Coronary Calcifications in the Detection of Coronary Artery Disease and Comparison with Electrocardiographic Exercise Testing

Results from the National Heart, Lung, and Blood Institute’s Type II Coronary Intervention Study

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SUMMARY Recent studies have noted the limitations of the exercise ECG as a screening test for coronary artery disease (CAD), particularly in asymptomatic patients. To improve the sensitivity and predictive accuracy of noninvasive screening studies, we analyzed the results of using cardiac fluoroscopy (to detect coronary calcifications) in conjunction with electrocardiographic exercise testing to detect CAD. We used these tests to screen patients for participation in the NHLBI Type II Coronary Intervention Study. The predictive accuracy of a positive test for identifying any degree of coronary artery stenosis among asymptomatic patients (n = 93) was 86% for cardiac fluoroscopy and 69% for exercise testing (p = 0.07). However, the predictive accuracy of a positive test for identifying lesions ≥50% in this same population was only 46% for cardiac fluoroscopy and 36% for exercise testing. The combination of a positive exercise test and positive cardiac fluoroscopy increased the predictive accuracy for lesions ≥50% to 82% (p < 0.05). Among symptomatic patients (n = 61), sensitivity for detecting lesions ≥50% increased from 40% for electrocardiographic exercise testing alone to 65% when fluoroscopic results were also considered. We conclude that either test used alone has a low predictive accuracy for detecting lesions ≥50% in asymptomatic subjects and a low sensitivity in symptomatic subjects. However, 1) predictive accuracy is significantly improved in asymptomatic type II patients when both tests are positive; 2) sensitivity for detecting lesions ≥50% in symptomatic type II patients is enhanced significantly by a combination of two tests rather than either one alone; and 3) the presence of coronary calcifications indicates some level of underlying coronary disease with a high predictive accuracy (86%).

RECENTLY, considerable attention has been focused on the need for a reliable noninvasive test to identify subjects with coronary artery disease (CAD). At the start of the National Heart, Lung, and Blood Institute’s Type II Coronary Intervention program in 1971, the only commonly used screening test was the exercise ECG. However, because of the reported pathologic and clinical relation between calcium in the coronary arteries and coronary atheroma, we chose to use fluoroscopy to evaluate the presence of coronary calcification and the exercise test as screening procedures for CAD in our patient population. Since then, reports have established a positive relation between the presence of calcium on fluoroscopy and angiographically demonstrated CAD in symptomatic patients. None of these studies, however, used fluoroscopy as a screening test for CAD in an asymptomatic population, or determined (when possible) its predictive accuracy, specificity, or sensitivity in asymptomatic vs symptomatic patients with angiographically identified CAD.

Controversy has arisen over the sensitivity and predictive accuracy of the electrocardiographic response to exercise in detecting the presence or absence of CAD. In fact, evidence has accumulated indicating that more than half of the asymptomatic patients with positive electrocardiographic responses to exercise have coronary arteries that are either normal or only minimally narrowed, as determined by coronary angiography. In addition, a relatively high percentage of asymptomatic patients with CAD have a negative electrocardiographic response to exercise.

We undertook this prospective study 1) to evaluate fluoroscopic detection of coronary calcifications as a screening test for CAD, 2) to compare the results of fluoroscopy with those of electrocardiographic exercise testing, and 3) to determine whether combining the results of the fluoroscopic determination of coronary calcifications with electrocardiographic response to exercise enhances the sensitivity and predictive accuracy for detection of CAD.

Methods

Patient Population

All patients were referred to the National Heart, Lung, and Blood Institute for evaluation of an
elevated cholesterol level and for possible participation in the Institute's Coronary Intervention Study. This study was a prospective, randomized, double-blind trial of the effect of a cholesterol-lowering regimen on the progression of angiographically demonstrable CAD. All patients had LDL cholesterol above the 90th percentile for age after 1 month of dietary therapy (All subjects were thoroughly instructed in a diet designed to limit daily cholesterol intake to less than 300 mg and result in a polyunsaturated-to-saturated fat ratio of 2:1); no laboratory or clinical evidence of hepatic, renal, or thyroid disease; fasting triglycerides <400 mg/100 ml; resting blood pressure <160/100 mm Hg; fasting blood sugar values <130 mg/100 ml; no congestive heart failure or severe, medically intractable angina; and no patient was taking any medications known to affect serum lipoprotein levels. Fully informed consent was obtained, and patients underwent coronary angiography only if they had both an elevated LDL cholesterol after following the type II diet for 1 month and had evidence suggestive of coronary artery disease, i.e., a history of chest pain or prior myocardial infarction, a positive ST response to exercise, or coronary calcifications seen on fluoroscopic examination.

We do not advocate the use of coronary arteriography as a screening test for asymptomatic subjects suspected of having coronary disease. We adopted this procedure as the critical endpoint in the NHLBI Type II Intervention Study after consultation with many experts in the field. It was approved by the NHLBI and NIH Research Review Committees and we obtained fully informed consent from the patients.

One hundred and eighty-one patients, 21-55 years of age, with nonidiotic type II hyperlipoproteinemia who met all of the above criteria, underwent coronary arteriography. We divided the patients into three groups. The "asymptomatic" group consisted of 93 patients who had no cardiac symptoms, but had a positive exercise test, coronary calcifications on cardiac fluoroscopy, or both. The "symptomatic" group consisted of 61 patients who had typical angina pectoris, a history of documented myocardial infarction, or both. The "atypical angina" group consisted of 27 patients with atypical angina pectoris (defined below). Thirty-seven of the 181 patients had no coronary artery disease detected on angiography. The other patients all had at least some degree of angiographically demonstrated CAD.

The clinical characteristics of the patients in the asymptomatic, symptomatic, and atypical angina groups are presented in Table 1. There were no significant differences between the groups regarding number of men and women, mean age, mean systolic and diastolic blood pressure, mean pack-years of smoking, or fasting blood sugar. The 2-hour postprandial blood sugar value was significantly higher for symptomatic than for asymptomatic patients (p < 0.01; Table 1). However, the value for both groups was within normal limits.

**Coronary Angiography**

We performed selective coronary arteriography in each patient by the Judkin's technique within 3 days of the fluoroscopic examination and exercise test. We took right and left anterior oblique cineangiograms, as well as right and left oblique and lateral cut films, during injection of each coronary artery. The arteriograms were read independently by a radiologist and a cardiologist. When differences in interpretation occurred, the arteriograms were reevaluated and a consensus was obtained.

**Fluoroscopy**

A radiologist skilled in the technique performed fluoroscopy on 181 patients 3 days before coronary arteriography and recorded the presence or absence of coronary artery calcifications. If present, the location and extent of calcification (trivial, moderate, or severe) were also recorded.

To assess intraobserver reproducibility, we examined the results of fluoroscopy done 3 months apart by the same radiologists. For the first reading, the radiologist was blinded and had no previous knowledge of the patient or his or her data; for the second reading, the radiologist did not know the results of the first reading, the patient was instructed not to tell him, and the chart was not readily available. We analyzed 157 of these readings: 139 (89%) were exactly reproduced — both readings showed calcification in 76 and no calcification in 63. Nine readings that originally showed calcification were reversed, as were nine readings that originally showed no calcification.

**Exercise Test**

The electrocardiographic response to exercise was determined during the upright bicycle ergometry with

<p>| Table 1. Clinical Characteristics of Asymptomatic, Symptomatic and Atypical Angina Patients |
|---------------------------------|------------|-------------------|--------------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Age (years) (mean ± SD) M</th>
<th>F</th>
<th>Blood pressure (mm Hg) (mean ± SD)</th>
<th>Pack-years of smoking (mean ± SD)</th>
<th>Smokers (%)</th>
<th>Fasting blood sugar (mg/100 ml) (mean ± SD)</th>
<th>2-hour PP blood sugar (mg/100 ml) (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>69</td>
<td>24</td>
<td>45.9 ± 6.7</td>
<td>123 ± 12.5</td>
<td>78 ± 11.3</td>
<td>16.9 ± 20.7</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>47</td>
<td>14</td>
<td>46.4 ± 6.9</td>
<td>123 ± 13.1</td>
<td>79 ± 9.8</td>
<td>21.3 ± 16.3</td>
</tr>
<tr>
<td>Atypical angina</td>
<td>17</td>
<td>10</td>
<td>45.8 ± 6.8</td>
<td>122 ± 10.5</td>
<td>77 ± 7.6</td>
<td>18.1 ± 14.6</td>
</tr>
</tbody>
</table>

There were no significant differences between any of the groups regarding clinical characteristics except for the 2-hour postprandial (PP) blood sugar: asymptomatic vs symptomatic; p < 0.01.
two training sessions preceding the final test. We increased the workload by 20-watt increments every 3 minutes until angina developed or until heart rate reached 85% of the predicted maximum for the subject's age and sex. We chose the initial workload so that the total duration of exercise was 3–8 minutes — long enough to allow a relatively steady state to be achieved but short enough to obviate the confounding effects of fatigue. Electrocardiographic leads were arranged in a modified CMS5 system with a reference electrode over the manubrium, an exploring electrode in the V1 position to assess ST-segment and T-wave changes with a horizontal vector, and a second exploring electrode over the lumbar spine to assess ST-segment and T-wave changes with an inferior vector. We recorded the ECG continuously during exercise and for 5 minutes thereafter.

Serum electrolytes were normal at the time of exercise (K+ values 3.5–5.5 mEq/l). The mean exercise time was 4.0 minutes and the mean initial workload was 120 watts. 170 patients exercised to 85% of predicted maximal heart rate, seven exercised to angina, two were stopped because of serious arrhythmias and two because of fatigue. The mean heart rate after exercise was 145 beats/min.

An exercise ECG was considered positive if, 0.08 second after the J point, the ST segment was depressed 0.1 mV or more below the resting baseline value, with the slope ≤0. The exercise tracings were read blindly and independently by four physicians. The tests were blinded so that no identifying information, including date, time and patient name or number, was available. They were then read and recorded independently without knowledge of any other reading or data. If any disagreement existed (i.e., negative or positive reading or any ST-segment difference >0.5 mV), all four physicians met to resolve the disputed interpretations and reach a consensus. In 166 of 181 readings (92%) performed in this manner, all four observers were in unanimous agreement concerning whether the test was positive or negative, and in 171 readings (94%), all four observers unanimously agreed on the maximum amount of ST-segment depression to within ±0.5 mm.

Definitions

Typical Angina Pectoris

We diagnosed typical angina pectoris when chest discomfort involved the sternum or left arm, occurred usually during exertion and had occurred more than once, usually disappeared within 10 minutes after the patient ceased or decreased the intensity of exertion, and was relieved in 2–5 minutes after sublingual administration of nitroglycerin.

Atypical Angina

We diagnosed atypical angina when two or three but not all of the above criteria were present.

Definite Myocardial Infarction

We diagnosed definite myocardial infarction if typical electrocardiographic evolution was present, or if a typical history was coupled with typical enzyme changes, or if ischemic electrocardiographic changes were coupled with typical enzyme changes.

Any coronary disease

This diagnosis included any disease from wall irregularities to 100% occlusion.

Formulas and Statistics

We used the following formulas to calculate predictive accuracy, specificity, and sensitivity:

\[
\text{predictive accuracy} = \frac{\text{true positive tests}}{\text{true positive + false positive tests}}; \\
\text{specificity} = \frac{\text{true negative tests}}{\text{true negative + false positive tests}}; \\
\text{sensitivity} = \frac{\text{true positive tests}}{\text{true positive + false negative tests}}.
\]

We performed all statistical analyses using standard parametric tests. We used the \( t \) test to make intergroup comparisons. Differences were considered significant for \( p \) values <0.05.

Results

Correlation of Fluoroscopy and Exercise Tests, Considered Separately and with Angiographic Results

Of the 181 patients in the study, 104 had coronary calcifications detected at fluoroscopy and 66 had a positive electrocardiographic response to exercise.

Predictive Accuracy

Patients with \( \geq 50\% \) coronary artery narrowing. These results are shown in figure 1. Predictive accuracy — the percent of subjects with positive tests who actually had disease — was 46% for fluoroscopy and 36% for exercise testing in asymptomatic subjects; among symptomatic subjects it was 96% for fluoroscopy and 95% for exercise testing; and in subjects with atypical angina it was 69% for fluoroscopy and 43% for exercise testing. Predictive accuracy of the fluoroscopy examination and the exercise test was not statistically different within any subgroup.

Patients with any degree of coronary artery narrowing. These results are shown in figure 2. In the asymptomatic subjects, the predictive accuracy of a positive fluoroscopic examination for identifying any degree of
PREDICTIVE ACCURACY FOR 
\(\geq 50\%\) CORONARY NARROWING

\[\begin{array}{c}
\text{PTS. WITH POSITIVE FLUOROSCOPY} \\
\text{PTS. WITH POSITIVE ECG RESPONSE TO EXERCISE}
\end{array}\]

**FIGURE 1.** Predictive accuracy of positive fluoroscopy or exercise test for detecting stenosis \(\geq 50\%\) of one or more coronary arteries. Patients with positive fluoroscopy and positive electrocardiographic response to exercise are included in both the fluoroscopy and exercise test data. Numbers at the base of columns indicate total number of patients. CAD = coronary artery disease; angio = coronary angiography; asym = patients with no symptoms of CAD; sym = patients with typical angina pectoris or previous myocardial infarction.

Coronary artery narrowing was 86% and that of the exercise test was 69% \((p = 0.07)\). Predictive accuracy of either a positive fluoroscopic examination or exercise test among the symptomatic groups was very high, but among the atypical angina group, predictive accuracy approximated that of the asymptomatic population. There were no significant differences in the predictive accuracy of the two tests in either of these latter groups.

**Sensitivity**

The sensitivity (the frequency of a positive test in a group of patients having disease) of fluoroscopy and the electrocardiographic exercise test for detecting CAD was calculated for the symptomatic patients (fig. 3). We could not calculate sensitivity for asymptomatic subjects because subjects with no symptoms and negative fluoroscopic and exercise tests were not studied by angiography.

**Patients with \(\geq 50\%\) coronary artery narrowing.** In the 48 symptomatic subjects (typical angina, prior myocardial infarction or both) who had one or more coronary stenoses that produced narrowing \(\geq 50\%\), fluoroscopy was positive in 46% and exercise testing was positive in 40% (NS).

**Patients with any degree of coronary artery narrowing.** In the 54 symptomatic patients who had any degree of coronary artery narrowing, fluoroscopy was positive in 43% and exercise testing was positive in 35% (NS).

**Correlation of Combined Results of Fluoroscopy and Exercise Tests with Angiography (table 2)**

**Predictive Accuracy**

**Patients with coronary artery narrowing \(\geq 50\%).** Figure 4 shows the predictive accuracy of the various
SENSITIVITY-SYMPTOMATIC SUBJECTS

Figure 3. Sensitivity of fluoroscopic examination and exercise testing for detecting coronary artery disease (CAD) in symptomatic (typical angina, prior myocardial infarction or both) subjects. There is no significant difference between the two tests for detecting any degree of coronary artery narrowing or for detecting one or more stenoses ≥50% by angiography. Numbers at the base of each column indicate total number of patients.

Table 2. Correlation of Fluoroscopy and Exercise Test Results with Angiography

<table>
<thead>
<tr>
<th>Group</th>
<th>Test results</th>
<th>Number</th>
<th>Patients with normal angiograms (%)</th>
<th>Patients with only lesions ≤ 50% (%)</th>
<th>Patients with one or more lesions ≥ 50% (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>-F/-GXT</td>
<td>0</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>-F/+GXT</td>
<td>28</td>
<td>11 (39)</td>
<td>12 (43)</td>
<td>5 (18)</td>
</tr>
<tr>
<td></td>
<td>+F/-GXT</td>
<td>54</td>
<td>8 (15)</td>
<td>25 (46)</td>
<td>21 (39)</td>
</tr>
<tr>
<td></td>
<td>+F/+GXT</td>
<td>11</td>
<td>1 (9)</td>
<td>1 (9)</td>
<td>9 (82)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>93</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atypical angina</td>
<td>-F/-GXT</td>
<td>8</td>
<td>3 (38)</td>
<td>3 (38)</td>
<td>2 (25)</td>
</tr>
<tr>
<td></td>
<td>-F/+GXT</td>
<td>3</td>
<td>2 (67)</td>
<td>1 (33)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>+F/-GXT</td>
<td>12</td>
<td>4 (33)</td>
<td>0 (0)</td>
<td>8 (67)</td>
</tr>
<tr>
<td></td>
<td>+F/+GXT</td>
<td>4</td>
<td>1 (25)</td>
<td>0 (0)</td>
<td>3 (75)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>27</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Typical angina, MI or both</td>
<td>-F/-GXT</td>
<td>28</td>
<td>6 (21)</td>
<td>5 (18)</td>
<td>17 (61)</td>
</tr>
<tr>
<td></td>
<td>-F/+GXT</td>
<td>10</td>
<td>1 (10)</td>
<td>0 (0)</td>
<td>9 (90)</td>
</tr>
<tr>
<td></td>
<td>+F/-GXT</td>
<td>13</td>
<td>0 (0)</td>
<td>1 (8)</td>
<td>12 (92)</td>
</tr>
<tr>
<td></td>
<td>+F/+GXT</td>
<td>10</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>10 (100)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>61</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: -F = negative fluoroscopy; +F = positive fluoroscopy; -GXT = negative exercise test; +GXT = positive exercise test; MI = myocardial infarction.
combinations of fluoroscopy and exercise test results for detecting one or more coronary lesions ≥50%. When both tests were positive, the predictive accuracy was 75% or higher, regardless of symptomatic status. However, when a positive exercise test occurred in combination with negative fluoroscopy among the asymptomatic and atypical angina subjects, predictive accuracy was low. Conversely, the likelihood of finding coronary narrowing ≥50% in the symptomatic subjects was 90% or higher when either or both tests were positive. However, 79% of all symptomatic patients had ≥50% narrowing of one or more coronary arteries on angiography.

Figure 5 shows how fluoroscopic examination can enhance the predictive accuracy of a positive electrocardiographic stress test. Thus, while predictive accuracy of a positive electrocardiographic stress test in asymptomatic subjects was only 36% when considered alone, it increased to 82% if coronary calcifications were detected in the same subject (p = 0.02) and decreased to 18% if no calcifications were seen (p < 0.001) (fig. 4). Predictive accuracy was already 95% in the symptomatic subjects with a positive electrocardiographic stress test before fluoroscopy and, therefore, could not be significantly improved.

Patients with any degree of coronary artery narrowing. As shown in figure 4, the trend for detecting any CAD is the same as for detecting narrowing ≥50%.

Sensitivity
As previously mentioned, the sensitivity for detecting existing CAD was calculated only among symptomatic patients and those with atypical angina because asymptomatic subjects with a negative fluoroscopic examination and exercise test were not studied by angiography.

Patients with coronary artery narrowing ≥50%. Among the 48 subjects in the symptomatic group (typical angina or prior myocardial infarction) with one or more lesions producing coronary artery narrowing ≥50%, 21% (10 of 48) had both fluoroscopic and exercise tests positive. However, 65%
had either a positive fluoroscopic examination, a positive electrocardiographic response to exercise, or both. The corresponding results for patients with atypical angina were 23% (three of 13) and 85% (11 of 13).

Patients with any degree of coronary artery narrowing. Among the 54 subjects in the symptomatic group with any degree of coronary artery narrowing, in 18% (10 of 54), both the fluoroscopic examination and exercise test were positive. In addition, of the 54 patients with any degree of coronary artery narrowing, 59% had either a positive fluoroscopic examination, a positive electrocardiographic response to exercise, or both. Among the patients with atypical angina, the corresponding results were 18% (three of 17) and 65% (11 of 17).

Correlation of Combined Results of Fluoroscopic Examination and Exercise Test in Detecting Extent of CAD

Of the entire group of 181 patients, 25 (11 asymptomatic, 10 symptomatic and four atypical angina patients) had both a positive fluoroscopic examination and a positive electrocardiographic response to exercise; 48% (four asymptomatic, six symptomatic and two atypical angina patients) had three or more vessels with stenosis ≥50%. Of the 156 patients who did not have both a positive fluoroscopic examination and electrocardiographic response to exercise, only 19 (12%) had three or more stenoses ≥50%. Thus, a patient with a positive fluoroscopic examination and a positive exercise test has a greater chance of having significant three-vessel disease than a patient with only one or no positive test \( (p < 0.01; \text{fig. 6}) \). Similar trends were also seen when the asymptomatic and symptomatic patients were evaluated separately. Of the 11 asymptomatic patients with both tests positive, four (36%) had three-vessel disease, while only five of 82 (6%) patients with one or both tests negative had three-vessel disease \( (p < 0.01) \). Of the 10 symptomatic patients with both tests positive, six (60%) had three-vessel disease, compared with 11 of 51 (22%) with one or both tests negative \( (p < 0.05) \). Furthermore, 22 of 25 (88%) patients with both tests positive had at least one vessel with narrowing ≥50%, compared with 74 of 156 (47%) with one or both tests negative \( (p < 0.001) \).

Correlation between Severity of Coronary Artery Calcifications by Fluoroscopy and Presence and Extent of CAD by Angiography

The data for all 104 patients with a positive fluoroscopic examination are presented in figure 7. Forty-three patients had trivial calcifications by fluoroscopy and 61 patients had moderate or severe calcifications. There was no significant difference in the severity of CAD detected by angiography between the patients with trivial and those with moderate or severe calcifications. Similar results were obtained when the asymptomatic and symptomatic groups were analyzed separately.

Location of Calcification by Fluoroscopy vs Location of CAD by Angiography

The results are presented in table 3. Twenty-nine patients had right coronary artery (RCA) calcifications on fluoroscopy and 25 (86%) did have CAD by angiography in the RCA. Fifteen (52%) of these patients had stenosis ≥50% by angiography. However, a negative fluoroscopic examination of the RCA failed to exclude RCA disease by angiography.

The results for the left system considered as a whole (fluoroscopy positive anywhere in the left system vs disease found anywhere in the left system by angiography) are similar to those for the RCA. Eighty-six (86%) of 100 patients with a positive fluoroscopy in the left system had CAD by angiography in the left system, and 52% of these had a stenosis ≥50%. The results for the left circumflex and
the left anterior descending coronary arteries when considered individually are similar to those for the RCA. A positive fluoroscopic examination correlated well with the presence of CAD by angiography in the same vessel, but a negative fluoroscopic examination did not reliably exclude the presence of CAD by angiography. By contrast, for the left main coronary artery, a positive fluoroscopic examination correlated poorly with the finding of CAD by angiography in the same vessel.

Discussion

In an asymptomatic hyperlipidemic type II population composed of patients younger than 55 years of age, the detection of coronary artery calcification by cardiac fluoroscopy has a predictive accuracy of 86%...
in identifying any degree of angiographically demonstrable CAD. However, the predictive accuracy of detecting asymptomatic patients with narrowing of major coronary vessels ≥50% was 46%; the corresponding figure for electrocardiographic exercise testing of the same patients was 36%. A predictive accuracy of only 36% for the electrocardiographic exercise test confirms the results of our first study of the initial group of 89 patients recruited for the NHLBI Type II Intervention Study. 16

While predictive accuracy in the asymptomatic population was relatively low (46%), fluoroscopy had a very high predictive accuracy (96%), as did exercise electrocardiography (95%), for detecting coronary artery narrowing ≥50% in patients with a history of typical angina pectoris, prior myocardial infarction, or both. Bartel and co-workers also found fluoroscopy to have a very high predictive accuracy in patients with symptomatic coronary disease. 25 However, in patients with atypical chest pain, the predictive accuracy of fluoroscopy was only 69%, and that of electrocardiographic exercise testing only 43%. These latter figures are not significantly better than the corresponding results in asymptomatic patients. Although the number of patients studied in this subgroup was small, the results are rather disappointing in view of the diagnostic dilemma that subjects with atypical chest pain represent.

As several studies have noted, 16, 25, 26 the variation in predictive accuracy among different subgroups of patients shown in this study is best explained by Bayes' theorem, which states that when the specificity and sensitivity of a test are <100%, the predictive accuracy of that test is proportional to the prevalence of the disease in the population under study. Bayes' theorem and our experimental results make clear the diagnostic inadequacy of a less-than-perfect single test in detecting CAD in a population of subjects with low disease prevalence, as is certainly the case with subjects who have no symptoms. Although the prevalence of CAD in patients with atypical chest pain has been reported to be 50% or higher, 27 more recent studies 28-31 suggest that it is considerably lower. This finding (and the small number of patients studied in this subgroup) probably explains the low predictive accuracy of fluoroscopy and electrocardiographic exercise testing in patients with atypical angina.

Because both fluoroscopy and exercise electrocardiography when used alone manifest important limitations in predictive accuracy for detecting coronary narrowing ≥50%, we assessed the efficacy of a combination of the two methods. These results are summarized in figures 5 and 6. Among asymptomatic subjects, the chance of finding narrowing ≥50% is markedly improved when both screening tests are positive. Thus, when a positive electrocardiographic stress test alone was considered, only 36% of patients had narrowing ≥50%. However, 82% had narrowing ≥50% when both tests were positive. A positive result on both screening tests also greatly increased a patient's chance of having three or more lesions ≥50% (fig. 6).

The value of combining the two tests is more limited in symptomatic patients (fig. 5), since 90% have coronary artery narrowing ≥50%, even if only one of the two tests is positive. However, a negative result on both tests significantly (p < 0.01) decreases the likelihood of coronary lesions ≥50%, and a combined positive result increases the likelihood of multivessel disease.

The combination of fluoroscopic examination and electrocardiographic exercise testing enhances the predictive accuracy for detecting coronary narrowing ≥50%. However, the requirement that both tests be positive to screen for CAD necessarily diminishes an already low sensitivity. Thus, of our asymptomatic patients with coronary narrowing ≥50%, 46% had a positive fluoroscopic examination and 36% had a positive electrocardiographic exercise test, but in only 21% were both tests positive.

Although fluoroscopic examination and exercise testing appear to be of limited value in improving the detection of significant coronary disease in symptomatic patients, our data suggest that in combination they can considerably enhance the detection of coronary lesions ≥50% in asymptomatic patients (fig. 8). Thirty-nine of our asymptomatic patients had a positive electrocardiographic exercise test, but only 14

![Table 3. Location of Calcification by Fluoroscopy vs Location of Coronary Artery Disease by Angiography](http://circ.ahajournals.org/)

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Positive fluoroscopy</th>
<th>Negative fluoroscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of patients</td>
<td>% with normal</td>
</tr>
<tr>
<td>RCA</td>
<td>29</td>
<td>14</td>
</tr>
<tr>
<td>Left system</td>
<td>100</td>
<td>14</td>
</tr>
<tr>
<td>LMCA</td>
<td>18</td>
<td>67</td>
</tr>
<tr>
<td>LCCA</td>
<td>37</td>
<td>24</td>
</tr>
<tr>
<td>LAD</td>
<td>80</td>
<td>16</td>
</tr>
</tbody>
</table>

The results concerning the right coronary artery (RCA) in three patients and the left main coronary artery (LMCA) in two patients were indeterminate and are not recorded.

Abbreviations: LCCA = left circumflex coronary artery; LAD = left anterior descending coronary artery.
of these patients had coronary lesions ≥50%, i.e., there were 25 false positive tests. Fluoroscopic examination was positive in nine of the 14 patients (64%) with coronary lesions ≥50% and negative in 23 of the 25 patients with a false positive exercise test. Thus, when exercise testing is being used as a primary screening test for CAD in an asymptomatic population, follow-up cardiac fluoroscopy performed on patients with a positive ST response helps to identify both true and false positives.

Although fluoroscopy is a relatively poor predictor of coronary stenosis ≥50% in asymptomatic subjects, it appears to be a particularly good predictor of coronary artery abnormalities when the range of severity includes any irregularity in a vessel wall. Thus, of the 65 asymptomatic subjects who had coronary calcifications observed at fluoroscopy, 86% had some degree of coronary narrowing on angiographic study. Although the clinical value of such information is unclear, it is likely that the presence of even clinically insignificant lesions identifies a group of patients at higher risk of developing future coronary events.32-35

The combination of exercise-induced ST-segment abnormalities and detection of coronary calcifications permits some separation between patients with three-vessel coronary artery narrowing ≥50% and those with less severe disease. Among the entire study group of 181 patients, 25 had both a positive fluoroscopy and a positive electrocardiographic exercise test. Forty-eight percent of these (12 of 25) had three-vessel disease by angiography. In contrast, only 12% (19 of 156) of patients with only one or neither test positive had three-vessel disease by angiography. The results of the analysis of combined abnormalities were similar when the asymptomatic and symptomatic patients were evaluated separately.

When calcium is seen by fluoroscopy, there is a close correlation between the location of calcium and the location of coronary disease in all vessels except the left main coronary artery (table 3). The poor correlation noted with the left main coronary artery probably results from the short length of this vessel, the difficulty in identifying its location fluoroscopically, and its proximity to the aortic valve which itself may be calcified. However, despite its usefulness in the localization of disease, the amount of calcium detected by fluoroscopy was not proportional to the anatomical severity of disease.

It may be argued that our patients are a specially selected subgroup, and therefore the relevance of data derived from these patients to data from other patients with CAD is questionable. Such an argument, however, neglects the fact that the patient population of any study from any institution must be selected. Therefore few, if any, clinical studies are immune from the criticism that the results derived cannot with certainty be applied to the “general patient population.”

Several points also should be made regarding the distinct characteristics of our patient population, and whether these patients can be considered more or less relevant than patients in other studies. The ratio of men to women and the amount of coronary disease in our study population were comparable to those in many studies. Our population appears to be unusual in that all of our patients had hyperlipidemia, were less than 55 years of age, did not have hypertension or diabetes, and most had fewer clinical symptoms than the patients included in studies from large referral centers. However, many patients reported from other centers have elevated serum cholesterol, and it would be difficult to argue that the results of a well-defined, younger (mean age 46 years) series of patients with elevated serum cholesterol levels and no hypertension or diabetes are not clinically relevant.

Moreover, as noted above, although our patient
population is a selected one, so is the population, by necessity, of any clinical study. Unfortunately, the selection factors influencing most of our current data based on patients with coronary disease derive from the populations of large cardiac centers to which patients who are more severely symptomatic and more difficult to manage are usually referred. We studied asymptomatic and mildly to moderately symptomatic patients, a fact which suggests that our population may be more representative of the patients seen in clinical practice than populations of other studies. Moreover, our patients were selected primarily because they had a cholesterol problem (not a coronary problem) and are, therefore, more likely to represent the full spectrum of coronary disease than patients reported in studies where a requirement for referral is usually a problem that the primary care physician feels should be handled by a large referral center. Most of our patients came from community screening or surveillance programs, and the criterion of admission was an elevated cholesterol level. Therefore, our patients were not more highly selected than patients studied at other referral centers.

For all of the above reasons, our patient population is just as appropriate for testing the reliability of noninvasive diagnostic techniques as the highly selected populations used traditionally. The information derived from our patients would be as "relevant" as and subject to less bias than that obtained from the usual, less well-defined referral populations.

In summary, these results demonstrate that detection of coronary artery calcifications by fluoroscopy in hyperlipidemic type II subjects 55 years of age or less, is highly correlated with the presence of some degree of CAD. Although neither detection of calcium nor the demonstration of ST-segment depression $\geq 1$ mm alone reliably predicts coronary artery narrowing $\geq 50\%$ in asymptomatic patients, the combination of coronary calcifications and an abnormal electrocardiographic response to exercise has a higher predictive accuracy and helps in identifying the presence of significant three-vessel coronary disease. The limitation of this approach, however, is that predictive accuracy is enhanced at the expense of diagnostic sensitivity.

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Prognosis After Acute Myocardial Infarction: A Multivariate Analysis of Mortality and Survival

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SUMMARY We examined early mortality (within 30 days) and survival (beyond 30 days) after acute myocardial infarction in 221 patients by screening 158 variables measured soon after the patient’s admission to the hospital. Nineteen of these measurements had predictive value, but each variable alone was relatively insensitive. Therefore, we subjected groups of variables to stepwise discriminant function analysis and classification rates were estimated by calculating 95% confidence intervals using a jackknife procedure. When factors from the history, physical examination, and noninvasive assessment were combined, we identified 70% of deaths (confidence interval 48–80%) and 94% (90–98%) of survivors; when 11 selected variables including hemodynamic data were combined, we identified 86% (66–98%) of deaths and 96% (92–100%) of survivors (93% overall accuracy). We further tested the validity of this method in a subsequent series of 150 patients. Using the original discriminant functions, classification rates based on noninvasive and hemodynamic data fell within predicted limits, although the number of patients studied hemodynamically was unrepresentative and too small to allow overall predictive accuracy. Therefore, we randomly divided the entire population (371 patients) into a base sample from which we constructed new discriminant functions, with which we classified the remaining patients. The classification rates for the validation sample fell within the predicted confidence intervals. Thus, our method provides a reliable approach for predicting the risk of early death or the likelihood of survival in patients soon after acute myocardial infarction.

IF STUDIES EARLY after hospital admission were reliably predictive of survival and mortality in patients with acute myocardial infarction, individual therapy and design of therapeutic trials might be improved. In previous studies, the usual approach has been to place subjects into prognostic categories, rather than to predict survival or nonsurvival in the individual patient. Single prognostic factors have been used, and prognostic indices have been constructed from multiple indicators, including data from the bedside examination, historical, clinical and laboratory information, and precisely measured or defined data; but large classification errors have been reported using predominantly clinical information. Multivariate statistical approaches have also been used to group patients with similar prognoses or obtain overall classification rates, rather than to identify patients predicted to die; these have used historical and clinical or hemodynamic data or both. The present investigation, directed toward predicting death or survival in the individual patient, is a retrospective study of patients with acute myocardial infarction who were carefully characterized by clinical and objective noninvasive measurements and in many instances by hemodynamic data as well. Risk factors were identified and used multivariately to predict early and late mortality by means of stepwise linear discriminant analysis. The approach could identify soon after hospital admission patients who would die within 1 month and those who would survive. We validated the methodology by determining confidence limits for the classification rates in the original population, applying the initial functions to a subsequent population, and testing the reliability of the general approach in the combined population using two randomized samples.

Methods

The initial population of 224 patients with acute myocardial infarction (77% males and 23% females, mean age 59.6 years) was studied between July 1969.

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