Prevalence and Prognostic Significance of Exercise-Induced Silent Myocardial Ischemia Detected by Thallium Scintigraphy and Electrocardiography in Asymptomatic Volunteers

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Although a silent ischemic electrocardiographic response to treadmill exercise in clinically healthy populations is associated with an increased likelihood of future coronary events (i.e., angina pectoris, myocardial infarction, or cardiac death), such a response has a low predictive value for future events because of the low prevalence of disease in asymptomatic populations. To examine whether detection of reduced regional perfusion by thallium scintigraphy improved the predictive value of exercise-induced ST segment depression, we performed maximal treadmill exercise electrocardiography (ECG) and thallium scintigraphy (201Tl) in 407 asymptomatic volunteers 40–96 years of age (mean=60) from the Baltimore Longitudinal Study on Aging. The prevalence of exercise-induced silent ischemia, defined by concordant ST segment depression and a thallium perfusion defect, increased more than sevenfold from 2% in the fifth and sixth decades to 15% in the ninth decade. Over a mean follow-up period of 4.6 years, cardiac events developed in 9.8% of subjects and consisted of 20 cases of new angina pectoris, 13 myocardial infarctions, and seven deaths. Events occurred in 7% of individuals with both negative 201Tl and ECG, 8% of those with either test positive, and 48% of those in whom both tests were positive (p<0.001). By proportional hazards analysis, age, hypertension, exercise duration, and a concordant positive ECG and 201Tl result were independent predictors of coronary events. Furthermore, those with positive ECG and 201Tl had a 3.6-fold relative risk for subsequent coronary events, independent of conventional risk factors. Thus, in an asymptomatic population, the presence of exercise-induced silent myocardial ischemia increases progressively with age and identifies a small group of subjects with a strikingly high incidence of subsequent coronary events. (Circulation 1990;81:428–436)

Although much recent attention has focused on the detection of silent myocardial ischemia in patients with known coronary artery disease, there remains considerable controversy concerning the prevalence and prognosis of silent ischemia in asymptomatic populations. Numerous studies1–11 have shown that an ischemic ST segment response to exercise is a risk factor for future coronary events (i.e., angina, myocardial infarction, or sudden cardiac death). However, the predictive value of such an ischemic electrocardiographic (ECG) response has been low for populations with a low prevalence of coronary artery disease (CAD) because of the high rate of false-positive responses.

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This observation has given rise to heated controversy concerning the value of using exercise tests for “screening” asymptomatic individuals.

Exercise thallium scintigraphy (201Tl), performed in conjunction with maximal treadmill testing, has superior sensitivity and predictive value for CAD in symptomatic patients compared with standard exercise ECG.12,13 Furthermore, isotopes such as 201Tl...
and $^{82}$Rb have been used to detect episodes of asymptomatic myocardial ischemia in patients with variant angina as well as individuals with stable effort-related angina pectoris.\textsuperscript{14} $^{201}$Tl has also accurately detected those individuals with coronary disease among apparently healthy male military personnel with abnormal exercise ECGs.\textsuperscript{15} In addition to its diagnostic use, thallium scanning is valuable in assessing the prognosis of individuals with documented CAD.\textsuperscript{16} Other investigations\textsuperscript{17–19} have shown that individuals with chest pain and normal thallium scans had very low cardiac event rates over the subsequent 2–3 years. The current report examines the ability of exercise ECG and $^{201}$Tl scintigraphy to predict future coronary events in community-dwelling volunteers in whom clinical signs, symptoms, and resting ECG indicators of CAD were absent. We hypothesized that the combination of exercise ECG and $^{201}$Tl would prove a more powerful predictor of coronary events than the exercise ECG alone or in combination with conventional risk factors.

**Methods**

Participants in the Baltimore Longitudinal Study of Aging (BLSA) are a community-dwelling, non–health care-seeking group of volunteers 21–96 years of age who have agreed to return to the Gerontology Research Center (GRC) every 2 years for 2\$\frac{1}{2}$ days of physical, physiological, and psychological examinations.\textsuperscript{20} The sample has been recruited continuously since 1958, and the majority (96%) are white; work in, or are retired from, scientific, professional, or managerial positions (80%); graduated from high school (93%) and college (71%); and are married (88%). Because studies of women were not introduced until 1978, fewer women were participants when the data for the present study were collected.

Beginning in 1977, asymptomatic BLSA subjects aged 40 years or older were asked to undergo a single exercise thallium scintigram at The Johns Hopkins Hospital on the final day of their visit. Four hundred fifty-nine of a possible 735 eligible subjects (mean age=60 years) volunteered. The data from 52 subjects were excluded from the present analyses because of resting ST segment abnormalities ($n=21$), bundle branch block ($n=4$), technical insufficiencies ($n=17$), or lack of follow-up data ($n=10$). Adequate exercise ECG and $^{201}$Tl data and follow-up information were collected on 407 subjects (288 men and 119 women) 40–96 years of age (mean=60), none of whom had clinical or resting ECG evidence of coronary artery disease as defined by the absence of significant Q waves (Minnesota Code 1:1 or 1:2) or major resting ST segment abnormalities (Minnesota Code 4:1).\textsuperscript{21}

**Procedures**

Maximal treadmill exercise testing was conducted according to a modified Balke protocol in which the treadmill speed was held constant (3.5 mph for men and 3.0 for women) and the elevation raised 3% every 2 minutes, starting from the horizontal, until exhaustion. A 12-lead ECG was recorded during the final 30 seconds of each 2-minute stage and every minute for 6 minutes into recovery. The exercise ECG was interpreted according to Minnesota Code criteria.\textsuperscript{21} A positive ECG response for ischemia was defined as horizontal or downsloping ST segment depression $\leq$1 mm. Lesser degrees of ST segment depression were interpreted as negative. The exercise duration (minutes) and the achieved percentage of age-adjusted maximal heart rate per minute, as predicted by the formula (220−age), were also recorded.

Thallium scintigraphy was performed after 1.5–2.0 mCi of $^{201}$Tl was injected intravenously 1 minute before anticipated exercise cessation. After postexercise ECG monitoring, myocardial scanning was begun 6 minutes after exercise cessation using a Technicare 420 or Technicare 100 gamma camera and a general all-purpose collimator. Planar images were obtained in the anterior, 40$^\circ$ left anterior oblique, 60$^\circ$ left anterior oblique, and left lateral positions to a preset count density greater than 500 K. Before January 1984, redistribution scans were designated only for subjects demonstrating a defect on the initial postexercise examination. During this period, thallium defects were found immediately after exercise in 50 subjects but, in fact, redistribution scans were obtained on only 30. After January 1984, redistribution scans were obtained 3 hours after the initial imaging on each of the 37 subjects tested, including five who demonstrated thallium defects immediately after exercise.

Thallium scintigrams were read by an experienced nuclear cardiologist (L.C.B.) who was unaware of the clinical history and the exercise ECG finding. Results were dichotomized as positive or negative. A positive $^{201}$Tl scintigram was defined by a segmental perfusion defect on the immediate postexercise images. Defects that were nonsegmental, particularly slitlike apical defects, and defects limited to the upper septum or basal lateral wall were considered normal variants. To further characterize the severity of the postexercise thallium defect, a computer-derived circumferential profile of thallium activity was performed as previously described on those subjects whose scans were read clinically as positive. The numerical score thus derived has been shown to correlate strongly with visual estimation of defect size.\textsuperscript{22}

**Follow-up Data and Subject Classifications**

Follow-up information was collected during subsequent biennial GRC visits for subjects who underwent $^{201}$Tl scintigraphy before April 1985. Participants were traced for at least 2 years or until death. The status of subjects who failed to return for subsequent visits within 1 year of their scheduled appearance was ascertained by telephone interview ($n=28$). Altogether, follow-up data were obtained on 98% (407 of 417) of subjects with interpretable ECG and $^{201}$Tl data.

Follow-up CAD status was ascertained from participant interviews and examinations on subsequent
visits. At each follow-up visit, the occurrence of interim cardiac events (angina pectoris or myocardial infarction) was ascertained from a standardized written questionnaire and an interview by a trained technician who was blind to subjects' prior exercise ECG and 201TI test results. Cardiac death was verified by death certificate, hospital records, private physician correspondence, and autopsy data, as available. For those individuals who developed a cardiac event, the follow-up interval was calculated as the time from the exercise 201TI test until the occurrence of the first event.

Statistical Analysis

Four subsets were defined on the basis of ECG and 201TI results: 1) subjects in whom neither test was positive (negative ECG and negative 201TI), 2) subjects with positive ECG alone (positive ECG result and negative 201TI), 3) subjects with positive 201TI alone (negative ECG and positive 201TI), and 4) subjects with concordant positive findings on both tests (positive ECG and 201TI).

Demographic and exercise data were compared among these groups by analysis of variance or χ² as appropriate. Continuous data are expressed as mean±SD. Sensitivity, specificity, and predictive accuracy for ECG result, 201TI result, and their combination for the development of future coronary events were calculated by standard formulae.23

Conventional risk factors and exercise-derived variables were analyzed by Cox's method of proportional hazards24,25 to determine the risk for future coronary events. We examined three models. In the first, we analyzed only conventional risk factors as predictors of future coronary events: age, sex, current smoking status (a smoker was defined by a habit of five or more cigarettes each day), hypertensive status (a positive response was defined by treatment with antihypertensive drugs or a resting blood pressure >160/95 mm Hg), fasting plasma glucose, total serum cholesterol, and body mass index. In the second model, we added two physiological exercise variables (exercise duration and percent of age-predicted maximal heart rate achieved) and two diagnostic exercise results (ECG and 201TI) to the first model's seven conventional risk factors. In the third model, we examined the risk for coronary events associated with the conventional risk factors plus concordant positive results on both tests (+ECG and +201TI) and two exercise test variables (exercise duration and percent age-predicted maximal heart rate achieved). A p value of less than 0.05 was considered significant for all analyses; all tests were two-tailed.

Results

Coronary Risk Profile and Exercise Response

The coronary risk profile of this generally well-educated, health-conscious, upper middle class sample was low. Hypertension, most often mild and easily controlled with diuretic monotherapy, was present in 37% of the sample; only 14% were current smokers. Serum cholesterol averaged 214.7±36.4 mg/dl with 10% exceeding 260 mg/dl, mean fasting plasma glucose was 101.2±18.5 mg/dl, and only 3% had a clinical diagnosis of diabetes mellitus; obesity was uncommon, as only 8% had a body mass index >30 kg/M². These values are consistent with those expected in an asymptomatic, health-conscious population 40 years of age or older.

Exercise duration for the entire sample averaged 10.7±4.1 minutes, and the percent of age-adjusted maximal heart rate attained was 97±8%. Only nine subjects (2%) with normal ECG and 201TI results failed to achieve 85% of their age-predicted maximal heart rate. Overall, positive ECG results were found in 66 subjects (16%) and positive 201TI scans in 55 subjects (14%). Concordant positive results on both tests were present in 23 subjects (6%), and concordant negative findings in 309 subjects (76%). Concordant abnormal ECG and 201TI results increased monotonically with age from 2% in the fifth and sixth decades to 15% in the ninth decade (Figure 1); conversely, concordant negative ECG and 201TI decreased with age from 85% in the fifth and sixth decades to 58% in the ninth decade. Thus, subjects with concordant positive results were 10.6 years older on average than those with concordant negative findings (68.7±8.2 vs. 58.1±10.9, p<0.001).

Coronary Event Rates

Over a mean follow-up interval of 4.6 years for the entire sample, cardiac events developed in 40 of 407 subjects (9.8%); events occurred in 34 of 288 men versus six of 119 women, p=0.07; five men experienced more than one event. The mean time to the first event was 4.5 years (range, 0.7–8.1). Initial coronary events consisted of angina pectoris (n=20), nonfatal myocardial infarction (n=13), and cardiac death (n=7, of which four were sudden). Three men whose initial event was angina pectoris subsequently experienced a “hard” coronary event (myocardial infarction in one and cardiac death in two). Two men who presented initially with nonfatal myocardial infarction later developed an additional event: angina pectoris in one and cardiac death in the other. Thus, according to the “hardest” end point reached (cardiac death>myocardial infarction>angina pectoris), there were 17 cases of angina pectoris, 13

<table>
<thead>
<tr>
<th>AGE</th>
<th>n=195</th>
<th>n=139</th>
<th>n=67</th>
<th>n=13</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;59</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60-69</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70-79</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;79</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FIGURE 1. Bar graph of the prevalence of concordant positive ECG and 201TI results by age decade. There is more than a sevenfold increase in prevalence from the fifth and sixth to the ninth decades (χ²=12.4, p<0.01).
TABLE 1. Distribution of Conventional Risk Factors and Exercise Results by Cardiac Event Status

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>No event (n=367)</th>
<th>Event (n=40)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>59.2±10.9</td>
<td>66.3±9.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>69.5</td>
<td>82.5</td>
<td>0.09</td>
</tr>
<tr>
<td>Smokers (% current)</td>
<td>14.7</td>
<td>12.5</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>33.8</td>
<td>62.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting plasma glucose (mg/dl)</td>
<td>101.0±19.1</td>
<td>102.8±13.6</td>
<td>NS</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>214.2±36.5</td>
<td>219.5±35.0</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index (kg/M²)</td>
<td>25.2±3.6</td>
<td>25.4±2.7</td>
<td>NS</td>
</tr>
<tr>
<td>Exercise variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration (min)</td>
<td>11.0±4.1</td>
<td>8.3±3.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MHR (% of predicted)</td>
<td>96.8±8.0</td>
<td>94.6±9.7</td>
<td>NS</td>
</tr>
<tr>
<td>+ECG (%)</td>
<td>13.6</td>
<td>40.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>+201TI (%)†</td>
<td>11.7</td>
<td>30.0</td>
<td>0.001</td>
</tr>
<tr>
<td>+ECG and +201TI (%)</td>
<td>3.3</td>
<td>27.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>−ECG and −201TI (%)</td>
<td>77.9</td>
<td>57.5</td>
<td>0.004</td>
</tr>
</tbody>
</table>

For continuous variables, values represent mean±SD.
ECG, electrocardiogram; MHR, maximal heart rate; 201TI, thallium scan.
Smokers were defined as those who smoked at least 5 cigarettes daily. Hypertension was defined by the presence of a blood pressure of ≥160/95 mm Hg or treatment with antihypertensive drugs.
†Includes all subjects with a positive ECG, irrespective of 201TI results.
*Includes all subjects with a positive 201TI, irrespective of ECG results.

myocardial infarctions, and 10 cardiac deaths. Three men whose only event was angina pectoris later underwent coronary angiography, which documented one or more significant coronary stenoses (>50%) in each. Five of the 10 cardiac deaths were sudden; the other five occurred during acute myocardial infarction.

The risk factor profile and exercise testing results are compared for the 40 subjects who developed a cardiac event and their event-free counterparts in Table 1. As anticipated, the 40 subjects experiencing an event were significantly older and more likely to be hypertensive. In contrast, the two groups did not differ with respect to current smoking status, total serum cholesterol level, or fasting plasma glucose. Although exercise duration was significantly reduced among those who later developed an event, there was no difference between groups in the percentage of maximal heart rate achieved. Positive ECG and positive 201TI were each nearly three times as prevalent in the cardiac event group as in event-free subjects; of note, concordant positive ECG and 201TI results were more than eight times as frequent in this former group.

Table 2 shows the cardiac event rates for the four subsets defined by ECG and 201TI results. The most striking finding is the disproportionately high incidence of coronary events (48%) for the subset in whom both tests were positive. In contrast to the high cardiac event rate in the concordant positive group, the event rate was generally low (3–12%) for the remaining three groups. No differences were found among the four groups in time to cardiac event or in the distribution of type of event. Of the four subjects whose initial event was sudden death, one belonged to the concordant positive group and three to the concordant negative group. The risk for an event in the concordant positive group was 6.3 times that of the remainder of the sample. Similarly, when only hard events were considered, an identical 6.3-fold risk was found. As shown in the survival curve in Figure 2, life table analysis confirmed the increased risk for a coronary event among those subjects in

FIGURE 2. Plot of event-free survival in subjects with concordant positive ECG and 201TI results versus all others. By proportional hazards analysis, a concordant positive result predicted a 3.6-fold risk for a coronary event, independent of conventional risk factors. Numbers along the x axis indicate the number of individuals at risk for each year in the All others (top) and the positive ECG and positive TI-201 (bottom) groups, respectively.

TABLE 2. Distribution of Initial Coronary Events by ECG and 201TI Test Results

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Follow-up (mean years)</th>
<th>Angina</th>
<th>Myocardial infarction</th>
<th>Cardiac death</th>
<th>% with events</th>
<th>Time to event (mean years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neither test positive</td>
<td>309</td>
<td>4.7</td>
<td>10</td>
<td>9</td>
<td>4</td>
<td>7%</td>
<td>4.7</td>
</tr>
<tr>
<td>Only ECG positive</td>
<td>43</td>
<td>3.9</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>12%</td>
<td>3.5</td>
</tr>
<tr>
<td>Only 201TI positive</td>
<td>32</td>
<td>4.4</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>3%</td>
<td>4.0</td>
</tr>
<tr>
<td>Concordant positive ECG and 201TI</td>
<td>23</td>
<td>4.5</td>
<td>6</td>
<td>3</td>
<td>2</td>
<td>48%*</td>
<td>4.0</td>
</tr>
<tr>
<td>Total</td>
<td>407</td>
<td>4.6</td>
<td>20</td>
<td>13</td>
<td>7</td>
<td>10%</td>
<td>4.5</td>
</tr>
</tbody>
</table>

*p<0.001 vs. each of the other three groups.
whom both tests were positive compared with the remainder of the sample, even after adjustment for standard coronary risk factors.

The sensitivity, specificity, and predictive value of ECG, 201TI, and their combination for predicting future coronary events is shown in Table 3. It is evident that the sensitivity of these tests was low, as further illustrated by the finding that 58% of all subjects experiencing an event had demonstrated both a normal ECG and 201TI result. The specificity and negative predictive value of ECG and 201TI were uniformly high. Noteworthy was the doubling of the positive predictive value for a future coronary event from 24% for a positive ECG to 48% for a concordant positive result on both tests. To ascertain whether the diagnostic use of such a concordant positive finding could be improved by incorporating additional variables, we further subdivided the sample using the conventional risk factors that were significant by univariate analyses. Adding hypertension to the concordant positive ECG and 201TI result was the most efficacious triad, yielding a positive predictive value of 67%, although the sensitivity decreased to 19%.

The high-risk group of 23 subjects defined by a concordant positive ECG and 201TI result contained three of the five subjects who experienced multiple coronary events, whereas only two subjects among the remaining 384 (p<0.001) developed multiple events. An additional subject in this former group who remained asymptomatic through 2.1 years of follow-up underwent prophylactic coronary artery bypass surgery after cardiac catheterization, prompted by strongly positive ECG and 201TI results, revealed three-vessel CAD. Within this high-risk group, no significant differences were found in mean age (71.5±7.9 vs. 66.3±8.0 years), minutes of exercise duration (7.3±4.1 vs. 9.0±2.8), or thallium circumferential profile score (0.88±0.89 vs. 0.78±0.92) between those 11 subjects suffering a coronary event and the 12 with no such event, respectively. However, age-adjusted percent maximal heart rate achieved was lower in the 11 concordant positives who suffered an event compared with those concordant positive subjects who did not (88±8 vs. 97±9, p<0.05). Among all 55 subjects with a visually abnormal thallium scan, the thallium score did not separate those experiencing an event from those who did not (0.83±0.90 vs. 0.63±0.80). Similarly, the regional distribution of thallium defects as well as the number of subjects with defects in more than one region were nearly identical in these two groups (Table 4). Furthermore, the risk of a coronary event was virtually identical among the 27 subjects whose scan demonstrated redistribution (22%) compared with the 28 subjects in whom 3 hour images were not obtained or a fixed defect was present (21%).

Model Testing

The relative risks from applying three proportional hazards models to the prediction of first coronary events are shown in Table 5. Among the seven conventional risk factors analyzed in the first model, only two, age and hypertension, were significant.

### Table 3. Accuracy of ECG, 201TI, and Concordant Positive ECG and 201TI Results for Predicting Coronary Events

<table>
<thead>
<tr>
<th>Descriptor</th>
<th>ECG result</th>
<th>201TI result</th>
<th>Concordant positive ECG and 201TI*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>40</td>
<td>30</td>
<td>28</td>
</tr>
<tr>
<td>Specificity</td>
<td>86</td>
<td>88</td>
<td>97</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>24</td>
<td>22</td>
<td>48</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>93</td>
<td>92</td>
<td>92</td>
</tr>
</tbody>
</table>

*Any combination of ECG and 201TI findings other than positivity on both tests was considered a negative result.

### Table 4. Number of Subjects With Abnormal 201TI Results by Thallium Defect Location and Coronary Event Status

<table>
<thead>
<tr>
<th>Defect location</th>
<th>No event (n=43)</th>
<th>Event (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior or septal</td>
<td>4 (9%)</td>
<td>3 (25%)</td>
</tr>
<tr>
<td>Inferior</td>
<td>17 (40%)</td>
<td>4 (33%)</td>
</tr>
<tr>
<td>Posterolateral</td>
<td>8 (19%)</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Apical</td>
<td>4 (9%)</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>More than one</td>
<td>10 (23%)</td>
<td>3 (25%)</td>
</tr>
</tbody>
</table>

Numbers in parentheses represent percentages of subjects with defects in specific locations by coronary event status.

Differences in the prevalence of specific defect locations were nonsignificant by event status.

### Table 5. Relative Risks From the Application of Three Models for Predicting Coronary Events

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>†††</td>
<td>†††</td>
<td>†††</td>
</tr>
<tr>
<td>Sex</td>
<td>1.3</td>
<td>1.8</td>
<td>1.6 (0.6–4.0)</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.7</td>
<td>2.3</td>
<td>2.3 (0.8–6.5)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3.3†</td>
<td>3.0†</td>
<td>2.8† (1.4–5.8)</td>
</tr>
<tr>
<td>Fasting plasma glucose</td>
<td>‡</td>
<td>‡</td>
<td>‡</td>
</tr>
<tr>
<td>Total serum cholesterol</td>
<td>‡</td>
<td>‡</td>
<td>‡</td>
</tr>
<tr>
<td>Body mass index</td>
<td>‡</td>
<td>‡</td>
<td>‡</td>
</tr>
<tr>
<td>Exercise duration</td>
<td>§</td>
<td>*‡</td>
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</tr>
<tr>
<td>Maximum heart rate</td>
<td>§</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>ECG finding</td>
<td>§</td>
<td>2.4*</td>
<td>§</td>
</tr>
<tr>
<td>201TI finding</td>
<td>§</td>
<td>1.4</td>
<td>§</td>
</tr>
<tr>
<td>Concordant positive findings on both tests</td>
<td>§</td>
<td>§</td>
<td>3.6† (1.6–8.1)</td>
</tr>
</tbody>
</table>

Comparison of conventional risk factors (model 1), conventional risk factors plus four exercise test variables separately (model 2), and conventional risk factors plus two exercise test variables and a concordant positive ECG and 201TI (model 3).

*p<0.05; †p<0.01; ‡relative risks shown only for dichotomous variables; §not included in model; NS=nonsignificant.
predictors. As shown in Table 5, older and hypertensive subjects were at greater risk for coronary events than the remainder of the sample. In model two, in addition to the two significant conventional risk factors, age and hypertension, only the ECG result was a significant predictor of coronary events. Subjects with positive exercise ECG results were 2.4 times more likely to have a coronary event. The third model, which substituted concordant positive ECG and \(^{201}\text{TI}\) tests for the separate influences of each, showed that in addition to the two significant conventional risk factors, only exercise duration and the concordant positive result were significant predictors of coronary events. A concordant positive result was associated with a 3.6-fold risk for a coronary event, even in these asymptomatic volunteers who have relatively low coronary risk profiles. In the third model, when age was dichotomized at the mean value, the relative risk for an event was 3.0 for subjects older than 60 years \((p<0.001)\), 2.5 for hypertensives \((p=0.01)\), and 3.8 for a concordant positive ECG and \(^{201}\text{TI}\) result \((p<0.001)\), while exercise duration was no longer significant.

To eliminate the possibility that the results of the proportional hazards modeling were dependent on the inclusion of individuals whose thallium defects may not have represented reversible exercise-induced ischemia, we repeated the analysis excluding the 20 subjects without redistribution scans and the eight subjects with fixed thallium defects. The results were virtually identical to those in Table 5 except that in model 2, a positive ECG was no longer significant. In particular, model 3 again demonstrated that age \((p=0.002)\), hypertension \((p=0.01, \text{relative risk}=2.8)\), and a concordant positive ECG and \(^{201}\text{TI}\) result \((p=0.03, \text{relative risk}=3.1)\) were independent predictors of a coronary event.

**Discussion**

In the present study, a concordant positive ECG and \(^{201}\text{TI}\) result was a potent predictor of coronary events independent of conventional risk factors. Subjects with positive findings on both tests had a 3.6-fold greater risk for a subsequent event compared with the remaining subjects; this relative risk was greater than that of the most powerful conventional risk factors, hypertension, sex, and age.

The concept of exercise screening for the prediction of future coronary events in asymptomatic subjects has been employed for over two decades.\(^1\)\textsuperscript{1}\textsuperscript{1}\textsuperscript{1} In previous studies, the ECG response to treadmill, bicycle, or Master 2-step exercise was employed to stratify subjects. In the majority of these studies, the positive predictive value of such testing for the development of a future coronary event has been low, averaging 21% in eight series comprising nearly 7,000 individuals.\(^26\) Such modest predictive value in asymptomatic subjects is not surprising, given the many factors in addition to ischemia that may affect the ST segment response including posture, hyperventilation, serum electrolyte concentrations, and ventricular hypertrophy. Furthermore, in low-risk populations, a low positive predictive value of exercise ECG is predicted from Bayes’ theorem.\(^27\)

We believe that our study is the first to employ exercise \(^{201}\text{TI}\) scintigraphy as a screening tool for predicting coronary events in an asymptomatic, community-dwelling population. \(^{201}\text{TI}\), a potassium analogue, distributes throughout the heart in proportion to myocardial blood flow. By directly assessing relative myocardial perfusion rather than monitoring ST-segment shift, thallium scintigraphy might be expected to yield a lower false-positive rate than ECG in a low-risk population. Applying Bayes’ theorem sequentially in such a general population, it would be predicted that individuals demonstrating an abnormal response to both tests would have a greater likelihood of CAD than the larger group with a positive ECG alone. Supporting this approach, Melin et al.\(^28\) found that a concordant abnormal ST segment and thallium scintigraphy response to maximal exercise predicted CAD, even within a group of 62 patients with a low (18%) CAD prevalence. Similarly, among 191 asymptomatic military aircrewmen with abnormal exercise ECGs, \(^{201}\text{TI}\) identified 97% of subjects correctly regarding the presence or absence of CAD.\(^15\)

Much recent attention has focused on assessing the prevalence and prognosis of silent myocardial ischemia in patients with known CAD, including those with unstable angina pectoris, stable CAD, or after a recent myocardial infarction. In these varied settings, the presence of silent ischemia, whether detected by exercise ECG or by Holter monitoring, increases the risk of subsequent coronary death, nonfatal infarction, and coronary revascularization for refractory symptoms.\(^29\)\textsuperscript{33} Because of the high false-positive rate of exercise ECG alone in asymptomatic subjects, however, the prevalence and prognosis of silent ischemia in totally asymptomatic populations has been difficult to determine. The best estimate to date of prevalence comes from an extensive study of 2,014 Norwegian men aged 40–59 years.\(^34\) Using a combination of positive ECG and angiographically documented CAD, these investigators detected silent ischemia in 2.5% of these middle-aged men.

In the present study, if we consider only a concordant positive result on both ECG and \(^{201}\text{TI}\) as indicative of silent myocardial ischemia, the overall prevalence was 6.2% in men and 2.2% in women. The increase in the prevalence of silent exercise-induced ischemia with age in our sample is noteworthy: from 2% in the 40s and 50s to 15% above the age of 80 years. Applying our 11% prevalence of concordant positive test results in those above the age of 65 years to the 28.5 million Americans in this age group and subtracting the estimated 15% with overt CAD, the number of totally asymptomatic individuals with silent ischemia would be approximately 2.7 million. These estimates are probably conservative. Several autopsy studies have documented stenoses greater than 50% in at least one major coronary artery in
60–70% of subjects above 70 years of age.35–37 Of course, such autopsy studies cannot assess the physiological significance of a given coronary stenosis and, therefore, may detect lesions that are not severe enough to cause exercise-induced myocardial ischemia.

Given their asymptomatic status, the development of clinical manifestations of CAD in nearly 50% of subjects with concordant positive findings on ECG and 201TI during the 4.6-year mean follow-up is striking; this figure represents a doubling of the positive predictive value of an abnormal ECG alone. The greater predictive value of a concordant positive ECG and 201TI response may relate to more severe CAD, a larger risk region, or fewer collaterals to the jeopardized myocardium than in those individuals positive by ECG or 201TI alone. A similar incidence of angina or infarction, 33% over 3 years, was noted in 12 asymptomatic men with positive exercise ECGs and coronary artery calcification on fluoroscopy.38 Slightly lower incidences of events in individuals with positive exercise ECGs and angiographically proven CAD, 28% over a mean follow-up of 4.8 years and 40% over an 8-year follow-up, were noted respectively in 78 asymptomatic military aircrewmen39 and 50 Norwegian middle-aged male workers.40 The lower morbidity in the latter two groups may be attributed to their younger age and perhaps less severe CAD.

Other studies have employed exercise thallium scintigraphy to predict the clinical course of patients with known or suspected CAD.17–19 The number of myocardial segments with transient thallium defects was the only significant predictor of cardiovascular death or nonfatal myocardial infarction in 100 medically treated CAD patients without prior infarction over a mean follow-up of 3.7 years.17 In a group of 1,689 similar patients without prior infarction, Ladenheim et al.16 developed a model in which a combination of severe and extensive thallium defects developing at a low heart rate predicted cardiac death, nonfatal infarction, or referral for coronary artery bypass grafting in 78% of subjects within 1 year compared with a rate of 0.4% in patients without these findings. Similarly, in three series of more than 1,100 patients with chest pain and normal exercise thallium scintigrams, the rate of cardiac death or nonfatal infarction was only 1%/yr.17–19

Certain limitations in the current study should be addressed. Because of the obvious ethical difficulty of performing cardiac catheterization on asymptomatic volunteers, we assessed future coronary events rather than coronary anatomy. The former end point is more clinically relevant, particularly given the imprecision of coronary angiography as well as the variability of functional collaterals in humans. A low event rate such as that found here might be expected in any clinically healthy population such as ours. De novo angina pectoris constituted half of our clinical events. Due to the subjective nature of chest pain complaints, angina is often considered a “soft” end point that does not always indicate anatomic CAD. However, the fact that all subjects developing angina during the course of follow-up were middle-aged men or elderly men and women, several of whom later experienced a myocardial infarction or were found to have angiographic CAD, enhances the likelihood that most anginal complaints truly represented CAD. Although we failed to obtain redistribution scans routinely on all subjects with perfusion defects on the initial postexercise 201TI scan, the exclusion of such individuals as well as those with fixed defects at 3 hours after exercise did not significantly affect our results, in particular, the importance of a concordant positive ECG and 201TI result. Recent studies46 indicate that many fixed defects on a 4-hour postexercise scan will undergo redistribution by 24 hours postexercise and that the results of such 24-hour redistribution studies correlate much better with myocardial viability than do the results of 4-hour scans.

Because only 407 individuals of a possible 735 eligible subjects underwent thallium scans and were included in the data analyses, the possibility of a selection bias exists in the decision to volunteer for this test. The fact that coronary events occurred in nearly identical proportions of the 407 subjects reported as among the remaining 328 eligible subjects (9.8% vs. 8.5%, respectively; $\chi^2 = 0.36, p = NS$) argues against any such selection bias.

Our results certainly reinforce the concept that screening with exercise electrocardiography, with or without thallium scintigraphy, is not a particularly effective strategy for the early diagnosis of CAD in unselected asymptomatic subjects, particularly if normotensive and younger than 60 years of age. Indeed, 58% of the subjects who developed an event did not demonstrate an abnormal result on either test. The low sensitivity of both ECG and 201TI, particularly for the development of hard coronary events, is consistent with a prior study using exercise ECG alone in asymptomatic police officers. These findings imply that other yet unidentified factors than inducible myocardial ischemia may be better predictors of these outcomes. The low sensitivity of 201TI in our study may reflect a relatively small amount of ischemic myocardium in these still asymptomatic volunteers, a tendency to read scans conservatively in order to preserve specificity, and the use of planar versus more sensitive tomographic imaging techniques. However, as demonstrated previously,8 exercise screening may be considerably more effective in subsets with multiple coronary risk factors, including those with family histories of premature CAD.

In the group with concordant positive exercise results, it might be argued that the development of angina pectoris as the presenting manifestation in half of those with clinical CAD end points would constitute a sufficient trigger for definitive evaluation and treatment. On the other hand, the recent findings that lowering serum cholesterol reduces both the incidence41,42 and progression43,44 of symptomatic
CAD, coupled with the recent advancements in percutaneous transluminal coronary angioplasty make detection of truly asymptomatic CAD an important clinical goal, particularly for older individuals commencing a program of strenuous aerobic training or those in positions of high public responsibility such as airline pilots or mass transit drivers.

In summary, we have demonstrated that in an asymptomatic volunteer population with a low coronary risk profile, a concordant positive response to both the standard exercise ECG and $^{201}$TI scintigraphy identifies a small group of predominantly older subjects (~10% of those over 65 years of age) with a strikingly high risk for coronary events over the subsequent 5 years. Such exercise-induced silent ischemia appears to be a potent predictor of subsequent coronary events independent of conventional risk factors. These results, although not supportive of generalized screening for CAD in low-risk populations, support the concept that such combination testing should be further investigated as a potentially useful diagnostic strategy in subjects with additional coronary risk factors.

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References


**KEY WORDS** • silent ischemia • treadmill exercise • asymptomatic volunteers • thallium scintigraphy • coronary events • exercise electrocardiography

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