Predictive Accuracy of Coronary Artery Calcification and Abnormal Exercise Test for Coronary Artery Disease in Asymptomatic Men

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SUMMARY To determine the predictive accuracy of fluoroscopically detected coronary artery calcification (CAC) and a positive submaximal exercise test, 129 asymptomatic men were screened; 13 had both coronary artery calcification and positive exercise test (≥ 1.0 mm ST-segment depression). These 13 men were studied at coronary arteriography. They had a mean age of 44 years (range 41–56 years); none had history or symptoms of heart disease and all had normal resting ECGs at entry.

CAC was detected in one artery in 10 men, in two arteries in two men, and in three arteries in one man. Coronary artery disease (CAD) was considered clinically significant if any major coronary branch was narrowed > 50%. Coronary arteriography revealed 12 men with clinically significant CAD (one-vessel CAD in four, two-vessel CAD in five and three-vessel CAD in three men) and one man with minor one-vessel CAD. The predictive accuracy was 100% for minor CAD and 92% for clinically significant CAD. The location of CAC and CAD correlated, but the absence of CAC did not rule out the presence of CAD at coronary arteriography. Furthermore, CAC did not indicate the location of the highest stenotic (most occlusive) lesions seen at arteriography. Follow-up for the 13 patients was 36 months; three patients developed typical angina and one patient developed a transmural myocardial infarction.

This study suggests that the predictive accuracy of CAC and a positive exercise test in the middle-aged nonhyperlipidemic asymptomatic male is very high (100% for CAD and 92% for clinically significant CAD) and that CAC and a positive exercise test predict an early appearance of angina or myocardial infarction in previously asymptomatic men.

THE EMPHASIS on early diagnosis and prevention of ischemic heart disease has stimulated a search for reliable noninvasive methods of detection.1–4 Risk factor screening and resting ECGs are useful in epidemiologic and mass screening programs but are not diagnostically helpful in the asymptomatic subject.

Although exercise electrocardiography4–6 is widely used as a noninvasive procedure to diagnose coronary artery disease, the large proportion of false-negative and false-negative results precludes its use as a standard screening device in the asymptomatic person.7–9 Clinical or laboratory markers that might identify those with asymptomatic coronary artery disease would be useful. Previous reports have established the positive relationship between the presence of coronary calcification on fluoroscopy and angiographically demonstrated coronary artery disease in symptomatic patients.10–12

In this study we used exercise electrocardiography and cardiac fluoroscopy to screen asymptomatic subjects as part of a prospective clinical research protocol. This report presents the value of combining the electrocardiographic response to exercise and fluoroscopically detected coronary artery calcification in asymptomatic subjects and the clinical course of asymptomatic subjects that have both an abnormal electrocardiographic response to exercise and coronary artery calcification on fluoroscopy.

Materials and Methods

The study group of 129 middle-aged males volunteered for two-part examinations consisting of (1) cardiac fluoroscopy and a submaximal exercise stress test; and (2) cardiac catheterization in subjects who had coronary artery calcification on fluoroscopy and an abnormal electrocardiographic response to sub-
maximal exercise. In addition, complete clinical follow-up information was gathered in the cohort population.

This prospective research protocol was reviewed and approved by the Yale University School of Medicine Human Investigation Committee. All volunteers gave informed consent before they were included in this study. No subject who participated in the study had a known history of congenital or acquired heart disease and all considered themselves in good health, without chronic illness or recent hospitalization. A questionnaire supplemented by direct questioning excluded any history of angina pectoris, myocardial infarction or congestive heart failure. The diagnosis of recent or remote myocardial infarction by ECG was excluded by the criteria established by the New York Heart Association. Any abnormal cardiac rhythm, a resting diastolic blood pressure greater than 100 mm Hg or an S3 gallop at rest were also bases for exclusion from the protocol. Additional data obtained including screening for history of hypertension (diastolic systemic pressure greater than 100 mm Hg); diabetes mellitus; lipid abnormalities (Frederickson classification); obesity (body weight 10% over ideal weight for sex and age); a family history of ischemic heart disease (angina pectoris, myocardial infarction, congestive heart failure and sudden death); and cigarette use (average daily consumption). Diabetes mellitus, lipid abnormalities, obesity, or smoking were not bases for exclusion from the protocol.

Cardiac Fluoroscopy

Cardiac fluoroscopy was performed by an experienced cardiovascular radiologist. It consisted in sequential visualization of the heart in four views (left lateral, 60° left anterior oblique, posteroanterior and 45° right anterior oblique), using a standard 10-inch cesium iodine image intensifier with a 0.6-mm small focal spot, a 1-mm focal spot and an adjustable shutter. The x-ray unit was equipped with a videotape recorder. All studies were reviewed for confirmation of initial impressions.

Criteria for identification of coronary calcium classification and classification according to its location has been published by this laboratory. In summary, coronary calcification was considered present if calcium deposits appeared during suspended respiration as small, rapidly moving densities distributed throughout the proximal portion of the coronary arteries overlaying the cardiac image. Calcification was classified by location in the left anterior descending, left circumflex or right coronary artery. We did not attempt to specify lesions located in the peripheral coronary tree or to distinguish proximal left anterior descending from left main coronary artery calcification.

Exercise Stress Testing

A resting ECG and a physical examination were performed before the stress test. Subjects were instructed to fast for 2 hours before the examination. Exercise testing was completed on a bicycle ergometer according to a method previously described. We attempted to exercise each subject to 90% of his age-predicted maximal heart rate. Premature termination of the exercise test most often resulted from fatigue, dyspnea or leg pain. No subject had severe anginal pain or electrocardiographic ST-segment depression greater than 3 mm from baseline. One person was asked to stop when premature ventricular complexes appeared in pairs. All ECGs were reviewed by one of the investigators, who had no knowledge of the cardiac fluoroscopic findings. An abnormal exercise electrocardiographic response was defined as equal to or greater than 1 mm of horizontal or downsloping ST-segment depression in any of the four continuously recorded leads. These leads included three orthogonal and a bipolar V₆ (CC₉). We required that these abnormalities be present during or immediately after exercise and persist for at least 2 minutes in the recovery period. One hundred eight of the original 129 subjects completed the submaximal exercise protocol by achieving at least 90% of their age-predicted maximal heart rate; these subjects make up the cohort population for this study.

Cardiac Catheterization

Cardiac catheterization was performed on all 13 subjects who demonstrated both coronary artery calcification on fluoroscopy and a positive exercise stress test. This study included routine hemodynamic measurements; a single-plane, 30° right anterior oblique, left ventriculogram; and selective coronary arteriography. This procedure was performed only in subjects who had both coronary artery calcification on fluoroscopy and an abnormal exercise ECG. All of these subjects had a cardiac catheterization an average of 8 months (range 5–12 months) after entering into the study.

Coronary artery disease was considered present when any major coronary artery (left anterior descending, circumflex or right coronary artery) or their respective large branches had at least a 30% discrete or diffuse reduction in caliber. Arterial stenoses were estimated by percent of narrowing of the vessel. Significant coronary artery disease was considered present if at least one major coronary artery or one of its major branches had a 50% or greater obstruction; insignificant coronary artery disease was present if the narrowing was 30–50%.

All angiographic data were read independently by the attending cardiologist and by one of the authors. When differences in interpretation occurred, the angiograms were reevaluated and a consensus was reached.

Follow-up

Since the initiation of this protocol in September 1976, all subjects were interviewed every 12 months. A detailed questionnaire was answered, with specific questions regarding the appearance of angina pectoris, myocardial infarction and congestive heart failure.
Subjects with coronary calcification on fluoroscopy and an abnormal exercise ECG were interviewed at 6-month intervals. In addition, follow-up physical examinations, resting ECGs and exercise stress tests were performed at yearly intervals.

Angina pectoris was defined as: (1) definite — a substernal, shoulder, jaw or arm discomfort precipitated by exertion, relieved by rest and/or nitroglycerin in less than 10 minutes, and with a typical radiation; (2) probable — having most of the features of classic angina but in some aspects not entirely typical; and (3) probably not angina — a constellation of symptoms that did not fit the description of definite angina.

Myocardial infarction was diagnosed if there was a history of myocardial infarction in which the hospital records, including information on cardiac enzymes and copies of the ECG were available. Probable myocardial infarction was diagnosed if the history was positive for electrocardiographic and enzyme changes (records not available), the patient had been hospitalized for longer than 2 weeks, but the current ECG did not show definite myocardial infarction, or there was no clear history of myocardial infarction but the current ECG showed previous myocardial infarction.

Congestive heart failure was diagnosed if there were clinical symptoms and/or radiographic signs of pulmonary congestion or evidence of elevated systemic venous pressure, congestive hepatomegaly, ascites or peripheral edema. An associated ventricular gallop, although often present, was not required.

Population

The mean age of the 108 men was 46 years (range 40–64 years). Of these 108 subjects, 85 (79%) had a history of smoking and 35 (32%) had a positive family history for ischemic heart disease. Eighteen subjects (16%) had hypertension; 45 (41%) were obese; two (1.8%) had diabetes mellitus; and eight (7%) had hyperlipidemia. The resting ECG was normal in 92 (85%) of the subjects and it revealed minimal, nonspecific ST-T-wave changes in 16 (15%) subjects. Only four of the 108 men (4%) had a previous exercise stress test as part of a routine annual physical examination and none had any abnormalities.

Analysis of Data and Statistical Methods

Predictive accuracy was obtained using the formula

\[
\text{True positive tests} \div \text{True positive + false positive tests}
\]

and was expressed as percent.

Chi-square analysis was used to examine all data. Uncorrected chi-square values were used in all instances, except for the 2 × 2 matrices where Fisher's exact values were used.13 A p value of less than 0.05 was considered statistically significant.

Results

Cardiac Fluoroscopy

Calcification of at least one coronary artery was detected by fluoroscopy in 37 (34%) of the 108 subjects. Left coronary artery calcification accounted for 34 of the 40 observed calcified vessels. The left anterior descending artery calcification was significantly more common than left circumflex (47.5% vs 37.5%) or the right coronary artery (15%). Solitary calcification of the right coronary artery was uncommon. Only three of the six subjects with right coronary artery calcification had a fluoroscopically normal left coronary system. Two- and three-vessel calcification was rare.

Exercise Stress Testing

Sixteen of the 108 subjects (15%) had an abnormal exercise ECG. Thirteen of the 16 (81%) had at least one calcified coronary artery on fluoroscopy. In contrast, 13 (35%) of the 37 subjects with coronary artery calcification of at least one coronary artery had a positive exercise test. Table 1 lists the results of cardiac fluoroscopy vs exercise stress testing.

Excluded Subjects

The 21 subjects who failed to attain heart rates within 10 beats of their target goal of the exercise test were considered to have insufficient stress on their cardiovascular systems to completely rule out exercise-induced ischemia. Although excluded from the analysis and report, they did not differ significantly from the remainder of the population in demographic, clinical or fluoroscopic findings.

Cardiac Fluoroscopy and Exercise Stress Testing

Thirteen of the original 108 subjects had at least one calcified coronary artery on fluoroscopy and an abnormal exercise ECG. These 13 men had a mean age of 44 years (range 41–56 years); eight (61%) had a history of smoking and seven (54%) had a positive history of ischemic heart disease in their family. None had hypertension and three (23%) had hyperlipidemia.

Coronary artery calcification was detected in one artery in 10 subjects; in two arteries in two subjects; and in all three arteries in only one subject. The distribution of calcification in the coronary tree followed the general trend seen in the overall group of 108 subjects. The left anterior descending artery was involved in 10 instances (eight as one-artery calcification and two as part of two- and three-vessel calcifications); the left circumflex artery was affected in five instances (two as single artery calcification and three as part of two- and three-vessel calcifications); and the right cor-

Table 1. Exercise Stress Test Results vs Coronary Artery Calcification on Fluoroscopy

<table>
<thead>
<tr>
<th>Exercise stress test (ECG)</th>
<th>Normal response (ECG) n</th>
<th>Abnormal response (ECG) n</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No coronary calcification</td>
<td>68</td>
<td>96</td>
<td>3</td>
</tr>
<tr>
<td>Coronary calcification</td>
<td>24</td>
<td>65</td>
<td>13</td>
</tr>
<tr>
<td>Total</td>
<td>92</td>
<td>85</td>
<td>16</td>
</tr>
</tbody>
</table>
Coronary arteriography revealed 12 men with significant coronary artery disease (≥ 50% stenoses): one-vessel coronary artery disease in four subjects, two-vessel disease in five subjects and three-vessel disease in three subjects. In addition, one subject had insignificant coronary artery disease (< 50% stenoses) that affected a single coronary artery (table 2). Although correlation was found between the location of coronary artery calcification detected at fluoroscopy and the location of angiographically detected coronary artery stenoses, coronary artery calcification did not necessarily indicate the presence of coronary artery stenosis (case 12; table 2). Also, the absence of coronary artery calcification did not rule out the presence of coronary artery disease at coronary arteriography.

The predictive accuracy of a calcified coronary artery at fluoroscopy and an abnormal submaximal exercise test for clinically significant angiographically proved coronary artery disease was 92% [(12/12 + 1) × 100]. Furthermore, including the additional subject with nonsignificant coronary artery disease, the predictive accuracy of combining both noninvasive tests to detect angiographically proved coronary artery disease was 100% (table 3). Note that these results were obtained in the subgroup of subjects who underwent cardiac catheterization. No information was obtained regarding sensitivity or specificity of an abnormal exercise test or positive coronary calcification on fluoroscopy in these asymptomatic men because subjects having only one abnormal test were not catheterized.

Follow-up

Angina Pectoris

Of the 108 subjects, five developed definite angina pectoris during the 36-month follow-up period, giving

<table>
<thead>
<tr>
<th>TABLE 3. Predictive Accuracy of Coronary Artery Calcification at Fluoroscopy and Abnormal Exercise Stress Test</th>
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<tbody>
<tr>
<td><strong>No. pts</strong></td>
</tr>
<tr>
<td>____________</td>
</tr>
<tr>
<td>Coronary calcification +</td>
</tr>
<tr>
<td>Abnormal exercise test</td>
</tr>
<tr>
<td>Predictive accuracy</td>
</tr>
</tbody>
</table>
a calculated occurrence of angina pectoris of 5% over this period. Of the five subjects with definite angina pectoris, three had at least one calcified coronary artery on fluoroscopy and an abnormal exercise ECG, one subject had coronary calcification and a normal exercise stress and one had neither coronary artery calcification nor an abnormal exercise stress test. Conversely, of the 13 subjects with coronary artery calcification and an abnormal exercise stress test, three (23%) developed definite angina pectoris. Of the 24 subjects with coronary artery calcification and a normal exercise stress test, one subject (4%) developed definite angina pectoris; and of the 68 subjects with no coronary artery calcification and a normal exercise stress test, one subject (1.5%) developed definite angina pectoris.

Three of the 108 subjects developed probable angina pectoris over the follow-up period: two of the 13 subjects (15%) with coronary artery calcification and an abnormal exercise stress test and one of the 68 subjects (1.5%) with no coronary artery calcification and a normal exercise stress test. Five of the 108 subjects developed chest pain that was considered to be probably not angina. All five subjects were not identified as having coronary artery calcification and an abnormal exercise stress test (table 4).

**Myocardial Infarction**

Two of the 108 subjects sustained a myocardial infarction during the follow-up period, giving an incidence of 1.8% over a 36-month period — one of the 13 subjects (8%) with coronary artery calcification and an abnormal exercise test and another one of the 68 subjects (1.5%) with no coronary artery calcification and normal exercise stress test. One of the 108 subjects had a probable myocardial infarction, and this man was in the group with no coronary calcification and a normal exercise stress test.

**Correlation Between Exercise Stress Test and Clinical Follow-up**

Table 5 displays the correlation between exercise stress testing and clinical follow-up (angina pectoris and/or myocardial infarction) during the 36-month follow-up period:

<table>
<thead>
<tr>
<th></th>
<th>Angina Pectoris</th>
<th>Myocardial infarction</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>+Ca Ab ET n %</td>
<td>-Ca Ab ET n %</td>
</tr>
<tr>
<td>Definite angina</td>
<td>3 23 1 4 1 1.5 0 0 5</td>
<td></td>
</tr>
<tr>
<td>Probable angina</td>
<td>2 15 0 1 1.5 0 3</td>
<td></td>
</tr>
<tr>
<td>Probably not angina</td>
<td>0 0 2 8 2 3 1 33 5</td>
<td></td>
</tr>
<tr>
<td>Not angina</td>
<td>8 62 21 87 64 94 2 67 95</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>13 100 24 100 68 100 3 100 108</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: Ab ET = abnormal exercise test; +Ca = coronary calcification; -Ca = no coronary calcification; NET = normal exercise test.

**Table 4. Follow-up Information: Angina Pectoris**

**Table 5. Correlation Between Exercise Stress Test and Clinical Follow-up (36 Months) in Asymptomatic Men With Coronary Artery Calcification and Abnormal Exercise Test**

**Abbreviations:** D = definite; No Ang = no angina; No MI = no myocardial infarction; P = probable; PNA = probably not angina; + = positive finding; − = negative finding.
period in the 13 asymptomatic men who had coronary artery calcification on cardiac fluoroscopy and an abnormal exercise ECG. Exercise-induced chest pain and the magnitude of exercise-induced ST-segment depression were not predictive of angina pectoris or the development of myocardial infarction in this group.

Discussion
Coronary Artery Calcification as a Predictor of Coronary Artery Disease

Despite considerable evidence from clinical and postmortem results that suggest the diagnostic value of detecting coronary artery calcification on fluoroscopy, only a few studies have correlated cardiac fluoroscopy with coronary arteriographic findings. Data derived from symptomatic patients undergoing cardiac catheterization indicated that approximately 90% of patients with coronary calcifications on fluoroscopy have significant coronary artery disease. In a subgroup of 93 asymptomatic patients from 181 type II hyperlipoproteinemic patients, Aldrich et al. found that the predictive accuracy of coronary artery calcifications to detect significant coronary artery disease was 46%. However, the predictive accuracy of a particular diagnostic test is largely determined by the prevalence of disease in the tested population.

Abnormal Exercise Test as a Predictor of Coronary Artery Disease

Since Master completed his pioneering studies on the use of exercise to induce electrocardiographic evidence of myocardial ischemia in the early 1940s, stress testing has been used widely as a simple, noninvasive method for diagnosis of coronary artery disease. Angiographic studies have confirmed its diagnostic accuracy in predicting coronary artery disease in symptomatic populations.

However, investigators have challenged the diagnostic accuracy of the exercise ECG in predicting coronary artery disease among asymptomatic subjects. Angiographic studies in asymptomatic populations with abnormal exercise stress tests have shown a very high false-positive rate. Indeed, in the study of Froelicher et al., the rate of false-positive exercise test was 56%, and in the study of Borer et al. it was 63%.

Coronary Artery Calcification and Abnormal Exercise Test as Predictors of Coronary Artery Disease

Theoretically, cardiac fluoroscopy and exercise stress tests are complementary techniques for evaluating coronary artery disease, because the finding of coronary artery calcification provides anatomic evidence of coronary sclerosis, whereas abnormal electrocardiographic response to exercise (exercise-induced ST-segment depression) suggests hemodynamic impairment to coronary flow.

Arteriographic data for combinations of cardiac fluoroscopy and exercise testing were reported by Aldrich et al. in type II hyperlipoproteinemic patients. They reported that the predictive accuracy to detect coronary artery disease when both tests were abnormal was 75% or higher, regardless of symptomatic status. When their asymptomatic group was considered alone, the predictive accuracy was still very high (82%).

The present study reports similar findings, but the cohort population was asymptomatic and had no coronary risk factors. In 13 asymptomatic males with both coronary artery calcifications on fluoroscopy and abnormal submaximal exercise stress test, the predictive accuracy was 92% if coronary arterial lesions that caused greater than 50% stenosis were considered as evidence of coronary artery disease. However, if the angiographic criteria for coronary artery disease was modified to include any irregularity in the course of the major coronary arteries on angiography, the predictive accuracy was 100%. These findings are not surprising if a quantitative estimate of the diagnostic potential of this approach is made. The combined use of cardiac fluoroscopy and exercise testing may substantially enhance diagnostic reliability when test results are concordant.

Aldrich et al. selected 181 patients from a National Heart, Lung, and Blood Institutes Type II Coronary Intervention Program. All those patients had type II hyperlipoproteinemia. Sixty-one patients (33%) had clinical evidence of ischemic heart disease (typical angina pectoris, myocardial infarction or both) and 27 (15%) had clinical manifestations suggestive of ischemic heart disease (atypical chest pain). The major criticism of that study is that they studied and reported on a highly selected population that may not resemble the general population. The authors defended their study by pointing out that although their patient population was selected, no clinical study is totally unsellected. They indicated that because their patients were young (below 55 years of age), did not have hypertension or diabetes and most were not highly symptomatic, that their population was appropriate for testing reliability of noninvasive techniques.

The present study has overcome the major deficits of the study of Aldrich et al. Subjects were recruited from a general population of healthy young males from a large service corporation based in Connecticut. They were asymptomatic and did not have hyperlipoproteinemia, hypertension or diabetes. Moreover, appropriate clinical follow-up was obtained over a 3-year period. Therefore, the results could be applied to a general asymptomatic population of males. Despite the disparity between these two studies, the clinical interpretation is significantly similar. Cardiac fluoroscopy and exercise stress testing deserve a stronger investigative effort and a wider clinical application.

Although the location of coronary calcification on fluoroscopy and the location of angiographically detected coronary stenoses were correlated, the presence of fluoroscopically detected coronary calcification did not necessarily indicate the presence
of a major coronary stenosis. Conversely, the absence of coronary calcification did not indicate a normal coronary artery.

Clinical Follow-up

Investigators have noted that up to 46% of asymptomatic persons with documented abnormal exercise stress tests develop coronary events over a 5-year follow-up period. The risk ratio among asymptomatic abnormal stress test responders for developing clinical manifestation of coronary artery disease have ranged from eight to 14 times that of normal responders.24-27 However, while epidemiologic studies24-27 showed a high risk ratio for a population with an abnormal exercise stress test, the actual number of asymptomatic persons who go on to manifest a coronary event is extremely low. Thus, a low predictive value limits the usefulness of exercise testing for asymptomatic subjects.

Hudson and Walker,28 who reported epidemiologic data relating to coronary artery calcifications and survival, failed to demonstrate a significant difference in survival between patients with coronary calcification and those without; but this study did have major deficits (population age — 85% were older than 60 years; failure to identify cause of death; and relating mortality to coronary results).

To our knowledge, no comparable studies in an asymptomatic population have been made. Define and probable angina pectoris occurred in five of the 13 subjects with coronary calcification and abnormal exercise tests over the 36 months follow-up period. Furthermore, one of these 13 had a myocardial infarction during follow-up. Therefore, the calculated incidence of future coronary events over 36 months in this population with coronary calcifications and abnormal exercise test is 45%, which is higher than expected from previous epidemiologic studies.24-27 Thus, the results from this small population sample suggest that the addition of cardiac fluoroscopy to submaximal exercise stress test could improve the low predictive value of exercise testing alone in larger epidemiologic and clinical studies.

A criticism to our follow-up data is obvious. Angina pectoris is a very subjective endpoint. Furthermore, our methodologic study design required a more frequent follow-up interview for subjects who had both tests positive than for the rest. Thus, the search for angina may have been subconsciously more diligent in this group, and a bias could have been introduced in this study.

Clinical Implications

Coronary artery calcification on fluoroscopy and coronary artery stenoses on angiography are not synonymous; postmortem and clinical studies in symptomatic and asymptomatic populations have demonstrated the clinical relevance of coronary artery calcification. The present study indicates (1) that the predictive accuracy of coronary artery calcifications and an abnormal exercise stress test in the middle-aged, nonhyperlipidemic asymptomatic male is very high (100% for some degree of coronary narrowing and 92% for clinically significant coronary stenoses); and (2) that coronary artery calcification and an abnormal exercise stress test predict an early appearance of clinical manifestations of coronary artery disease in previously asymptomatic men. However, the exercise electrocardiographic criteria we used were very stringent, and they should be carefully noted in applying these observations to other tested populations.

References

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