Detecting Occult Coronary Disease in a High-Risk Asymptomatic Population

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Background—Exercise stress testing alone or with perfusion imaging is the standard screening method to determine the presence of obstructive coronary artery disease (CAD) in people with chest pain. In asymptomatic individuals with a family history of premature CAD, it is unclear whether abnormalities on these functional exercise tests represent significant coronary disease.

Methods and Results—An abnormal exercise test, thallium scan, or both occurred in 153 (21%) of 734 asymptomatic siblings of persons with documented CAD, of whom 105 underwent coronary angiography with quantitative analysis of stenosis severity. Overall, 95% had coronary atherosclerosis, but only 39% had 1 or more stenoses with ≥50% narrowing. Of 30 siblings in whom the exercise test and perfusion scan were both abnormal, 70% had ≥50% stenoses. The mean stenosis in arteries that fed perfusion defects was only 43±31%, and 68% of such stenoses were <50%. However, in 71% of all defects, the location matched arteries with the most severe stenoses.

Conclusions—In asymptomatic persons with a family history of CAD, abnormal exercise scintigraphy identifies predominantly mild coronary atherosclerosis. Perfusion defects may be caused by coronary vasomotor dysfunction in addition to atherosclerotic plaque. (Circulation. 2003;107:702-707.)

Key Words: coronary disease ■ exercise tests ■ scintigraphy

Exercise electrocardiography and perfusion imaging remain the mainstays of chest pain evaluation and are used to determine whether obstructive coronary artery disease (CAD) is present.1 An exercise perfusion defect or an ischemic ECG change usually signifies hemodynamically significant CAD in symptomatic persons.2 In asymptomatic individuals, however, the degree to which noninvasive test abnormalities represent obstructive CAD remains unknown, although in the general population, it is thought to be poor.3

In high-risk asymptomatic individuals, noninvasive tests may be more accurate.3 Noninvasive testing may add information to risk factor screening in high-risk populations with a high a priori probability of disease. This could result in more aggressive guidelines for preventive therapies.4 Noninvasive testing may also define factors associated with the progression of occult CAD to clinical events and help refine concepts of preclinical disease. Whereas some studies of exercise testing and perfusion imaging report a high false-positive rate,5 others have suggested that test abnormalities correctly identify individuals at high risk of subsequent CAD, even in the absence of flow-limiting stenoses.6

We have found that stress thallium scintigraphy predicts CAD events in apparently healthy 30- to 59-year-old siblings from index cases with premature CAD.7 To better define the accuracy of noninvasive tests, we determined the extent to which noninvasive testing identifies coronary lesions in asymptomatic adults.

Methods

Study Population and Recruitment

The Johns Hopkins Sibling Study is a prospective study of CAD and risk factors in apparently healthy brothers and sisters of individuals hospitalized with documented CAD before 60 years of age.7 The study was approved by the Johns Hopkins Institutional Review Board, and all index cases and participating siblings gave informed consent.

Siblings were eligible if they were <60 years old, had no known CAD, and had no limitations that precluded testing. Siblings were asked to participate in a screening that included a cardiovascular history and physical examination, risk factor assessment, and a graded treadmill test with thallium scintigraphy.8 If the stress test, scintigram, or both demonstrated ischemia, subjects were approached for coronary angiography.

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TABLE 1. Sample Characteristics by ETT and Scintigraphy Group (Scan) and by Presence or Absence of Coronary Stenoses of ≥50%

<table>
<thead>
<tr>
<th>Variable</th>
<th>ETT+/Scan− (n=19)</th>
<th>ETT−/Scan+ (n=56)</th>
<th>ETT+/Scan+ (n=30)</th>
<th>P</th>
<th>No Stenoses ≥50% (n=64)</th>
<th>Stenoses ≥50% (n=41)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>49±8</td>
<td>49±7</td>
<td>50±6</td>
<td>0.776</td>
<td>49±8</td>
<td>50±5</td>
<td>0.254</td>
</tr>
<tr>
<td>Education, y</td>
<td>12±2</td>
<td>13±3</td>
<td>13±4</td>
<td>0.617</td>
<td>13±3</td>
<td>12±3</td>
<td>0.363</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>4.22±1.0</td>
<td>4.43±1.2</td>
<td>4.87±1.9</td>
<td>0.248</td>
<td>4.25±1.1</td>
<td>4.79±1.7</td>
<td>0.077</td>
</tr>
<tr>
<td>mg/dL</td>
<td>163±39</td>
<td>171±48</td>
<td>188±72</td>
<td></td>
<td>164±43</td>
<td>185±67</td>
<td></td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>1.32±0.36</td>
<td>1.17±0.31</td>
<td>1.09±0.28</td>
<td>0.067</td>
<td>1.19±0.34</td>
<td>1.13±0.28</td>
<td>0.313</td>
</tr>
<tr>
<td>mmol/L</td>
<td>51±14</td>
<td>45±12</td>
<td>42±11</td>
<td></td>
<td>46±13</td>
<td>44±11</td>
<td></td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>136±17</td>
<td>140±14</td>
<td>138±16</td>
<td>0.579</td>
<td>137±16</td>
<td>141±13</td>
<td>0.125</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>85±10</td>
<td>89±8</td>
<td>86±8</td>
<td>0.083</td>
<td>87±9</td>
<td>89±9</td>
<td>0.128</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27±3</td>
<td>30±6</td>
<td>30±5</td>
<td>0.208</td>
<td>29±5</td>
<td>30±6</td>
<td>0.465</td>
</tr>
<tr>
<td>Framingham score, %</td>
<td>10±6</td>
<td>15±8</td>
<td>16±10</td>
<td>0.038</td>
<td>13±7</td>
<td>17±9</td>
<td>0.016</td>
</tr>
<tr>
<td>Male, %</td>
<td>53</td>
<td>89</td>
<td>77</td>
<td>0.003</td>
<td>80</td>
<td>78</td>
<td>0.850</td>
</tr>
<tr>
<td>Black, %</td>
<td>21</td>
<td>25</td>
<td>20</td>
<td>0.852</td>
<td>28</td>
<td>15</td>
<td>0.108</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>0</td>
<td>11</td>
<td>20</td>
<td>0.097</td>
<td>8</td>
<td>17</td>
<td>0.146</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>42</td>
<td>64</td>
<td>53</td>
<td>0.212</td>
<td>55</td>
<td>61</td>
<td>0.525</td>
</tr>
<tr>
<td>Current smoking, %</td>
<td>16</td>
<td>36</td>
<td>27</td>
<td>0.238</td>
<td>27</td>
<td>34</td>
<td>0.406</td>
</tr>
</tbody>
</table>

BP indicates blood pressure. Values are mean±SD for continuous variables.

Physical Examination and Risk Factor Assessment
A cardiologist examined all siblings. Blood was obtained, after subjects had fasted for 12 hours overnight, for measurement of total cholesterol, HDL cholesterol, and triglycerides. Blood pressure readings were obtained at standard intervals during an 8-hour screening day. Risk factor data were used to compute a global 10-year CAD risk prediction score with the Framingham Risk Equation.8,9

Maximal Graded Exercise Testing
All siblings had a maximal symptom-limited graded treadmill test (ETT) with a modified Bruce protocol.7 Two of the siblings developed chest pain and 10 developed prominent ST changes that led to stoppage of the test.

Exercise Thallium Scintigraphy
One minute before the end of exercise, 3- to 4-mCi of ²⁰¹Tl was injected intravenously, and tomographic imaging was begun 5 minutes later.7 After 3 hours, delayed imaging was performed without reinjection. A positive tomogram was defined by a segmental perfusion defect on the immediate postexercise images in ≥2 contiguous slices and 2 image orientations, with definite improvement on delayed images.

Defects were scored as mild, moderate, or severe, and the location was designated as being anterior (including apical and septal), inferior, or lateral. Results were coded as negative (normal) or positive (abnormal) if reversible ischemia was present. Borderline reversible defects and mild to moderate fixed defects were recorded as negative. Three mutually exclusive groups were constituted for analysis: (1) persons with a positive ETT and negative scan, (2) persons with a negative ETT and positive scan, and (3) persons with concordant positive ETT and scan.

Coronary Angiography
Angiography was performed with standard 6F Judkins diagnostic catheters and injections of standard nonionic contrast media. Intracoronary nitroglycerin (400 μg) was injected before the series of contrast injections. Images in multiple views were recorded at a rate of 30 frames/s. Lesions in each of the 3 epicardial arteries and the left main artery were marked on the film, and computerized algorithms were used to quantify the diameter stenoses of the lesions (ImageComm, Inc.10,11

In siblings with an abnormal scintigram, the coronary artery that fed the area of the perfusion defect was identified on the basis of the anatomic distribution of the vessels. The anterior wall, septum, and apex were considered to be perfused by the left anterior descending coronary artery (LAD), the lateral wall by the left circumflex artery (LCx), and the inferior/posterior wall by the right coronary artery (RCA) or the LCx, depending on whether the circulation was right or left dominant. The maximal stenosis in the artery or its major branches corresponding to the perfusion defect was recorded.

Statistical Analysis
Variables were examined with means and SDs and tested statistically with Student’s t tests and ANOVAs for continuous variables. For categorical variables, comparisons were made with contingency table arrays and the χ² statistic. Crude and adjusted ORs and 95% CIs were calculated. Analyses were performed with SAS version 8.2 (SAS Institute Inc). Multivariate analyses were done with logistic regression techniques. All significance tests were 2-tailed at an α of 0.05.

Results

Sample Characteristics
Of the 734 consecutive siblings screened, 153 (21%) had an abnormal exercise test, scintigram, or both. Primary physicians agreed to angiography for 137 siblings (90%), and 113 siblings accepted (83%). Eight films were technically limited, which left 105 siblings for analysis (94 different families). Risk factor levels and demographics were not significantly different between siblings with and without angiography. The sample was primarily middle-aged, male, and white and was educationally heterogeneous (Table 1).
Detection of Myocardial Ischemia

Distribution of Abnormal Tests
Among the 105 subjects undergoing angiography, 86 (82%) had an abnormal scan, whereas 49 (47%) had an abnormal ETT (of these, only 2 had an abnormal ETT alone). Among male siblings, the greatest number had a normal ETT and an abnormal scan (Figure 1). Among women, the largest number had an abnormal ETT and normal scan. The ETT was abnormal in 33 (40%) of 83 men and 16 (73%) of 22 women (P<0.006). The average metabolic equivalent (MET) level was 12±3 in men and 10±3 in women (P=0.008).

Thallium Scintigram
An abnormal scintigram occurred in 13 females (59%), 73 males (88%), 66 whites (81%), and 20 blacks (83%). Among the 86 siblings with an abnormal scan, there were 94 perfusion defects; 78 siblings (91%) had a single defect (33 anterior, 44 inferior, and 1 lateral). Two separate vascular distributions were involved in 8 siblings (7 anterior/inferior and 1 anterior/lateral). All 94 defects were reversible; 59 were mild, 33 were moderate, and 2 were severe. In those with both an abnormal ETT and scan, defects were more often moderate or severe and were more often in 2 vascular distributions.

Risk Factors by Test-Positive Groups
There were no significant differences in traditional risk factors (Table 1). There was a trend for the concordant abnormal group to have higher levels of LDL cholesterol, lower HDL cholesterol, slightly higher body mass index, and more diabetes. The Framingham risk score was significantly higher in people with an abnormal scan or with both tests abnormal.

Coronary Angiography Findings

Degree of Stenosis
Overall, 100 (95%) of 105 siblings had coronary atherosclerosis, but only 41 siblings (39%) had ≥1 coronary artery with ≥50% stenosis. Figure 2A and 2B show the distribution of lesions ≥50% and ≥70%, respectively, according to the exercise test/scan groups. Five siblings with abnormal noninvasive tests did not have any detectable atherosclerosis (2 with abnormal ETT alone and 3 with an abnormal scan alone). Whereas the minority of subjects with a single abnormal test had stenoses ≥50%, the majority of those with concordantly abnormal tests did (P<0.001).

Table 2 shows the angiographic findings associated with the 3 exercise test/scan groups. MET level and maximal blood pressure did not differ among the groups. Lesions were similar where only 1 test was abnormal, but a greater stenosis was noted for those with concordant abnormal tests. Only 1 sibling had a left main stenosis ≥50%; 26% had an RCA stenosis ≥50%, 24% had an LAD stenosis ≥50%, and 15% had an LCx stenosis ≥50%.

Hemodynamically significant CAD (≥70%) occurred in 23% (11% with a single abnormal test and more than half with concordant abnormal tests, P<0.0001). No sibling had a left main lesion ≥70%; 15% had an RCA stenosis ≥70%, 9% had an LAD stenosis ≥70%, and 7% had an LCx stenosis ≥70%.

Number of Affected Vessels
A coronary stenosis of ≥50% occurred in 1 vessel in 18% of siblings, in 2 vessels in 14%, and in 3 vessels in 4%; 1 sibling
had 4-vessel disease. For lesions of ≥70% diameter stenosis, 1 vessel was involved in 18% of siblings, 2 vessels in 2%, 3 vessels in 1%, and 4 vessels in none.

Risk Factors by Angiographic Findings
Although most risk factor levels and prevalences tended to be higher in siblings with ≥50% stenosis than in those without lesions of this magnitude (Table 1), there were no significant differences except for the Framingham risk score (P = 0.016). Controlling for age, race, sex, and education, and including all major risk factors (none of which were significant alone), persons with concordant abnormal tests had nearly 6 times the probability of having a lesion of ≥50% compared with individuals with a single abnormal test (OR 5.7, 95% CI 2.0 to 16.3).

Relationship of Perfusion Defects to Angiographic Findings
Overall, the mean diameter stenosis for epicardial arteries that fed perfusion defects was modest (43±31%). Only 32% of such vessels had lesions ≥50%. Figure 3 shows that the distribution of maximum stenosis severity in arteries feeding perfusion defects was skewed toward less severe stenoses. There was a notable incremental severity of stenosis by the severity of the defect (Figure 4). Among mild defects (n = 59), the mean stenosis in the artery that fed the defect was 36±25%; for moderate defects (n = 33), it was 54±36%; and for severe defects (n = 2), it was 72±40% (ANOVA, P = 0.023). Among mild defects, 24% were perfused by arteries with ≥50% lesions and 12% by arteries with ≥70% stenosis. For moderate defects, the corresponding values were 46% and 39%, respectively. For the 2 severe defects, 1 was perfused with an artery with a 100% stenosis and the other by an artery with a 43% stenosis.

Of the 78 siblings with a single defect, only 3 had apparently normal vessels, and 53 siblings (71%) had defects that matched the most stenotic artery. In 8 siblings with 2 perfusion defects, 14 (88%) of 16 defects were located in the same distribution of the 2 most stenotic arteries. Despite the modest severity of the coronary stenosis involved, 67 (71%) of 94 total defects observed matched the anatomy. The LAD was the most stenotic vessel in most anterior, septal, or apical perfusion defects (Figure 5). The RCA (or LCx in the event of a left-dominant circulation) was the most narrowed artery in most defects in the inferior region, and of the 2 lateral wall defects, the LCx artery was the most stenotic vessel in both. Figure 6 demonstrates the scintigraphic perfusion images and coronary angiogram of a patient with “matching” between perfusion defect location and coronary anatomy despite having a maximum stenosis severity of 28%.

Discussion
This is the first study to describe the angiographic substrate associated with exercise ischemia in apparently healthy subjects with a family history of premature CAD. Although all

<table>
<thead>
<tr>
<th>Table 2. Comparison of Mean Levels of Treadmill Exercise Characteristics and Percent Diameter Stenosis by Group (N = 105)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximal MET level (n=19)</td>
</tr>
<tr>
<td>-------------------------</td>
</tr>
<tr>
<td>11±3</td>
</tr>
<tr>
<td>(n=19)</td>
</tr>
<tr>
<td>12±3</td>
</tr>
<tr>
<td>11±3</td>
</tr>
<tr>
<td>0.179</td>
</tr>
</tbody>
</table>

LM indicates left main. Values are mean±SD.
subjects had an abnormal exercise test, scintigram, or both, only 39% had a stenosis $\geq 50\%$, and most had minimal or mild obstructive disease. In symptomatic populations, perfusion defects usually signify hemodynamically significant stenoses. However, the present results show that exercise ischemia may be caused by mild stenoses.

Most studies of the accuracy of exercise screening tests for CAD in asymptomatic populations have concluded that the exercise test, with or without imaging, yielded many false-positives. In subjects with ischemia in the present study, we do not believe that these results represent false-positive tests. The location of the defect most often matched the artery with the most severe stenosis, even when the stenosis was mild.

It is not clear whether perfusion defects that occur in the context of mild stenoses are caused by a relative obstruction to flow at the site of the narrowing or whether the stenosis is a marker of more diffuse atherosclerosis. Because of vascular remodeling, luminal obstruction is usually a late event. Perfusion defects in a given vascular territory could result from diffuse involvement of the epicardial vessel and its branches, with a progressive accumulation of resistance to blood flow.

A normally functioning vascular endothelium is required for appropriate dilatation of arteries during exercise. Endothelial dysfunction is among the earliest events in atherosclerosis and has been demonstrated in people with risk factors or a family history of premature CAD. During exercise, endothelial dysfunction could result in a lack of normal flow-mediated dilatation, or even coronary vasoconstriction at the site of a mild stenosis. The rise in catecholamines that occurs during exercise may also contribute to vasoconstriction at the stenotic site.

The site of obstruction to blood flow during exercise could also be in the microvasculature. Exercise ischemia could result from inadequate dilatation of resistance vessels in the distribution of 1 or more of the major arteries. Zeiher et al found that in the absence of significant stenoses, patients with perfusion defects had reduced blood flow responses to acetylcholine (an index of microcirculatory function) but normal dilation of epicardial arteries. Similarly, Hasdai et al reported that in patients with mild coronary narrowings, perfusion defects induced by acetylcholine were associated with reduced blood flow responses. A defective integration of the vasodilator response that involves both small and large vessels may contribute to perfusion defects with "insignificant" coronary stenoses.

We previously showed that there is a 64% incidence of CAD events over 5 years in siblings who have abnormalities of both the exercise test and scan. We now demonstrate that siblings with these characteristics have the most severe atherosclerosis; 70% had $\geq 50\%$ stenoses, and 53% had $\geq 70\%$ stenoses in $\geq 1$ artery. In addition, 6 of 7 women with abnormalities in both tests had lesions of $\geq 50\%$ in $\geq 2$ vessels and also had lesions of $\geq 70\%$ in $\geq 1$ of the 2 vessels affected. These results are similar to the study of Uhl et al, which reported that 74% of asymptomatic male air crewmen with an abnormal ETT and scan had lesions of $\geq 50\%$.

Individuals with abnormalities of either test are also likely at increased risk despite having only mild lesions. Endothelial dysfunction likely contributes to ischemia and has been shown to be an independent predictor of outcome (independent of CAD severity). Endothelial dysfunction may predispose to plaque rupture and thrombosis at the site of a nonobstructive lesion.

Although the risk of siblings developing CAD is much higher than that of the general population, current guidelines do not target such families for aggressive preventive efforts. Targeted testing in high-risk families clearly identifies individuals with occult CAD. If Framingham scores alone are
used to identify persons for aggressive therapy, most siblings with occult CAD would fail to be targeted and would not be treated with lower goal levels, which are recommended for those with CAD. The information provided by exercise thallium scintigraphy likely identifies individuals who would benefit most from therapy to prevent the transition of occult disease to a clinically manifest CAD event.

Although the cost/benefit ratio of targeting high-risk families for screening and aggressive therapy remains unknown, on the basis of our prior studies, such screening would likely identify a very high-risk group. Traditional global risk assessment alone fails to perform well in identifying high-risk status in these families. Other screening approaches are becoming more available and potentially may have a role in screening of high-risk families.28–30 Sdringola et al documented the presence of significant dipyridamole-induced perfusion abnormalities on PET in half of asymptomatic adults with a parent or sibling with CAD.

Therapy to lower levels of LDL cholesterol and blood pressure, even in persons without hyperlipidemia or hyper-tension, results in a reduction in the number of CAD events.4,31,32 Similarly, aspirin reduces CAD events in certain asymptomatic populations.3 Noninvasive testing of high-risk families for preclinical CAD and tailored aggressive therapy for those with abnormal results represents a potentially fruitful approach for reducing the burden of death and disability from CAD.

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References
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