44 new coronary events in the 833 subjects who demonstrated no ST segment abnormalities during initial or serial exercise testing (table 1). The initial coronary event was angina pectoris in 12 (27.3%), acute myocardial infarction in 25 (56.8%), and sudden cardiac death in seven (15.9%). The new coronary event occurred within 12 months of the last normal exercise test in eight (18%), within 24 months in 17 (37%), within 36 months in 26 (59%), within 48 months in 33 (75%), and within 60 months in 40 (91%).

We separately analyzed the results from the 37 subjects with mild hypertension during the initial evaluation to determine any influence this subgroup may have had on our overall results. Only five (13.5%) of these subjects demonstrated an initial or serial abnormal ST segment response to exercise and none of the five had labile ST segment or T wave changes; two of these subjects developed symptoms (both angina) while three remained asymptomatic. Of the remaining 32 hypertensive subjects without abnormal exercise test results, seven (21.9%) developed a new coronary event (five myocardial infarction, two angina) while 25 remained asymptomatic.

Discussion

The predictive value (true positives/true positives + false positives × 100) of an abnormal ST segment response to exercise for new coronary events in otherwise apparently healthy men has been previously reported to be between 14% and 27% over follow-up periods ranging from 3 to 6 years.1-5,12,13 The predictive value in our study group was 25.3% when we included those subjects with labile ST-T wave changes before exercise. When these subjects were excluded, the predictive value was 34.4% (table 1).

Consistent with the results of a previous report from our laboratory dealing with a different asymptomatic study population,10 we found no greater incidence of new coronary events in subjects who demonstrated conversion to an abnormal ST segment response during serial exercise testing than in subjects with an abnormal response during initial testing (table 1). Some investigators have postulated that conversion from a normal to an abnormal ST segment response during serial exercise testing might prove to be more specific for underlying coronary artery disease than is an initially abnormal response.6,14 However, our results do not support this assumption.

Previous coronary cineangiographic studies have documented that less than 50% of apparently healthy subjects who demonstrate an abnormal ST segment response to exercise will have significant coronary artery disease.6-7,15 However, there have been virtually no studies to elucidate the natural cardiac history one can expect in those subjects who do prove to have underlying coronary artery disease. Although our numbers are relatively small, with only 21 subjects followed to date, our experience with the Indiana State Police has been that the large majority of these subjects (18/21) develop angina pectoris as their initial symptom. Five of the subjects who developed angina went on to experience an acute myocardial infarction, but only one did so in less than 3 months after the initial onset of symptoms.

The frequency with which angina pectoris occurred as the initial coronary event in our population of asymptomatic subjects with abnormal ST segment responses to exercise differed from that recently reported by Giagnoni et al.4 These authors observed 136 apparently healthy subjects (99 men, 36 women) with abnormal ST segment responses to submaximal, supine bicycle exercise for a median follow-up period of 6 years. During this time there were 21 new coronary events: nine cases of myocardial infarction and 12 of angina. These subjects were followed up with annual examinations at the authors’ medical facility or with other undefined follow-up mechanisms. It is not clear from this report whether the nine subjects who experienced an acute myocardial infarction had this complication as their initial or presenting symptom. The authors did not specify how many of the 21 subjects were
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women or whether the types of events observed differed between men and women.

Of particular interest is our finding that the majority of subjects who experienced a new coronary event in face of a previously normal ST segment response to exercise had acute myocardial infarction (56.8%) or sudden death (15.9%) rather than angina pectoris (27.3%). The significance of this finding is uncertain, but one can hypothesize that those subjects who do not manifest evidence of exercise-induced myocardial ischemia before a new event are more likely to develop an acute coronary event as the result of thrombosis or vasospasm at the site of a coronary stenosis that was not sufficiently critical to stimulate development of adequate coronary collateral circulation. On the other hand, those subjects who have manifested an abnormal ST segment response to exercise before an event are more likely to have developed coronary collateral circulation that might protect them from developing acute myocardial infarction.

It is possible that the subjects with normal exercise ST segment responses who experienced a fatal myocardial infarction or sudden cardiac death had angina pectoris as a premonitory symptom, but this did not seem to be the case based on our follow-up interviews with patients' families and personal physicians. Likewise, our follow-up interviews with those subjects who survived an acute myocardial infarction did not reveal a history of angina pectoris preceding the acute event. It is also possible that some of these subjects would have manifested an abnormal ST segment response to exercise before their coronary event had we been able to obtain serial tests on a more frequent basis. However, 37% of these subjects had undergone exercise testing within 24 months of their coronary event and 59% within 36 months.

On the basis of these results we conclude that the types of initial coronary events observed in apparently healthy middle-aged men differ depending on whether or not they demonstrate an abnormal ST segment response to exercise before the event. An abnormal exercise electrocardiographic response in this asymptomatic population seems to be a predictor for the development of angina pectoris but not myocardial infarction or sudden cardiac death as an initial coronary event. Similar studies involving populations of older men or populations of subjects with different prevalence rates for coronary artery disease may yield different results.

References

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