Prognostic utility of the exercise thallium-201 test in ambulatory patients with chest pain: comparison with cardiac catheterization

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ABSTRACT The goal of this study was to determine the prognostic utility of the exercise thallium-201 stress test in ambulatory patients with chest pain who were also referred for cardiac catheterization. Accordingly, 4 to 8 year (mean ± 1SD, 4.6 ± 2.6 years) follow-up data were obtained for all but one of 383 patients who underwent both exercise thallium-201 stress testing and cardiac catheterization from 1978 to 1981. Eighty-three patients had a revascularization procedure performed within 3 months of testing and were excluded from analysis. Of the remaining 299 patients, 210 had no events and 89 had events (41 deaths, nine nonfatal myocardial infarctions, and 39 revascularization procedures ≥ 3 months after testing). When all clinical, exercise, thallium-201, and catheterization variables were analyzed by Cox regression analysis, the number of diseased vessels (when defined as ≥ 50% luminal diameter narrowing) was the single most important predictor of future cardiac events ($\chi^2 = 38.1$) followed by the number of segments demonstrating redistribution on delayed thallium-201 images ($\chi^2 = 16.3$), except in the case of nonfatal myocardial infarction, for which redistribution was the most important predictor of future events. When coronary artery disease was defined as 70% or greater luminal diameter narrowing, the number of diseased vessels significantly ($p < .01$) lost its power to predict events ($\chi^2 = 14.5$). Other variables found to independently predict future events included change in heart rate from rest to exercise ($\chi^2 = 13.0$), ST segment depression on exercise ($\chi^2 = 13.0$), occurrence of ventricular arrhythmias on exercise ($\chi^2 = 5.9$), and â-blocker therapy ($\chi^2 = 4.3$). The exclusion of myocardial revascularization procedures as an event did not change the results significantly. Although the number of diseased vessels was the single most important determinant of future events, the exercise thallium-201 stress test when considered as a whole (which included the number of segments demonstrating redistribution on delayed thallium-201 images, change in heart rate from rest to exercise, ST segment depression on the electrocardiogram, and ventricular premature beats on exercise) was equally powerful ($\chi^2 = 41.6$). Combination of both catheterization and exercise thallium-201 data was superior to either alone ($\chi^2 = 57.5$) for determining future events. Exercise stress test alone (without thallium-201 data) was inferior to the exercise thallium-201 stress test or cardiac catheterization for predicting future events ($\chi^2 = 30.6$). Thus the exercise thallium-201 stress test provides important prognostic information in ambulatory patients presenting with chest pain. When cardiac catheterization findings are known, exercise thallium-201 stress test data are additive in identifying patients at high risk for subsequent events.

patients with multivessel disease have the same prognosis. For example, patients with three-vessel disease and left ventricular dysfunction during exercise are at greater risk for subsequent events than those with three-vessel disease and normal left ventricular function during exercise. Similarly, patients with multivessel disease and poor left ventricular function at rest have a worse prognosis than those with multivessel disease and normal left ventricular function. It has also been reported that patients with stenosis of the proximal left anterior descending coronary artery (LAD) do not have as favorable an outcome as patients with multivessel disease without a proximal LAD stenosis. Therefore, the number of diseased vessels alone may not itself be the best predictor of prognosis.

However, even if the number of diseased vessels were the most important predictor of future cardiac events, and even if cardiac catheterization were considered a safe procedure, it would be logistically impossible to perform it as a routine procedure for risk stratification in all patients with suspected CAD. Therefore, to identify patients with CAD at increased risk for future events, the optimal test should be (1) noninvasive and therefore easily performed, (2) cost effective, and (3) useful physiologically, providing information pertaining to myocardial ischemia such as perfusion or function. We have previously reported the utility of exercise thallium-201 imaging in separating high- and low-risk subsets at 15 months of follow-up in patients who have suffered an uncomplicated myocardial infarction. We also reported a very low cardiac event rate in patients with predominantly atypical chest pain and normal exercise thallium-201 images. Based on these earlier observations, we postulated that the exercise thallium-201 stress test should provide important and useful prognostic information in ambulatory patients also undergoing cardiac catheterization for suspected or known CAD. Several groups of investigators have demonstrated the superiority of exercise thallium-201 test over exercise electrocardiography for risk assessment in such patients. In the present study we sought to determine which invasive and noninvasive variables best predicted outcome in a sequential group of ambulatory patients who underwent both exercise thallium-201 imaging and cardiac catheterization for assessment of chest pain and who did not undergo a coronary artery revascularization procedure within 3 months of such testing.

Methods

Patients. The study population consisted of 383 patients (326 men, 57 women, age 58 ± 10 years [mean ± 1SD]) with chest pain who underwent both exercise testing with thallium-201 imaging and cardiac catheterization at the University of Virginia Medical Center in the 4 year period between 1978 and 1981. The mean interval between the two tests was 12 ± 21 days. Seventy-eight percent of the patients underwent exercise thallium-201 imaging before catheterization, while in 22% it was performed after catheterization. The total number of patients who had exercise thallium-201 imaging during this period was 3872. Therefore the patient population for this study constituted 10% of patients who had exercise thallium imaging at our institution between 1978 and 1981.

Ninety-three of these patients did not have significant CAD on coronary angiography (when defined as ≥ 50% luminal diameter narrowing of major coronary arteries or their major branches), 70 had one-vessel disease, 77 had two-vessel disease, 125 had three-vessel disease, and 18 had left main disease. One hundred seventy-four of these patients had a documented prior myocardial infarction. Follow-up was obtained in these patients over a 4 to 8 year period terminating in December 1986. Follow-up was obtained by contacting the patient or patient’s family directly and confirming the occurrence of an event by medical records from our or another institution. The average follow-up period was 4.6 ± 2.6 years. Only one patient was lost to follow-up. The Appendix lists the clinical, exercise, thallium-201 imaging, and cardiac catheterization variables analyzed in these patients.

Eighty-three patients underwent coronary artery bypass graft surgery (CABG) within 3 months of cardiac catheterization. As their surgery could have been influenced by the results of the catheterization or the exercise stress test, these patients were excluded from analysis. Of the remaining 299 patients, 210 had no events, 39 had either CABG (n = 37) or coronary angioplasty (n = 2) later than 3 months after catheterization, nine had nonfatal myocardial infarction, and 41 died of cardiac or presumably cardiac causes (figure 1).

Exercise testing. Of the 299 patients analyzed for this study, 216 underwent maximal symptom-limited exercise testing according to the Bruce protocol; 83 patients were exercised according to other protocols. The medications were not stopped before the exercise test. Of the 299 patients, 177 were on β-blockers and 122 were not on β-blockers. Baseline electrocardiogram (ECG), heart rate, and blood pressure were recorded at rest, at each minute of exercise, and at 1, 2, 3, and 5 min after exercise. Exercise was terminated when fatigue, claudication, angina, dyspnea, hypotension, or ventricular tachycardia (≥ 10 beats) occurred. An exercise ECG was considered abnormal

\[
\begin{align*}
&383 \text{ patients} \\
&(1978-1981) \\
&4-8 (4.6 \pm 2.6) \text{ years followup} \\
&1 \text{ patient} \\
&\text{no followup} \\
&392 \text{ patients} \\
&\text{followup} \\
&89 \text{ pts} \\
&83 \text{ pts} \\
&210 \text{ pts} \\
&39 \text{ pts} \\
&9 \text{ pts} \\
&41 \text{ pts} \\
&\text{late MI DEATH} \\
&\text{CABG} \\
\end{align*}
\]

**FIGURE 1.** Schematic diagram of the follow-up from the original cohort of 383 patients. Late CABG = coronary artery bypass graft surgery performed ≥ 3 months after testing; MI = nonfatal myocardial infarction; early CABG = coronary artery bypass graft surgery performed < 3 months after testing.
when it exhibited a normal baseline ST segment at rest with horizontal or downsloping depression of 1 mm or more or upsloping depression of 2 mm or more 0.08 sec after the J point. It was also considered abnormal despite the presence of baseline ST segment depression (in the absence of left bundle branch block, left ventricular hypertrophy, or digitalis therapy) if the ST segment depression increased by more than 2 mm during exercise. The exercise ECG was considered nondiagnostic if (1) it was normal during exercise but the patient did not achieve 85% or more of maximal predicted heart rate,\textsuperscript{18} (2) left ventricular hypertrophy or left bundle branch block was present on the rest ECG,\textsuperscript{19} or (3) the patient’s medical regimen included a digitalis preparation at the time of study.\textsuperscript{20} For purposes of analysis, all nondiagnostic tests were considered negative. Exercise blood pressure response was considered abnormal if it either fell or failed to rise above 10 mm Hg from that at rest. All exercise and ECG variables analyzed in this study are listed in the Appendix.

Thallium imaging. At peak exercise, 1.5 to 2.0 mCi of thallium-201 (Dupont/New England Nuclear, North Billerica, MA) was injected intravenously and the patient was encouraged to exercise for an additional 30 to 60 sec. Initial (5 min after exercise) and delayed (2 to 3 hr later) images were acquired in the anterior, 45 degree left anterior oblique (LAO), and 70 degree LAO projections according to previously reported methods.\textsuperscript{21} Quantitative analysis of the seven myocardial segments was performed with a computer-aided method described previously\textsuperscript{21} and analyzed by two independent blinded observers. Thallium-201 activity in a segment was considered abnormal in the initial images if it was reduced by 25% or more compared with the segment with the greatest count intensity in that view, except in the inferior segment where the activity had to be reduced by 35% or more to be considered abnormal.\textsuperscript{21} Redistribution was considered present if the ratio of activity in the segment with reduced uptake vs that with the greatest count activity was greater in the delayed image compared with the initial image.\textsuperscript{21} For the purposes of this study, an isolated abnormality in clearance of thallium from a myocardial segment was not considered to be abnormal unless a defect was present elsewhere on the images. Lung thallium activity was assessed visually on the unprocessed initial image in the anterior view and considered to be normal or increased.\textsuperscript{15} Differences in opinion between the two observers were settled by input from a third experienced blinded observer, and the majority opinion prevailed. The Appendix depicts all thallium-201 variables analyzed for this study.

Cardiac catheterization. Coronary angiograms were assessed by visual analysis aided by a hand-held caliper and ruler. CAD was defined in two ways: (1) 50% or greater or (2) 70% or greater luminal narrowing of one or more major coronary arteries or their major branches.\textsuperscript{22} The major branches included the major diagonal branch of the LAD, the obtuse marginal branch of the left circumflex coronary artery, and the posterior descending branch of the right coronary artery in a right dominant system or a left circumflex coronary artery in a left dominant system. If an intermedial artery was present, it was considered equivalent to the major diagonal branch of the LAD. The most severe stenosis was recorded in each vessel and each patient was classified as having one-, two-, or three-vessel or left main disease. In addition, the presence or absence of proximal LAD stenosis (≥ 50% luminal diameter narrowing) was also recorded. In 88% of the patients, additional information from catheterization was recorded, including left ventricular end-diastolic pressure (LVEDP), assessment of wall motion in five segments (anterobasal, anterolateral, apical, inferior, and posterobasal) in the right anterior oblique view on cineangiography (normal, hypokinetic, akinetic, or dyskinetic\textsuperscript{22}) and left ventricular ejection fraction (LVEF) calculated by the modified Dodge equation.\textsuperscript{23} The catheterization data analyzed for this study were reviewed by a single blinded experienced observer and are listed in the Appendix.

Data analysis. CABG (or angioplasty) performed later than 3 months after cardiac catheterization, nonfatal myocardial infarction, and death were considered cardiac events. If multiple events occurred in the same patient, the first event was considered for analysis. However, if death occurred during hospitalization for a myocardial infarction, it was analyzed as an event. The variables analyzed as predictors of events are depicted in the Appendix.

Data were expressed as either mean ± 1 SD or as proportions. Univariate analysis of mean data between groups was performed by either t test with pooled variance (when two groups were compared) or one-way analysis of variance (when more than two groups were compared) (RS/1 Bolt, Beraneck, and Newman, Cambridge, MA).\textsuperscript{24} Univariate analysis of proportions between groups was performed by the chi-square test.\textsuperscript{24} Differences between groups were considered significant at a p value of <.05 (two-sided).

A multivariate analysis (Cox regression, BMDP, University of California, Los Angeles) was then performed to determine which of the simultaneously analyzed variables could predict the occurrence of future events.\textsuperscript{25} Cox regression analysis was used because the follow-up period was not the same for each patient. By this analysis, models were created that either included all variables (full model) or selected variables (constrained model) at the onset of analysis. To compare the ability of these separate models to predict future events, the Wald, Likelihood, and Score function tests were performed.\textsuperscript{25} In addition to these analyses, secondary analyses were also performed as follows: (1) excluding CABG as an event, (2) excluding patients who did not undergo the exercise test with the Bruce protocol, and (3) excluding patients who were on β-blockers. The analysis excluding CABG was performed to determine whether exclusion of an event based on physician judgment significantly alters the results. The analyses excluding patients not undergoing exercise testing with the Bruce protocol and those on β-blocker therapy was performed to determine whether these factors affected the prognostic implications of the exercise test. When event-free survival was classified based on the presence or absence of a variable, the resulting survival curves were compared by the Mantel-Cox and Breslow tests embodied in life table (Kaplan-Meier) analysis (BMDP).\textsuperscript{26}

Results

Comparison of patients with and without events and those who had CABG within 3 months of testing. Table 1 depicts a comparison of data from 210 patients with no cardiac events vs 89 patients with events. In comparison to patients who did not experience events, those who experienced events were older, had a higher incidence of prior myocardial infarction, and were more likely to be on β-blockers. These patients were more likely to develop ST segment depression on exercise lasting longer into recovery. However, the number of leads showing ST segment depression and the percentage of patients showing horizontal or downsloping vs upsloping ST depression was the same in both groups. Patients who experienced events had a lower heart rate, systolic blood pressure, and double product at peak
TABLE 1
Comparison of clinical, exercise, thallium, and angiographic variables between the different groups of patients

<table>
<thead>
<tr>
<th></th>
<th>No event (n = 210)</th>
<th>Event (n = 89)</th>
<th>Early CABG (n = 83)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>56 ± 10</td>
<td>59 ± 11</td>
<td>60 ± 10</td>
<td>.0075</td>
</tr>
<tr>
<td>% Male</td>
<td>80</td>
<td>87</td>
<td>98</td>
<td>.0002</td>
</tr>
<tr>
<td>% Typical angina</td>
<td>47</td>
<td>52</td>
<td>76</td>
<td>.0001</td>
</tr>
<tr>
<td>% Previous MI</td>
<td>42</td>
<td>56</td>
<td>43</td>
<td>.0690</td>
</tr>
<tr>
<td>% on β-blockers</td>
<td>55</td>
<td>70</td>
<td>77</td>
<td>.0005</td>
</tr>
<tr>
<td>% on digitalis</td>
<td>8</td>
<td>15</td>
<td>12</td>
<td>.0712</td>
</tr>
<tr>
<td>Exercise</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Patients with ST dep.</td>
<td>30</td>
<td>45</td>
<td>71</td>
<td>.0001</td>
</tr>
<tr>
<td>Maximum ST dep. (mm)</td>
<td>0.56 ± 1.0</td>
<td>0.74 ± 0.9</td>
<td>1.48 ± 1.2</td>
<td>.0001</td>
</tr>
<tr>
<td>No. of Leads with ST dep.</td>
<td>1.23 ± 2.1</td>
<td>1.73 ± 2.4</td>
<td>3.43 ± 2.8</td>
<td>.0001</td>
</tr>
<tr>
<td>% With H/D ST dep.</td>
<td>44</td>
<td>43</td>
<td>50</td>
<td>.0010</td>
</tr>
<tr>
<td>Duration of ST dep. (min)</td>
<td>0.9 ± 1.8</td>
<td>1.4 ± 1.0</td>
<td>2.5 ± 2.6</td>
<td>.0001</td>
</tr>
<tr>
<td>HR at peak exercise</td>
<td>133 ± 25</td>
<td>124 ± 24</td>
<td>115 ± 29</td>
<td>.0001</td>
</tr>
<tr>
<td>% Maximal pred. HR</td>
<td>78 ± 13</td>
<td>75 ± 13</td>
<td>71 ± 16</td>
<td>.0002</td>
</tr>
<tr>
<td>Δ HR from rest to exercise</td>
<td>58 ± 22</td>
<td>50 ± 21</td>
<td>44 ± 21</td>
<td>.0010</td>
</tr>
<tr>
<td>SBP at peak exercise</td>
<td>159 ± 27</td>
<td>151 ± 24</td>
<td>150 ± 29</td>
<td>.0107</td>
</tr>
<tr>
<td>Δ SBP from rest to exercise</td>
<td>32 ± 22</td>
<td>23 ± 24</td>
<td>22 ± 23</td>
<td>.0004</td>
</tr>
<tr>
<td>% Abnormal SBP response</td>
<td>14</td>
<td>26</td>
<td>27</td>
<td>.0049</td>
</tr>
<tr>
<td>DP at peak exercise (HR × SBP/1000)</td>
<td>21.4 ± 6.3</td>
<td>18.7 ± 4.8</td>
<td>18.0 ± 5.9</td>
<td>.0001</td>
</tr>
<tr>
<td>Δ DP from rest to exercise</td>
<td>2.04 ± 1.8</td>
<td>1.27 ± 1.54</td>
<td>1.16 ± 1.49</td>
<td>.0011</td>
</tr>
<tr>
<td>% With CP during exercise</td>
<td>16</td>
<td>20</td>
<td>30</td>
<td>.0495</td>
</tr>
<tr>
<td>% With PVCs during exercise</td>
<td>36</td>
<td>51</td>
<td>49</td>
<td>.0239</td>
</tr>
<tr>
<td>Duration of exercise (min)</td>
<td>6.5 ± 2.9</td>
<td>6.0 ± 2.8</td>
<td>5.2 ± 2.0</td>
<td>.0008</td>
</tr>
<tr>
<td>Workload (mets)</td>
<td>6.7 ± 2.8</td>
<td>5.9 ± 2.7</td>
<td>5.3 ± 2.3</td>
<td>.0002</td>
</tr>
<tr>
<td>Thallium</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. segs. with defects</td>
<td>1.6 ± 1.4</td>
<td>2.2 ± 1.4</td>
<td>2.5 ± 1.5</td>
<td>.0001</td>
</tr>
<tr>
<td>No. segs. with redis.</td>
<td>0.7 ± 1.1</td>
<td>1.4 ± 1.3</td>
<td>1.8 ± 1.4</td>
<td>.0001</td>
</tr>
<tr>
<td>% ↑ lung thallium</td>
<td>19</td>
<td>27</td>
<td>33</td>
<td>.1400</td>
</tr>
<tr>
<td>Catheterization</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of dis. vessels (≥50%)</td>
<td>1.2 ± 1.1</td>
<td>2.09 ± 1.06</td>
<td>2.4 ± 0.7</td>
<td>.0001</td>
</tr>
<tr>
<td>No. of dis. vessels (≥70%)</td>
<td>0.7 ± 0.8</td>
<td>1.16 ± 0.90</td>
<td>1.5 ± 0.8</td>
<td>.0001</td>
</tr>
<tr>
<td>% Proximal LAD disease</td>
<td>19</td>
<td>44</td>
<td>51</td>
<td>.0001</td>
</tr>
<tr>
<td>No. of segs. with AWM</td>
<td>1.04 ± 1.4</td>
<td>1.40 ± 1.6</td>
<td>1.3 ± 1.6</td>
<td>.0330</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>0.61 ± 0.13</td>
<td>0.59 ± 0.13</td>
<td>0.60 ± 0.12</td>
<td>.2650</td>
</tr>
<tr>
<td>LVEDP (mm Hg) (%)</td>
<td>13 ± 5</td>
<td>15 ± 7</td>
<td>14 ± 7</td>
<td>.0656</td>
</tr>
</tbody>
</table>

MI = myocardial infarction; dep. = depression; H/D = horizontal/downsloping; HR = heart rate; pred. = predicted; AWM = abnormal wall motion; dis. = diseased; SBP = systolic blood pressure; DP = double product; CP = chest pain; PVCs = premature ventricular contractions; segs. = segments; redis. = redistribution; LAD = left anterior descending coronary artery; LVEF = left ventricular ejection fraction; LVEDP = left ventricular end-diastolic pressure.

Data available in 338 of 383 patients.

Denotes where the difference lies when all three groups are compared.

Exercise, and they were more likely to demonstrate an abnormal blood pressure response and ventricular arrhythmias during exercise. Although these patients achieved a lower workload, their exercise duration was similar to those with no events, as was the incidence of chest pain during exercise. Patients who experienced events had a greater number of segments demonstrating reduced uptake of thallium-201 in the initial images and redistribution in the delayed images. However, visually assessed lung thallium-201 activity did not appear to be increased in this group of patients. These patients had a greater number of diseased vessels, a higher preponderance of proximal LAD disease, a greater number of myocardial segments showing abnormal wall motion, and higher LVEDP at cardiac catheterization; however, the LVEF in this group was similar to that in the group with no events.

When the patients who underwent early CABG (and were subsequently excluded from analysis) were compared with those experiencing events and those not experiencing events, they resembled the former group more closely (table 1). However, they had a greater
frequency of typical angina, a more positive exercise ECG with greater frequency, degree, extent, and duration of ST segment depression. They also had a greater frequency of horizontal and downsloping ST segment depression and exercised for a shorter duration. However, their thallium-201 and catheterization findings were not different from patients who experienced subsequent cardiac events. It is likely that the decision to offer this group of patients early surgery was based on more typical symptoms and a strongly positive exercise stress test.

Table 2, A, illustrates the frequency of events in patients with different degrees of CAD (≥50% luminal diameter narrowing). Ten of the 93 patients with no CAD on initial angiography had a cardiac event. Five of these patients continued to have chest pain, and on repeat coronary angiography 2 to 6 years later were found to have significant CAD for which they underwent CABG. Three patients died suddenly 4 to 7 years after testing, and one died during hospitalization for acute myocardial infarction 5 years after testing. One patient had a nonfatal myocardial infarction. The frequency of events in patients with one- and two-vessel disease (26% and 30%, respectively) was significantly less than in patients with three-vessel and left main disease (60%; p < .001). Of the five patients who did not have early CABG despite 50% narrowing of the left main coronary artery, three were thought to be inoperable on the basis of diffuse CAD with poor distal runoff. In two patients, additional disease was minimal, and their physicians opted against surgery. These two patients had no events. Of patients who underwent revascularization and who died, the majority had three-vessel disease (p < .01). The percentage of patients who experienced nonfatal myocardial infarction was the same in all categories.

Table 2, B, depicts the frequency of events in patients with no redistribution on delayed thallium-201 images compared with those demonstrating redistribution. Nineteen percent of patients with no redistribution had events vs 41% with redistribution (p < .01). Patients who experienced nonfatal myocardial infarction or those who died were more likely to have redistribution (p < .01). Among the patients who experienced events,

**TABLE 2**

Relationship of important catheterization, thallium imaging, and exercise electrocardiographic variables to the occurrence of all events

A. Relationship of events to diseased vessels (>50% luminal diameter narrowing) at cardiac catheterization

<table>
<thead>
<tr>
<th></th>
<th>OVD</th>
<th>IVD</th>
<th>2VD</th>
<th>3VD</th>
<th>LMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of patients</td>
<td>93</td>
<td>61</td>
<td>63</td>
<td>77</td>
<td>5</td>
</tr>
<tr>
<td>Patients with no events</td>
<td>83</td>
<td>45</td>
<td>44</td>
<td>36</td>
<td>2</td>
</tr>
<tr>
<td>Patients with events</td>
<td>10</td>
<td>16</td>
<td>19</td>
<td>41</td>
<td>3</td>
</tr>
<tr>
<td>Revascularization</td>
<td>5</td>
<td>9</td>
<td>7</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Death</td>
<td>4</td>
<td>5</td>
<td>9</td>
<td>20</td>
<td>3</td>
</tr>
</tbody>
</table>

B. Relationship of events to presence/absence of redistribution on delayed thallium images

<table>
<thead>
<tr>
<th></th>
<th>No redistribution</th>
<th>Redistribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of patients</td>
<td>149</td>
<td>150</td>
</tr>
<tr>
<td>Patients with no events</td>
<td>121 (81%)&lt;sup&gt;A&lt;/sup&gt;</td>
<td>89 (59%)&lt;sup&gt;A&lt;/sup&gt;</td>
</tr>
<tr>
<td>Patients with events</td>
<td>28 (19%)&lt;sup&gt;A&lt;/sup&gt;</td>
<td>61 (41%)&lt;sup&gt;A&lt;/sup&gt;</td>
</tr>
<tr>
<td>Revascularization</td>
<td>16</td>
<td>23</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>2&lt;sup&gt;B&lt;/sup&gt;</td>
<td>7&lt;sup&gt;B&lt;/sup&gt;</td>
</tr>
<tr>
<td>Death</td>
<td>10&lt;sup&gt;B&lt;/sup&gt;</td>
<td>31&lt;sup&gt;B&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

C. Relationship of events to presence/absence of ST segment depression on exercise

<table>
<thead>
<tr>
<th></th>
<th>No ST depression</th>
<th>ST depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of patients</td>
<td>197</td>
<td>102</td>
</tr>
<tr>
<td>Patients with no events</td>
<td>148 (75%)&lt;sup&gt;A&lt;/sup&gt;</td>
<td>62 (61%)&lt;sup&gt;B&lt;/sup&gt;</td>
</tr>
<tr>
<td>Patients with events</td>
<td>49 (25%)&lt;sup&gt;B&lt;/sup&gt;</td>
<td>40 (39%)&lt;sup&gt;B&lt;/sup&gt;</td>
</tr>
<tr>
<td>Revascularization</td>
<td>16</td>
<td>23</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Death</td>
<td>27&lt;sup&gt;B&lt;/sup&gt;</td>
<td>14&lt;sup&gt;B&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

OVD = no coronary artery disease; IVD = one-vessel disease; 2VD = two-vessel disease; 3VD = 3-vessel disease; LMD = left main disease.

<sup>A</sup>p < .0001; <sup>B</sup>p < .01.
there were 20 who had no redistribution on exercise thallium-201 images despite significant CAD at catheterization. Seventeen of these patients had multivessel disease, and three had one-vessel disease. However, apart from a higher incidence of prior myocardial infarction (75% vs 50%; p = .05) and a lower number of initial thallium defects (1.6 ± 1.5 vs 2.4 ± 1.4; p = .02), these patients were identical to the other patients experiencing events in terms of their clinical and exercise variables.

Table 2, C, shows the frequency of events in patients without ST segment depression vs those with ST segment depression during exercise. Twenty-five percent of patients with no ST segment depression had events vs 39% of patients with ST segment depression (p < .01). Patients who died were less likely (p < .01) to have ST segment depression on exercise.

Comparison of patients with different types of events. Table 3 illustrates the characteristics of patients who experienced different events. Patients who died were more likely to be on digoxin, had the lowest double product at peak exercise, and exercised to the least workload. These patients had more segments showing abnormal wall motion and lowest LVEF on cineangiography. However, the thallium-201 findings, number of diseased vessels, and incidence of proximal LAD

---

**TABLE 3**

Comparison of clinical, exercise, thallium, and angiographic variables in patients with different events

<table>
<thead>
<tr>
<th>Variables</th>
<th>Late CABG (n = 39)</th>
<th>MI (n = 9)</th>
<th>Death (n = 41)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>58 ± 11</td>
<td>54 ± 9</td>
<td>61 ± 11</td>
<td>.129</td>
</tr>
<tr>
<td>% male</td>
<td>90</td>
<td>78</td>
<td>85</td>
<td>.611</td>
</tr>
<tr>
<td>% typical angina</td>
<td>62</td>
<td>67</td>
<td>68</td>
<td>.814</td>
</tr>
<tr>
<td>% previous MI</td>
<td>56</td>
<td>44</td>
<td>59</td>
<td>.742</td>
</tr>
<tr>
<td>% on β-blockers</td>
<td>69</td>
<td>78</td>
<td>68</td>
<td>.852</td>
</tr>
<tr>
<td>% on digitalis</td>
<td>8</td>
<td>0</td>
<td>24b</td>
<td>.045</td>
</tr>
<tr>
<td>Exercise</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% patients with ST dep.</td>
<td>59</td>
<td>33</td>
<td>34</td>
<td>.063</td>
</tr>
<tr>
<td>Maximum ST dep. (mm)</td>
<td>1.0 ± 1.0b</td>
<td>0.4 ± 0.7</td>
<td>0.5 ± 0.8</td>
<td>.034</td>
</tr>
<tr>
<td>No. of leads with ST dep.</td>
<td>2.3 ± 2.6</td>
<td>1.1 ± 2.3</td>
<td>1.3 ± 2.3</td>
<td>.144</td>
</tr>
<tr>
<td>No. with H/D ST dep.</td>
<td>49</td>
<td>22</td>
<td>34</td>
<td>.222</td>
</tr>
<tr>
<td>Duration of ST dep. (min)</td>
<td>1.6 ± 1.9</td>
<td>0.9 ± 1.7</td>
<td>1.3 ± 2.4</td>
<td>.645</td>
</tr>
<tr>
<td>HR at peak exercise</td>
<td>127 ± 26</td>
<td>121 ± 17</td>
<td>123 ± 24</td>
<td>.701</td>
</tr>
<tr>
<td>% Maximal pred. HR</td>
<td>76 ± 13</td>
<td>70 ± 8</td>
<td>74 ± 14</td>
<td>.466</td>
</tr>
<tr>
<td>Δ HR from rest to exercise</td>
<td>56 ± 23b</td>
<td>49 ± 15</td>
<td>43 ± 17</td>
<td>.020</td>
</tr>
<tr>
<td>SBP at peak exercise</td>
<td>157 ± 20</td>
<td>153 ± 36</td>
<td>146 ± 25</td>
<td>.140</td>
</tr>
<tr>
<td>Δ SBP from rest to exercise</td>
<td>26 ± 24</td>
<td>30 ± 32</td>
<td>18 ± 22</td>
<td>.290</td>
</tr>
<tr>
<td>% abnormal SBP response</td>
<td>26</td>
<td>22</td>
<td>27</td>
<td>.959</td>
</tr>
<tr>
<td>DP at peak exercise (HR × SBP/1000)</td>
<td>20 ± 54</td>
<td>19 ± 5</td>
<td>17 ± 22b</td>
<td>.010</td>
</tr>
<tr>
<td>Δ DP from rest to exercise</td>
<td>2 ± 2</td>
<td>2 ± 2</td>
<td>1 ± 1b</td>
<td>.029</td>
</tr>
<tr>
<td>% with CP during exercise</td>
<td>23</td>
<td>11</td>
<td>20</td>
<td>.714</td>
</tr>
<tr>
<td>% with PVCs during exercise</td>
<td>46</td>
<td>44</td>
<td>56</td>
<td>.625</td>
</tr>
<tr>
<td>Duration of exercise (min)</td>
<td>6.7 ± 2.8</td>
<td>5.3 ± 0.9</td>
<td>5.5 ± 0.9</td>
<td>.139</td>
</tr>
<tr>
<td>Workload (mets)</td>
<td>6.7 ± 3.1</td>
<td>6.1 ± 1.8</td>
<td>5.1 ± 2.3</td>
<td>.071</td>
</tr>
</tbody>
</table>

**Thallium**

| No. of segs with defects   | 1.9 ± 1.4         | 1.8 ± 1.1  | 2.1 ± 2.3      | .041    |
| No. of segs. with redis.   | 1.2 ± 1.3         | 1.3 ± 1.0  | 1.6 ± 1.4      | .346    |
| % ↑ lung thallium          | 18                | 33         | 32             | .328    |

**Catheterization**

| No. of dis. vessels (≥50%) | 2.0 ± 1.1         | 1.9 ± 1.1  | 2.2 ± 1.0      | .444    |
| No. of dis. vessels (≥70%) | 1.0 ± 0.7         | 0.9 ± 0.6  | 1.3 ± 1.1      | .099    |
| % proximal LAD disease     | 33                | 44         | 54             | .187    |
| No. of segs. with AWM^     | 0.9 ± 1.1         | 0.9 ± 1.1  | 2.1 ± 1.7b     | .004    |
| LVEF^                       | 0.65 ± 0.09       | 0.59 ± 0.13| 0.52 ± 0.17b   | .001    |
| LVEDP (mm Hg)^             | 14 ± 6            | 14 ± 5     | 17 ± 9         | .271    |

Abbreviations as in table 1.

^Data available in 75 of 89 patients.

bDenotes where the difference lies when all three groups are compared.
main disease. The other independent variables found to influence prognosis adversely were occurrence of redistribution on delayed thallium-201 images, a lower double product at peak exercise, occurrence of ventricular arrhythmias during exercise, and β-blocker therapy (table 4, A). However, when CAD was defined as 70% or greater luminal diameter narrowing, the ability of the number of diseased vessels for predicting future events was lower than that of exercise thallium-201 imaging ($\chi^2 = 14.5$).

When the number of diseased vessels was excluded from the variables being analyzed, the number of segments with redistribution on delayed thallium-201 images became the most important variable determining events (table 4, B). The other independent variables included in the model were change in heart rate from rest to peak exercise, occurrence of ST segment depression on exercise, and occurrence of ventricular arrhythmias on exercise (table 4, B). Exclusion of the number of diseased vessels, however, significantly ($p = .0001$) decreased the power of the model to determine events.

Figure 3 illustrates the survival curves of patients without and with redistribution. The difference between the two curves, although significant, is not as great as that noted in figure 2 (patients with and without multivessel disease). The mean ± 1 SEM 5 year survival in patients demonstrating redistribution was 60 ± 4% compared with a 82 ± 3% in patients not demonstrating redistribution. Although the exclusion of the number of segments with redistribution from the variables being analyzed also decreased the power of the model to determine events, the decrease was not as significant.

### TABLE 4

<table>
<thead>
<tr>
<th>Variables selected</th>
<th>Improvement in $\chi^2$</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. When all variables were used</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of diseased vessels (≥50% luminal diameter narrowing)</td>
<td>38.1</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Change in heart rate from rest to exercise</td>
<td>9.4</td>
<td>.0020</td>
</tr>
<tr>
<td>Occurrence of ventricular arrhythmias on exercise</td>
<td>5.9</td>
<td>.0150</td>
</tr>
<tr>
<td>No. of segments with thallium redistribution</td>
<td>4.4</td>
<td>.0350</td>
</tr>
<tr>
<td>β-Blocker therapy</td>
<td>4.3</td>
<td>.0400</td>
</tr>
<tr>
<td>B. When number of diseased vessels was excluded from analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of segments with thallium redistribution</td>
<td>16.3</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Change in heart rate from rest to exercise</td>
<td>10.3</td>
<td>.0010</td>
</tr>
<tr>
<td>Occurrence of ST segment depression on exercise</td>
<td>9.1</td>
<td>.0030</td>
</tr>
<tr>
<td>Occurrence of ventricular arrhythmias on exercise</td>
<td>4.9</td>
<td>.0260</td>
</tr>
<tr>
<td>C. When both number of diseased vessels and number of segments with redistribution were excluded from analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in heart rate from rest to exercise</td>
<td>13.0</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Occurrence of ST segment depression on exercise</td>
<td>13.0</td>
<td>.0001</td>
</tr>
<tr>
<td>Occurrence of ventricular arrhythmias on exercise</td>
<td>5.9</td>
<td>.0140</td>
</tr>
</tbody>
</table>

$^a$Relates to improvement in the prognostic utility of the model to predict events on addition of each variable.

disease in these patients were not different from patients who underwent late CABG or those that experienced a nonfatal myocardial infarction. In contrast, patients undergoing late CABG demonstrated a greater change in heart rate from rest to peak exercise compared with the other two groups despite a greater magnitude of ST segment depression.

Results of Cox analysis for determining occurrence of events. When all variables were analyzed by Cox regression analysis, the most important variable that determined the occurrence of events was the number of diseased vessels (when CAD was defined as ≥ 50% luminal diameter narrowing) (table 4, A). Figure 2 illustrates the survival curves in patients with no CAD, single-vessel disease, and multivessel or left main disease over the 8 year follow-up period. The curves are significantly different. The mean ± 1 SEM 5 year event-free survival of patients with no CAD was 91 ± 3% compared with 75 ± 6% in patients with one-vessel disease, and 58 ± 4% in those with multivessel or left
as when the number of diseased vessels was excluded from analysis (p = .02). However, when all the noninvasive variables considered to be significant predictors of future events by Cox regression analysis (table 4, B) were not included for analysis, the power of the model to determine events decreased further (p = .003) compared with that when redistribution alone was excluded.

When both the number of diseased vessels and the number of segments demonstrating redistribution were excluded from analysis, change in heart rate from rest to exercise, occurrence of ST segment depression on exercise, and occurrence of ventricular arrhythmias on exercise became the most important variables determining occurrence of events (table 4, C). Figure 4 illustrates the survival curves of patients without and with ST segment depression. Once again, although the two curves are significantly different, the difference between those with and without ST depression is not as great as that noted in figure 2 (those with and without multivessel disease) or figure 3 (those with and without redistribution). The mean ± 1 SEM 5 year event-free survival in patients with ST segment depression was 66 ± 5% compared with 75 ± 3% in those not showing ST segment depression. Exclusion of both the number of segments demonstrating redistribution and the number of diseased vessels from analysis further decreased the power of the model to predict events (p = .02) compared with the exclusion of either alone.

When only noninvasive variables were analyzed by Cox regression, multiple variables were determined to be important predictors of events (table 4, B). In contrast, when cardiac catheterization variables were analyzed, only the number of diseased vessels was a predictor of future events. When noninvasive data selected by the Cox regression analysis to predict future events (table 4, B) were compared with coronary angiography, their overall power to determine future events was similar (table 5). In contrast, exercise stress test data alone (excluding thallium-201 data) had less power for determining future events while combination of all data (angiographic and exercise thallium-201 stress test) had greater power for predicting future cardiac events (table 5).

When each event was considered separately, the number of diseased vessels was the most important variable for determining occurrence of CABG and death. However, it was not a significant variable for determining nonfatal myocardial infarction; the number of segments demonstrating redistribution was the most important variable in this regard.

Results of the secondary analyses. When late CABG was excluded as an event, the results did not change significantly. The number of diseased vessels still remained the most important determinant of future events with change in heart rate from rest to peak exercise and number of segments demonstrating redistribution on delayed thallium-201 images being next in importance. However, the occurrence of ventricular arrhythmias on exercise, and β-blocker therapy were no longer significant predictors of future events.

In our study both low peak exercise heart rate and β-blocker therapy were independent predictors of poor outcome. We examined all variables to determine how the 177 patients on β-blocker therapy differed from the 122 patients who were not on β-blockers. Table 6 lists

![FIGURE 3. Difference in the survival of patients with and without redistribution in the delayed thallium-201 images. The numbers in parentheses denote the number of patients still at risk at that time during the follow-up. The mean ± 1 SEM 5 year event-free survival is 82 ± 3% for patients with no redistribution vs 60 ± 4% for those with redistribution (p < .0001).](http://circ.ahajournals.org/)

![FIGURE 4. Difference in survival of patients with and without ST segment depression on exercise. The numbers in parentheses denote the number of patients still at risk at that time during the follow-up. The mean ± 1 SEM 5 year event-free survival is 75 ± 3% for patients with no ST segment depression vs 66 ± 5% for those with ST segment depression (p = .005).](http://circ.ahajournals.org/)
the variables that were significantly different in the two groups. Only the hemodynamic variables were significantly lower in patients receiving β-blocker therapy. There were no differences in any of the clinical, thallium-201, and angiographic variables between the two groups. Patients on β-blocker therapy had a worse 5 year event-free survival (mean ± 1 SEM) than those not taking β-blockers (68 ± 4% vs 77 ± 4%; p = .03). When Cox analysis was performed separately on patients not taking β-blockers, double product at peak exercise replaced peak exercise heart rate as a significant predictor of future events. The other predictors were unchanged.

Similarly, we examined all variables between 216 patients who exercised with the Bruce protocol and 83 patients who exercised with other protocols. Table 7 lists the variables that were significantly different between the two groups. The patients who exercised with the Bruce protocol were more likely to be men, were younger, exercised to a higher workload, and achieved higher exercise heart rates and double products. However, there were no significant differences between the two groups in relation to thallium-201 and catheterization data. Patients who used other protocols had a worse mean ± 1 SEM 5 year event-free survival (63 ± 6% vs 75 ± 3%; p = .03). However, excluding

### Table 6
Comparison of variables that were different among patients on β-blockers and those not on β-blockers

<table>
<thead>
<tr>
<th>Variables</th>
<th>β-blockers (n = 177)</th>
<th>No β-blockers (n = 122)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR at peak exercise</td>
<td>122 ± 22</td>
<td>143 ± 22</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>% maximal predicted HR</td>
<td>72 ± 11</td>
<td>84 ± 11</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Δ HR from rest to exercise</td>
<td>52 ± 22</td>
<td>60 ± 22</td>
<td>.02</td>
</tr>
<tr>
<td>SBP at peak exercise</td>
<td>154 ± 26</td>
<td>161 ± 27</td>
<td>.04</td>
</tr>
<tr>
<td>Δ SBP from rest to exercise</td>
<td>26 ± 23</td>
<td>33 ± 22</td>
<td>.01</td>
</tr>
<tr>
<td>% abnormal SBP response</td>
<td>23</td>
<td>10</td>
<td>.004</td>
</tr>
<tr>
<td>DP at peak exercise</td>
<td>19 ± 5</td>
<td>23 ± 6</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Δ DP from rest to exercise</td>
<td>2.1 ± 1.8</td>
<td>1.6 ± 1.7</td>
<td>.01</td>
</tr>
</tbody>
</table>

Abbreviations as in table 1.

### Table 7
Comparison of variables that were different among patients exercising by the Bruce protocol and those not using the Bruce protocol

<table>
<thead>
<tr>
<th>Variables</th>
<th>Bruce protocol (n = 216)</th>
<th>Other protocols (n = 83)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>56 ± 10</td>
<td>60 ± 11</td>
<td>.0020</td>
</tr>
<tr>
<td>% male</td>
<td>85</td>
<td>77</td>
<td>.0100</td>
</tr>
<tr>
<td>HR at peak exercise</td>
<td>135 ± 23</td>
<td>117 ± 23</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>% maximal predicted HR</td>
<td>79 ± 12</td>
<td>71 ± 13</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Δ HR from rest to exercise</td>
<td>61 ± 21</td>
<td>43 ± 19</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>DP at peak exercise</td>
<td>22 ± 6</td>
<td>18 ± 5</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Δ DP from rest to exercise</td>
<td>2.0 ± 1.8</td>
<td>1.3 ± 1.4</td>
<td>.010</td>
</tr>
<tr>
<td>Workload (mets)</td>
<td>7.5 ± 2.4</td>
<td>3.8 ± 2.0</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

Abbreviations as in table 1.

### Discussion

Our results indicate that cardiac catheterization data and exercise thallium-201 imaging data are comparable in determining long-term prognosis in ambulatory patients with chest pain. Combination of angiographic and pertinent noninvasive variables was superior to either alone in determining risk of future cardiac events in our patients. Combined exercise thallium-201 stress test variables include the number of segments demonstrating redistribution on delayed thallium-201 images, presence of ischemic ST depression on ECG, a poor heart rate response during exercise, and the occurrence of ventricular arrhythmias during exercise. Exercise stress data alone (without thallium-201 imaging variables) are inferior to exercise thallium-201 imaging data or cardiac catheterization data with respect to prognostication. When all variables were analyzed simultaneously, the number of diseased vessels at cardiac catheterization was the single most important determinant of future events. The only exception was the occurrence of nonfatal myocardial infarction, for which redistribution on the delayed exercise thallium-201 images was found to be a better predictor than angiographic data. Caution, however, should be invoked, since 83 patients in the initial cohort who underwent both noninvasive and invasive evaluations were excluded from analysis because they underwent CABG within 3 months of catheterization. This subgroup included some of the highest-risk patients (including 13 of our 18 patients with left main disease). Although it remains undetermined whether exercise thallium-201 variables would have been as powerful as angiographic variables for predicting subsequent events had these patients not undergone early CABG, there were no
differences in the thallium-201 imaging and angiographic characteristics between these patients and the 89 patients who experienced events and were included for analysis.

**Role of exercise thallium imaging vs coronary angiography.** Although the number of diseased vessels (defined as ≥ 50% luminal diameter narrowing) was the most important single predictor of future cardiac events in this study, the combination of exercise stress test and thallium-201 imaging variables makes the exercise thallium-201 stress test as powerful a predictor of subsequent events as cardiac catheterization data. Unlike the exercise thallium-201 stress test, in which several exercise and imaging variables contribute to the overall predictive power of the test for determining events, no cardiac catheterization variable (including proximal LAD disease and LVEF at rest) other than the number of diseased vessels was found to be a useful predictor of future cardiac events. These findings are in contrast to previously published studies, in which LVEF at rest and the presence of proximal LAD stenosis have been reported to be independent predictors of future cardiac events. Additionally, when CAD was defined as 70% or greater luminal diameter narrowing, the number of diseased vessels was no longer the most significant single predictor of future events. This finding is also of significance because important CAD is sometimes defined as 70% or greater rather than 50% or greater luminal diameter narrowing of coronary arteries.

Once the number of diseased vessels was excluded from analysis, the most important variable predictive of future cardiac events was the number of segments demonstrating redistribution on delayed thallium-201 images. In addition, this variable was the most important predictor for determining the occurrence of non-fatal myocardial infarction, even when catheterization data were included for analysis. As reported by Kaul et al. in the study from the Massachusetts General Hospital, we found the number of segments showing redistribution to be more significant than merely its presence. Another important determinant of prognosis in the present study was the presence of ST segment depression on exercise, which has also been previously reported as an important predictor of prognosis. However, unlike certain prior studies, the duration of ST segment depression, the type of ST segment depression (horizontal or downsloping vs upsloping), and the number of leads with ST segment depression were not found to be prognostically important in the presence of other angiographic and imaging variables.

We found that the change in heart rate from rest to exercise was also a significant independent predictor of future events. Patients who experienced events had lower heart rates at peak exercise independent of the workload or duration of exercise. As would be expected, patients on β-blocker therapy and those who underwent exercise testing with modified protocols, had lower heart rates on peak exercise. When the patients receiving β-blocker therapy were excluded from analysis, the double product at peak exercise replaced peak exercise heart rate as a significant predictor of future events. Exclusion of patients who did not undergo exercise with the Bruce protocol did not alter our results. These results are similar to those observed by other investigators. As in the Massachusetts General Hospital study, we did not find an abnormal blood pressure response during exercise to be an important determinant of future events. Patients who had events were more likely to be receiving β-blocking drugs, which may merely reflect that they were probably more symptomatic. However, the prevalence of typical anginal chest pain was not different between patients with or without events, nor was the development of chest pain during exercise testing.

Another significant noninvasive predictor of future events in our study was the prevalence of exercise-induced ventricular arrhythmias. This variable was an important determinant of events independent of coronary anatomy, extent of exercise-induced ischemia (redistribution on delayed thallium-201 images and ST segment depression on the ECG), left ventricular function at rest, and presence of prior myocardial infarction. There is controversy regarding the clinical significance of exercise-induced ventricular arrhythmias, and few studies have been performed to examine its prognostic importance. Our study, in which we used multivariate analysis, suggests that the occurrence of ventricular arrhythmias during exercise is an important independent predictor of prognosis in ambulatory patients with chest pain.

**Comparison with previous studies.** Our present findings are consistent with our previous observations in patients undergoing predischarge submaximal exercise thallium-201 imaging and coronary arteriography after uncomplicated myocardial infarction. In these patients, exercise thallium-201 imaging variables were significant predictors of subsequent cardiac events (death, nonfatal myocardial infarction, and unstable angina), and were superior to angiography in separating high- and low-risk subsets. The findings in the present study are also consistent with previously reported exercise thallium-201 data in ambulatory patients. Brown et al. demonstrated that in patients with CAD who did not have angina, the number of diseased vessels and the combination of exercise thallium-201 imaging variables were significant independent predictors of future cardiac events, even when angiography was not performed.
not have a prior myocardial infarction, the number of segments with redistribution on delayed thallium-201 images was the most significant predictor of future cardiac events. Hakki et al.\textsuperscript{36} found that the number of defects on the initial images was the only significant predictor of subsequent cardiac events in 704 patients undergoing exercise thallium-201 testing. In a study of more than 500 patients, Staniloff et al.\textsuperscript{37} found that a normal thallium-201 image was associated with a 1 year cardiac event rate of 0.1%, whereas patients with multiple defects on initial thallium-201 images had an event rate of 16% and those with severe defects, an event rate of 21%. In another study of 1698 symptomatic patients who did not have a prior myocardial infarction, the same group of investigators found the number of myocardial regions with redistribution, the magnitude of hypoperfusion, and the maximal heart rate during exercise to be the only independent predictors of future events.\textsuperscript{38} Iskandrian et al.\textsuperscript{39} also found that the number of myocardial segments with initial defects was a better predictor of future cardiac events than clinical and exercise data in 743 consecutive patients who underwent exercise thallium-201 imaging at their institution.

Several studies have indicated that patients with chest pain and normal exercise thallium-201 images have an excellent prognosis even if underlying CAD has been demonstrated angiographically. Pamelaia et al.\textsuperscript{14} from our institution reported a yearly cardiac mortality of 0.5% in 345 patients with chest pain and normal thallium-201 images. Similarly, Wackers et al.\textsuperscript{40} reported no deaths and two nonfatal infarctions during a 2 year follow-up of 95 patients with normal exercise thallium-201 images. Kaul et al.\textsuperscript{41} also reported that 20 patients with chest pain and insignificant CAD on angiography who had normal exercise thallium-201 images had no events in a 4 to 8 year follow-up compared with four of 24 patients with insignificant CAD but abnormal thallium-201 images.

Previous studies have also shown that high-risk thallium-201 findings are more prevalent than high-risk stress ECG findings in patients with left main and three-vessel disease. Canhasi et al.\textsuperscript{15} detected high risk thallium-201 images in 38 of 40 patients with three-vessel CAD. In these same patients, only 15 (38%) had ST segment depression of 2 mm or greater within 6 min of exercise. Nygaard et al.\textsuperscript{16} from our institution found that 70% of patients with 50% or greater left main stenosis and 50% of patients with proximal three-vessel disease had high-risk thallium-201 images that were more prevalent than high-risk ECG findings during exercise stress testing. The explanation for why thallium-201 variables are more predictive of future cardiac events in comparison to the exercise stress test alone may be related to the better detection of multivessel ischemia than can be accomplished with exercise ECG. Our findings are also consistent with the reported studies that have used exercise radionuclide angiography for risk stratification and prognostication.\textsuperscript{8, 9, 42–45}

Some differences are apparent between results of the present study and those reported by Kaul et al.\textsuperscript{27} Whereas in our study the number of diseased vessels was the most significant single predictor of future events, a quantitative estimation of the lung/heart ratio of thallium-201 was the most important predictor of events in the latter study, making the exercise thallium-201 stress test a more powerful predictor of future events than cardiac catheterization.\textsuperscript{27} Certain important differences in the patient populations in these studies might in part explain the seeming disparities. For example, in the present study, 41 of the 89 (46%) patients with events died during follow-up compared with 20 of 91 (22%) in the Massachusetts General Hospital study, suggesting that a higher-risk population was followed medically in the present study, perhaps because during the period that patients were enrolled (between 1978 and 1981), CABG was not being offered as frequently as in later years to patients with extensive multivessel disease and poor left ventricular function or those with multivessel disease and relatively poor distal runoff. Some of these patients with high-risk anatomy and depressed left ventricular function may not have had extensive ischemia during exercise, which would favor the number of diseased vessels as a stronger predictor of future events than the number of segments demonstrating redistribution.

Another possible explanation for the superior predictability of thallium-201 exercise data compared with angiographic variables in the study by Kaul et al.\textsuperscript{27} is a higher incidence of nonfatal infarctions as an event (23% vs 9%). Because redistribution on the delayed thallium-201 images is the most important determinant of nonfatal infarctions in both studies, a smaller proportion of such events in the present study could diminish the value of redistribution on thallium-201 images in determining prognosis for the entire group. The findings in our previous postinfarction follow-up study are consistent with this explanation. In that study, only 14% of the 50 events were fatal, the remaining being nonfatal infarction or unstable angina.\textsuperscript{13} As seen in the Massachusetts General Hospital study, in which subsequent mortality was also low compared with other events,\textsuperscript{27} exercise thallium-201 imaging variables were
superior to cardiac catheterization in predicting all events in our postinfarction study.13 Taken together, findings from the studies cited above indicate that when most of the ischemic events are nonfatal, then the exercise thallium-201 stress test may be more predictive of outcome than the number of diseased vessels. In contrast, when there are a substantial number of deaths comprising an event group, the exercise thallium-201 stress test may be comparable or less predictive than angiographic variables.

Another difference between the similar study reported by Kaul et al.27 and the present study is that we did not find increased lung uptake to be an important predictor of subsequent events. Perhaps this disparity can be attributed to the fact that in the present study, lung thallium uptake was assessed solely by visual analysis, whereas in the earlier study the lung/heart ratio was determined quantitatively. When these investigators excluded lung/heart ratio from analysis, like us, they found the number of diseased vessels to be the most important determinant of future events.27 In contrast, our data are not in agreement with those of Gill et al.,46 who recently reported that the lung uptake of thallium-201 assessed visually was the most important determinant of future cardiac events in ambulatory patients with suspected CAD undergoing planar thallium-201 imaging. Their results are even more surprising, since a previous report from the same group did not find this to be the case when they analyzed visually assessed exercise thallium-201 images.35 These authors might not have detected as many segments showing redistribution on visual assessment as they might have had they used quantitative techniques.47, 48

Limitations of the study. There are several limitations to this study that deserve comment. First, it is retrospective and deals with a selected patient population. For instance, only 10% of patients undergoing thallium-201 imaging between 1978 and 1981 also underwent cardiac catheterization. Furthermore, patients in this study form a heterogeneous group that did not undergo early coronary revascularization after cardiac catheterization and exercise testing either because their CAD was considered inoperable or too risky, their CAD was too “mild” to warrant CABG, or it was the preference of the primary physician to defer CABG for any number of reasons. Nevertheless, this study is not biased by the practice of sending patients to surgery merely on the basis of high-risk thallium-201 images without concomitant refractory symptoms or left main disease, because at the time this study was undertaken, few if any patients were being sent to surgery solely on

the basis of the findings on exercise thallium-201 images.

Conclusions. The results of this study demonstrate that cardiac catheterization and exercise thallium-201 stress tests are comparable in determining the long-term prognosis in ambulatory patients with chest pain. Nonfatal myocardial infarction was better predicted by redistribution on delayed thallium-201 images than by the number of diseased vessels at cardiac catheterization. Proximal LAD disease and reduced LVEF at rest were not found to be important independent predictors of future events in the presence of other angiographic and exercise thallium-201 imaging variables. In addition, when CAD was defined as 70% or greater luminal diameter narrowing, the ability of the number of diseased vessels to predict future events was reduced significantly as compared with that when CAD was defined as 50% or greater luminal diameter narrowing. Exercise stress test data alone were inferior to thallium-201 imaging data or cardiac catheterization data for predicting earlier events. When cardiac catheterization findings are known, exercise thallium-201 information is additive in identifying patients at increased risk for subsequent events. Since the exercise thallium-201 stress test is easy to perform, noninvasive, safe, and less expensive than cardiac catheterization, it might be the preferred screening method for risk stratification in symptomatic patients with suspected CAD. Under such conditions, low-risk patients by thallium-201 imaging criteria would be spared further invasive evaluation, whereas patients with high-risk findings would be candidates for cardiac catheterization even if they had minimal symptoms.

Appendix

Clinical, exercise, thallium, and angiographic variables analyzed

Clinical
1. Age
2. Gender
3. Type of chest pain (typical/atypical)
4. Previous myocardial infarction
5. Use of β-blockers
6. Use of digitalis

Exercise
1. Percentage of patients with ST segment depression
2. Maximum ST segment depression
3. Number of leads with ST segment depression
4. Type of ST segment depression (horizontal or downsloping vs upsloping)
5. Duration of ST segment depression
6. Heart rate at peak exercise
7. Peak exercise heart rate as a percentage of maximal predicted heart rate
8. Change in heart rate between rest and peak exercise
9. Systolic blood pressure at peak exercise
10. Change in systolic blood pressure between rest and peak exercise
11. Abnormal blood pressure response (fall in systolic blood pressure during exercise or failure to rise by ≥ 10 mm Hg)
12. Double product at peak exercise
13. Change in double product between rest and peak exercise
14. Occurrence of chest pain during exercise
15. Occurrence of ventricular premature beats during exercise
16. Duration of exercise
17. Workload achieved during exercise

Thallium
1. Number of segments demonstrating initial defects
2. Number of segments demonstrating redistribution
3. Increased or normal lung thallium activity

Catheterization
1. Number of diseased vessels (≥ 50% luminal diameter narrowing)
2. Number of diseased vessels (≥ 70% luminal diameter narrowing)
3. Disease (≥ 50% luminal diameter narrowing) of the proximal LAD
4. Number of segments (out of 5) demonstrating abnormal wall motion at rest in the right anterior oblique projection*
5. LVEF at rest*
6. LVEDP at rest*

*In 338 of 383 patients.

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