The Importance of Clinical Subsets in Interpreting Maximal Treadmill Exercise Test Results: the Role of Multiple-Lead ECG Systems

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SUMMARY Two hundred men with normal ECGs at rest had maximum treadmill tests using 14 ECG leads 1 day before their coronary arteriogram. The prevalence of coronary stenoses $\geq 70\%$ was 86% in 87 men with typical angina, 65% in 64 men with probable angina, and 28% in 49 men with nonspecific chest pain ($p < 0.001$). Among the 117 men who had coronary disease and probable or typical angina, there was more three-vessel ($32\%$ vs $7\%; p = 0.06$) and proximal left coronary disease ($41\%$ vs $14\%; p < 0.05$) than among the 14 men with coronary lesions and nonspecific chest pain. Prevalence, extent and location of coronary stenoses, therefore, were different among the clinical subsets.

The predictive value of a positive test in any one of 14 leads was 45% (nine of 20) in men with nonspecific chest pain vs 82% (36 of 44) in men with probable angina and 100% (65 of 65) in men with typical angina ($p < 0.001$). The predictive value of a negative test in 14 leads was 83% (24 of 29) in men with nonspecific chest pain vs 70% (14 of 20) in men with probable angina and 55% (12 of 22) in men with typical angina (NS). In men with probable or typical angina, 92% (33 of 36) of those with a positive test and treadmill work time $\leq 360$ seconds had multivessel disease; only one man in 40 with a negative test in 14 leads and treadmill work time $> 540$ seconds had three-vessel disease.

The diagnostic impact of maximal treadmill testing using 14 ECG leads is greatest in men with typical and probable angina. In these two clinical subsets the presence or absence of horizontal or downsloping ST-segment depression $\geq 1$ mm, ST-segment elevation $\geq 1$ mm, or a slowly upsloping ST-segment depression $\geq 2$ mm at 0.08 seconds after the $J$ point in any of 14 leads is highly predictive of multivessel disease when used in conjunction with treadmill work time. The predictive value of maximal treadmill testing using 14 ECG leads in men with nonspecific chest pain is less useful. The lower predictive value of a positive test occurs because this clinical subset has less severe coronary disease and a lower prevalence of disease than men with anginal symptoms. Recording a single lead such as CM$_4$ would suffice for the majority of patients in this subset using either horizontal or downsloping ST-segment depression $\geq 1$ mm or ST-segment elevation $\geq 1$ mm as criteria for positivity.

THE SENSITIVITY AND EFFICIENCY of maximal treadmill testing in men with angina pectoris can be increased by recording multiple ECG leads and combining the results with physiological data collected during exercise. Little information is available on multiple-lead exercise testing in subsets of patients with a lower disease prevalence, such as asymptomatic patients, those with nonspecific chest pain, and women. Several investigators have reported decreased specificity of exercise test results in selected populations with a low disease prevalence. There is concern that the use of multiple ECG leads could increase the false positive rate in this type of population.

Using mathematical formulas derived from the Bayes theorem, it can be shown that more false positive tests are to be expected when disease prevalence is low. However, the probability curves generated by these equations depend on the exercise test results taken from papers dealing with symptomatic patients undergoing coronary arteriography. One must assume that differences in clinical populations are caused only by different prevalences of disease. An implicit assumption that the extent and location of coronary stenoses are similar in different subsets of patients is necessary for these extrapolations since the sensitivity of exercise testing has been shown to vary with the severity of disease. In order to test these assumptions with practical examples, we have compared 14-lead ECG and physiological exercise test results with coronary arteriographic findings in three clinical subsets of men with normal ECGs at rest. Among the three clinical groups patients in the first group had typical angina pectoris, those in the second had symptoms suggestive of angina pectoris, and those in the third had nonspecific chest pain and were at low suspicion for coronary disease. In the latter group, coronary arteriography was often performed because of difficulty in eliminating the possibility of coronary disease in patients, most of whom had a long history of chest pain which interfered with their quality of life and work status.
Methods

Patient Selection

Maximal treadmill tests were performed on 680 consecutive patients using a 14-lead ECG system 1 day before a coronary arteriogram. From this population, 200 consecutive men who had a normal resting ECG were selected for further study. Their clinical histories were recorded by two physicians. Typical angina pectoris was defined as a substernal discomfort precipitated by exertion, relieved by rest or nitroglycerin or both, and with typical radiation to either shoulder, jaw, or inner arm. Probable angina pectoris had most of the features of typical angina pectoris, but in some aspects was not entirely typical, e.g., chest pain in unusual location or not always relieved by nitroglycerin, or inconstant precipitating factors. Nonspecific chest pain was defined as chest pain which did not meet the criteria for typical or probable angina pectoris and included chest pain unrelated to activity and unrelieved by nitroglycerin or rest or both.

The indication for cardiac catheterization was typical angina pectoris in 87 men, probable angina pectoris in 64 men, and nonspecific chest pain in 49 men. Of those patients with probable or typical angina pectoris, 91 were Canadian Heart Angina class II and 37 were class III. No patient had valvular heart disease or a cardiomyopathy and none was receiving digitalis preparations. Other than nitroglycerin, β-blockers and other medications were stopped for at least 2 days before the test. The average age of men with nonspecific chest pain was younger than that of men with probable or definite angina pectoris (46 vs 49 years; p < 0.05) (table 1).

Exercise Protocol

Upright exercise on a motor-driven treadmill was performed following a Bruce protocol modified by a preliminary 3-minute stage at 1.7 mph and 5% grade. After the initial 60 seconds, patients were not allowed to grasp the front rail for support, since holding onto the rail prolongs treadmill time and estimated work capacity. Exercise was stopped because of exhaustion in 93 men, angina pectoris in 83 men, dyspnea in 15 patients and ST-segment depression more than 3 mm in nine asymptomatic men. All 71 men with a negative test achieved ≥ 85% of their maximum age-predicted heart rate and 61 were able to achieve ≥ 90%. A standard 12-lead ECG (excluding aVR) and leads CCa, CMa, and CL were recorded. The CL lead has the positive electrode in the left flank, 1.5–2 inches above the left posterior iliac crest and 5 inches from the midline; the negative electrode is at the manubrium. This lead reflects primarily inferior wall changes. Siemens exercise patient cable, ECG junction box, and nondisposable electrodes were used in conjunction with a Cambridge three-channel direct-writing recorder (model 3038). Technical details relating to sequence of ECG recordings and patient position after exercise have been previously described. The ECG criteria for a positive test in any lead were 1) horizontal or downsloping ST-segment depression ≥ 1 mm for 0.08 seconds, 2) ST-segment elevation ≥ 1 mm for 0.08 seconds or 3) a slowly upsloping ST-segment depression ≥ 2 mm, 0.08 seconds after the J point in at least three consecutive complexes. A slowly upsloping ST-segment depression ≥ 2 mm, 0.08 seconds after the J point has been shown to increase sensitivity without decreasing specificity in symptomatic patients. Cranio-caudal sagittal and caudo-cranial sagittal angulation views of the left coronary artery were done routinely to visualize more clearly the proximal divisional branches which are often superimposed in the standard transverse angiographic projections. Each arteriogram was interpreted by an experienced radiologist unaware of the

Table 1. Clinical Data

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Age</th>
<th>LV function</th>
<th>Coronary stenosis ≥ 70%</th>
<th>Proximal LAD stenosis ≥ 70%</th>
<th>Left main stenosis ≥ 50%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ejection fraction</td>
<td>% abnormal wall motion</td>
<td>N %</td>
<td>N %</td>
</tr>
<tr>
<td>Typical angina</td>
<td>87</td>
<td>49 ± 0.8</td>
<td>0.58 ± 0.01</td>
<td>29/87 33%</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>Probable angina</td>
<td>64</td>
<td>49 ± 1.0</td>
<td>0.61 ± 0.01</td>
<td>12/64 19%</td>
<td>22</td>
<td>35</td>
</tr>
<tr>
<td>Nonspecific chest pain</td>
<td>49</td>
<td>46 ± 1.1*</td>
<td>0.61 ± 0.01</td>
<td>5/47 11%†</td>
<td>35</td>
<td>72</td>
</tr>
</tbody>
</table>

* p < 0.05.
† p < 0.01.
‡ p < 0.001.
§ p = 0.06.
Nonspecific chest pain vs typical or probable angina.
Abbreviations: LV = left ventricle; LAD = left anterior descending.
exercise test results. A stenosis ≥ 70% of the arterial intraluminal diameter was considered significant except for left main coronary disease where stenoses ≥ 50% were considered significant. Proximal left anterior descending disease was coded when a stenosis ≥ 70% occurred before the first septal branch. A proximal stenosis of a large diagonal or marginal branch was considered as a stenosis of the left anterior descending or circumflex coronary artery, respectively. Table 1 shows the types of coronary lesion observed in each group. The prevalence of coronary disease was 86% in men with typical angina pectoris, 65% with probable angina pectoris, and 28% in men with nonspecific chest pain. Proximal left anterior descending stenoses were noted in 25% of men with typical angina, 28% of those with probable angina, and 2% of men with nonspecific chest pain. Three-vessel disease was coded in 24% of men with typical angina, 25% with probable angina, and 2% of men with nonspecific chest pain.

The left ventricle was opacified in the 30° right anterior oblique view before the arteriogram. Ejection fraction, calculated by the area-length method, was 0.58 in men with typical angina pectoris and 0.61 in men with probable angina and nonspecific chest pain. Wall motion abnormalities occurred in 29 men with typical angina pectoris, 12 with probable angina, and five with nonspecific chest pain.

Analysis of Results

In each of the three groups of patients, lead V₆ was compared to bipolar leads CC₅ and CM₅ and to the following multiple lead systems: 1) standard 11-lead ECG (aVR excluded); 2) three bipolar leads (CM₅, CC₅, CL); and 3) all 14 leads. The sensitivity, specificity, predictive values of a positive or negative test, and efficiency of the exercise test were determined for each lead system. Intergroup and intragroup differences in these parameters were examined using the chi square test. Parametric differences were determined using the t test.

Sensitivity was defined as the number of true positives/true positives + false negatives;

Specificity = true negatives/true negatives + false positives;

Predictive value of a positive test = true positives/all positive tests;

Predictive value of a negative test = true negatives/all negative tests;

Efficiency = true positives + true negatives/total population.

The likelihood ratio* for an abnormal test was defined as sensitivity/1 — specificity, and the likelihood ratio for a normal test as specificity/1 — sensitivity.

Results

Table 1 compares the coronary anatomy and ventricular function of patients with typical and probable angina pectoris with the group of patients with nonspecific chest pain. The prevalence of coronary disease was 28% (14 of 49) in men with nonspecific chest pain vs 65% (42 of 64) in men with probable angina and 86% (75 of 87) in men with typical angina (p < 0.001). The extent and distribution of coronary stenoses were similar in men with probable and typical angina in contrast to men with nonspecific chest pain. Only 7% (one of 14) of patients with coronary disease and nonspecific chest pain had three-vessel disease vs 32% (37 of 117) of patients with probable or typical angina (p = 0.06). Multivessel disease occurred in 50% (7 of 14) of patients with nonspecific chest pain vs 68% (79 of 117) of men with probable or typical angina (NS). The location of coronary disease was also less severe in men with nonspecific chest pain. Proximal left anterior descending stenoses were present in only 7% (one of 14) of patients with nonspecific chest pain vs 34% (40 of 117) of patients with probable or typical angina (p < 0.05). Since the extent, distribution, and prevalence of coronary disease in men with nonspecific chest pain were different from those in men with probable or typical angina, we compared the exercise test results using different lead systems with each clinical presentation to determine which lead system would be optimal for each patient group.

Typical Angina Pectoris

Detection of Coronary Disease

Table 2 shows that of the 75 men in this group with disease, 49 (65%) were detected in V₆ vs 64 (85%) in CC₅, CM₅, CL (p < 0.03), and 65 (87%) in 14 leads (p < 0.005). There were no false positive tests. The predictive value of a negative test in V₆ was 32% vs 55% of patients using 14 leads (NS). The efficiency of the test was significantly improved using CC₅, CM₅, CL (87%; p < 0.03) or 14 leads (89%; p < 0.005) compared with an isolated V₆ lead (70%). The CC₅, CM₅, CL system was positive in eight patients in whom the 11-lead system was negative. The 11-lead system was positive in one patient in whom the CC₅, CM₅, CL system was negative. Of 64 men with a positive test in CC₅, CM₅, CL, the CM₅ lead was positive in eight men in whom CC₅ and CL were negative; the CC₅ lead was positive in five men in whom CM₅ and CL were negative; and the CL lead was not positive without positive changes in CC₅ or CM₅. Leads I, II, III, aVF, V₁, V₆, and CL did not increase sensitivity or decrease specificity in this subgroup.

Only two of 200 men (1%) had ST-segment elevation during exercise. Both had typical angina, significant ST-segment depression in other leads, and severe multivessel disease.

Detection of High-Risk Lesions

The sensitivity for high-risk patients was improved when CC₅, CM₅, CL, or 14 leads were used compared with a V₆ lead (table 3). Of 21 patients with three-vessel disease, 18 (86%) were detected using V₆, 18 (86%) using CC₅, CM₅, CL, and 20 (95%) using 14 leads. Of 49 patients with multivessel disease, 36
Table 2. Predictive Value of Exercise Test Results for Each Lead System in the Different Clinical Subsets

<table>
<thead>
<tr>
<th></th>
<th>Unipolar leads</th>
<th>Bipolar leads</th>
<th>Multiple leads</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$V_3$</td>
<td>$V_4$</td>
<td>$V_5$</td>
</tr>
<tr>
<td>Typical angina</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>20/75 (27%)</td>
<td>41/75 (55%)</td>
<td>49/75 (65%)</td>
</tr>
<tr>
<td>Specificity</td>
<td>12/12 (100%)</td>
<td>12/12 (100%)</td>
<td>12/12 (100%)</td>
</tr>
<tr>
<td>Predictive value of a positive test</td>
<td>20/20 (100%)</td>
<td>41/41 (100%)</td>
<td>49/49 (100%)</td>
</tr>
<tr>
<td>Predictive value of a negative test</td>
<td>12/67 (18%)</td>
<td>12/46 (26%)</td>
<td>12/38 (32%)</td>
</tr>
<tr>
<td>Efficiency</td>
<td>32/87 (37%)</td>
<td>53/87 (61%)</td>
<td>61/87 (70%)</td>
</tr>
<tr>
<td>Probable angina</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>10/42 (24%)</td>
<td>18/42 (43%)</td>
<td>22/42 (52%)</td>
</tr>
<tr>
<td>Specificity</td>
<td>21/22 (96%)</td>
<td>18/22 (82%)</td>
<td>19/22 (86%)</td>
</tr>
<tr>
<td>Predictive value of a positive test</td>
<td>10/11 (91%)</td>
<td>18/22 (82%)</td>
<td>22/25 (88%)</td>
</tr>
<tr>
<td>Predictive value of a negative test</td>
<td>21/53 (40%)</td>
<td>18/42 (43%)</td>
<td>19/39 (49%)</td>
</tr>
<tr>
<td>Efficiency</td>
<td>31/64 (48%)</td>
<td>36/64 (56%)</td>
<td>41/64 (64%)</td>
</tr>
<tr>
<td>Nonspecific chest pain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>5/14 (36%)</td>
<td>7/14 (50%)</td>
<td>7/14 (50%)</td>
</tr>
<tr>
<td>Specificity</td>
<td>33/35 (94%)</td>
<td>30/35 (86%)</td>
<td>30/35 (86%)</td>
</tr>
<tr>
<td>Predictive value of a positive test</td>
<td>5/7 (71%)</td>
<td>7/12 (58%)</td>
<td>7/12 (58%)</td>
</tr>
<tr>
<td>Predictive value of a negative test</td>
<td>33/42 (79%)</td>
<td>30/37 (81%)</td>
<td>30/37 (81%)</td>
</tr>
<tr>
<td>Efficiency</td>
<td>38/49 (78%)</td>
<td>37/49 (76%)</td>
<td>37/49 (76%)</td>
</tr>
</tbody>
</table>

Intragroup comparisons: $V_3$ vs other leads; *$p < 0.03$; †$p < 0.005$.

Intergroup comparisons: predictive value of a positive test: nonspecific chest pain vs typical angina $p < 0.001$ in lead $V_5$ and 14 leads. Nonspecific chest pain vs probable angina $p < 0.01$ in 14 leads; predictive value of a negative test in lead $V_5$ - nonspecific chest pain vs probable angina $p < 0.01$. Nonspecific chest pain vs typical angina $p < 0.001$; efficiency: nonspecific chest pain vs typical angina, $p < 0.01$ in 14 leads.
Table 3. Sensitivity of Lead Systems for High-Risk Lesions

<table>
<thead>
<tr>
<th>Group</th>
<th>V₅</th>
<th>CM₅</th>
<th>11</th>
<th>CC₅, CM₅, CL</th>
<th>14</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Typical angina</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Three-vessel disease</td>
<td>18/21</td>
<td>86%</td>
<td>18/21</td>
<td>86%</td>
<td>20/21</td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>36/49</td>
<td>73%</td>
<td>41/49</td>
<td>84%</td>
<td>41/49</td>
</tr>
<tr>
<td>Proximal LAD or LM disease</td>
<td>19/28</td>
<td>68%</td>
<td>24/28</td>
<td>86%</td>
<td>21/28</td>
</tr>
<tr>
<td><strong>Probable angina</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Three-vessel disease</td>
<td>11/16</td>
<td>69%</td>
<td>12/16</td>
<td>75%</td>
<td>15/16</td>
</tr>
</tbody>
</table>
| Multivessel disease          | 20/30 | 67% | 22/30 | 73% | 27/30 | 90% | 26/30 | 87% | 29/30 | 97% *
| Proximal LAD or LM disease   | 15/19 | 79% | 15/19 | 79% | 17/19 | 90% | 17/19 | 90% | 19/19 | 100% |
| **Nonspecific chest pain**   |     |     |    |              |     |
| Three-vessel disease         | 0/1  | 0   | 0/1  | 0   | 0/1  | 0   | 1/1   | 100% | 1/1   | 100% |
| Multivessel disease          | 3/7  | 43% | 4/7  | 57% | 3/7  | 43% | 5/7   | 71%  | 5/7   | 71%  |
| Proximal LAD or LM disease   | 1/2  | 50% | 2/2  | 100% | 1/2  | 50% | 2/2   | 100% | 2/2   | 100% |

*p < 0.01.

Intragroup comparisons: V₅ vs other leads.
Abbreviations: LAD = left anterior descending stenosis ≥ 70%; LM = left main coronary stenosis ≥ 50%.

(73%) were detected using V₅, 43 (88%) using CC₅, CM₅, CL, and 44 (90%) using 14 leads. Finally, of 28 patients with proximal left anterior descending or left main coronary artery disease, 19 (68%) were detected using V₅, 25 (89%) using CC₅, CM₅, CL, and 25 (89%) using 14 leads.

Multivessel disease was more frequent when the maximum degree of ST-segment depression in any one of the 14 leads was ≥ 3 mm or when final treadmill work time was 360 seconds or less (fig. 1). Of 21 patients with ST-segment depression ≥ 3 mm in any one of 14 leads, four had single-vessel, nine had two-vessel and eight had three-vessel disease. Seven patients had stenosis of either the proximal left anterior descending or left main coronary arteries. Of 21 patients with a positive test and final treadmill work time ≤ 360 seconds, nine had three-vessel disease and 10 had stenosis of either the proximal left anterior descending or left main coronary arteries. A negative test in Bruce stage III or greater was observed in 20 patients, eight (40%) of whom had coronary disease. Of these eight, only two had three-vessel disease or a proximal left anterior descending artery stenosis. Therefore, in this group of patients, treadmill time and depth of ST-segment depression were helpful in determining the severity of disease.

**Probable Angina Pectoris**

**Detection of Coronary Disease**

Of the 42 patients in this group with coronary disease, 22 (52%) had a positive test in V₅ vs 33 (79%; *p < 0.03) in bipolar leads CC₅, CM₅, CL, and 36 (86%; *p < 0.005) in 14 leads (table 2). Although sensitivity was increased by the addition of multiple leads, specificity decreased from 86% in V₅ to 64% using CC₅, CM₅, CL, or 14 leads (NS). The predictive value of a positive test result was 88% (22 of 25) in V₅ compared to 82% (36 of 44) using 14 leads. The predictive value of a negative test was 70% in 14 leads vs 49% using V₅ alone (NS). The CC₅, CM₅, CL lead system was positive in seven patients in whom the 11-lead system was negative; two of these seven patients were false positives. The 11-lead system was positive in three patients in whom the three-lead system was negative; all three were true positives. Modified limb leads I, II, III, aV₁, aV₅ detected two patients with multivessel disease in the absence of changes in precordial leads V₂ and/or V₃, both patients had a positive test in CC₅, CM₅, CL.

Of 33 men with a positive test in CC₅, CM₅, CL, the CM₅ lead was positive in three men in whom CC₅ and CL were negative, causing one false positive; the CC₅ lead was positive in four men in whom CC₅ and CL were negative; and the CL lead was positive in one patient with three-vessel disease when CC₅ and CM₅ were negative. Thus, multiple leads increase the value of exercise testing in this subgroup.

**Detection of High-Risk Lesions**

Table 3 shows which patients were detected using bipolar leads CC₅, CM₅, CL, or 14 leads. Of 16 men with three-vessel disease, 11 (69%) were detected by a positive test in V₅ vs all 16 (100%) using 14 leads. Of 30 patients with multivessel disease, 20 (67%) were detected using lead V₅ and 22 (73%) using CM₅ vs 29 (97%) using 14 leads (*p < 0.01). Finally, of 19 men with proximal left anterior descending stenosis ≥ 70% or left main stenosis ≥ 50%, 15 (79%) were detected in V₅ vs 19 (100%) using 14 leads. Although other combinations of lead systems also increased sensitivity for high-risk lesions, none were a sensitive as 14 leads.

Figure 2 shows the relationship between treadmill work time and depth of ST-segment depression in 14 leads. Of 15 men with a final treadmill time ≤ 360 seconds, all had multivessel disease, and 12 (80%) had three-vessel disease. Performance in Bruce stage III or
greater was not useful in separating normal patients from those with obstructive coronary disease even if ST-segment depression of 2–3 mm occurred. However, of the 10 patients with multivessel disease who performed in Bruce stage III, only two had three-vessel disease and both had a positive test. All six patients who had ST-segment depression ≥ 4 mm had coronary disease; five patients had proximal left anterior descending disease or a left main stenosis and the sixth had multivessel disease.

Nonspecific Chest Pain

Seven of the 14 patients in this group with coronary disease had a positive test in V6 compared with eight in CM5 and nine using all 14 leads (table 2). Both additional patients detected by 14 leads had multivessel disease (table 3).

Coronary disease was present in 40–71% of patients who had a positive test, depending on the lead system used. Lead V6 was most predictive of coronary disease when positive (71%), but sensitivity was unacceptably low (36%). The addition of multiple leads did not significantly increase the predictive value of a negative test result compared to V6 alone (83% vs 81%).

The CM5 lead was positive when CC5 and CL were negative in the only patient with left main coronary disease by the slowly upsloping criterion. Lead CC5 was positive in one patient resulting in a false positive when CM5 and CL were negative. The CL lead was positive in two men when CC5 and CM5 were negative: one patient had three-vessel disease, the other was a false positive. Leads CM5 and CL were positive in four patients when lead CC5 was negative, three of whom were false positives. Frontal leads and leads V1–2 neither improve sensitivity nor decrease specificity.

In order to increase the predictive power of a positive test result, a slowly upsloping ST-segment depression ≥ 2 mm at 0.08 seconds after the J point was excluded from the positive criteria and only 2 mm of horizontal or downsloping ST-segment depression for 0.08 seconds in any lead was used. Of eight patients with this ECG response in V6, five (63%) had coronary disease. Corresponding increases in the predictive value of a positive test were observed in lead CC5 (five of six, 83%), CM5 (seven of 13, 54%) and 14 leads (seven of 13, 54%). Although the predictive value of a positive test using these criteria was generally increased, the predictive potential of some leads were increased more than others. For example, the predictive value of a positive result increased by 0.37 in lead CC5, compared with an increase of only 0.09 in lead CM5. Increasing the criteria for positivity decreased sensitivity to 36% (five of 14) in lead V6 and CC5 and 50% (seven of 14) in 14 leads.

A slowly upsloping ST-segment depression ≥ 2 mm at 0.08 seconds after the J point was observed in five patients. In each case, there was horizontal or downsloping ST-segment depression in other leads. Four of the five had coronary disease, including both patients with proximal left coronary lesions.

The relationship between treadmill work time and depth of ST-segment depression in 14 leads is given in figure 3. As might be expected, most patients were not limited by angina and entered Bruce stage III. Thus,
in this subset of patients, treadmill work time was not a useful parameter in separating normal patients from those with obstructive coronary disease. Depth of ST-segment depression was more useful since eight of 14 (57%) patients with ST-segment depression ≥ 2 mm had coronary disease. Both patients with ST-segment depression ≥ 2 mm who were unable to perform Bruce stage III had coronary disease.

**Number of Positive Leads**

Figure 4 shows the relationship between the number of positive leads and the number of vessels with stenoses ≥ 70% for each clinical subset. A positive test in men with typical angina was associated with more positive leads when two- and three-vessel disease was present (5.2 ± 0.5 and 6.3 ± 0.5 positive leads, respectively) than single-vessel disease (3.6 ± 0.4) (p < 0.03). Since false positive tests did not occur in this group of patients, the number of positive leads was useful in separating multivessel from single vessel disease. Left main and proximal left anterior descending artery stenosis did not increase the number of positive leads: e.g., in men with typical angina and three-vessel disease, 6.4 ± 0.6 leads were positive in those with proximal left coronary lesions vs 6.3 ± 0.7 leads in those without proximal left coronary stenoses. Similar results were obtained in men with two-vessel and single-vessel disease.

In men with probable angina, two- and three-vessel disease also produced more positive leads than single-vessel disease; however, false positive responders had an average of 4.9 ± 1.3 positive leads, reducing the usefulness of this parameter for identifying high-risk patients. Similarly, men with nonspecific chest pain and coronary disease could not be distinguished from those without coronary disease by the number of positive leads.

**Intergroup Comparisons**

**Single Leads**

A positive test in lead V₅ predicted coronary disease in 58% of men with nonspecific chest pain and 100% of men with typical angina (p < 0.001). A negative test predicted absence of coronary disease in 81% of men with nonspecific chest pain vs 49% of men with probable angina (p < 0.01) and 32% of men with typical angina (p < 0.001).

**Multiple Leads**

A positive test in 14 leads predicted coronary disease in 45% of men with nonspecific chest pain vs 82% of men with probable angina (p < 0.01) and 100% of men with typical angina (p < 0.001). A negative test predicted absence of coronary disease in 83% of men with nonspecific chest pain vs 55% of men with typical angina (NS). The test was less efficient using 14 leads in men with nonspecific chest pain (67%) than men with typical angina (89%) (p < 0.01). Results obtained using CC₅, CM₅ and CL were similar.

**Likelihood Ratios**

The above intergroup comparisons show that there are significant differences in the predictive value of an exercise test result depending on the clinical subset being examined. Table 4 shows the likelihood ratio (odds that the test result was a true one) for each lead system in men with typical or probable angina and men with nonspecific chest pain. Using lead V₅, the likelihood
ratio of a positive test was 6.78 in men with typical or probable angina and 3.57 in men with nonspecific chest pain. Likelihood ratios were consistently lower in men with nonspecific chest pain for each lead system examined. The likelihood ratio of a negative test in 14 leads was 5.43 in men with typical or probable angina and 1.92 in men with nonspecific chest pain. Thus, likelihood ratios for a positive or negative test were different in men with typical or probable angina compared with men with nonspecific chest pain. Table 4 also shows that the use of multiple leads slightly decreases the predictive potential of a positive result in exchange for increased potential in predicting the absence of coronary artery disease.

Discussion

In a recent review of eight exercise-test papers, sensitivity varied from 53–81% and specificity from 82–97%. The populations studied in these reports varied considerably, e.g., ECG evidence of transmural myocardial infarction from 0–37%, women from 9–34%, typical angina from 35–100% of patients studied. Since 95% of men with ECG evidence of transmural myocardial infarction and 80–96% of those with typical angina have obstructive coronary disease, one could predict by mathematical formulas that the incidence of false positives would be low in studies with a high prevalence of this type of patient. Since only 50–62% of women with typical angina and only 11–26% of those with atypical angina have obstructive coronary disease, one could predict that there would be an increased incidence of false positives in studies with a high prevalence of women. If the number of women and the prevalence of patients with ECG transmural myocardial infarction were approximately equal in any given study, the increase and decrease in false positives would cancel out, giving averaged results not applicable to either subset. In an attempt to control for some of these variables, we have correlated exercise test results to coronary arteriographic findings in 200 men with a normal ECG at rest. The predictive values of nine different lead systems were studied in relation to quality of chest pain symptoms.

Coronary Anatomy

Our data show that the prevalence of coronary disease increased as the clinical index of suspicion for coronary disease increased, confirming other reported series. The prevalence of significant coronary disease in patients with atypical angina undergoing arteriography has been reported at 42–66%. The range of observed prevalences depends upon the type of population referred to each of these institutions, the number of women in each series, and the definition of atypical angina pectoris.

The extent and location of coronary disease in our series was similar in men with typical or probable angina pectoris in contrast to those with nonspecific chest pain. Among our 49 men with nonspecific chest pain, 28% had coronary disease, more than the 4–16% reported in other series. Of the 136 men with disease in our study, those with nonspecific chest pain had less three-vessel and proximal left coronary disease than men with probable and typical angina pectoris. Friesinger and colleagues have reported similar findings in 106 patients. They reported significantly more extensive obstructive disease in patients with
typical angina than those with atypical angina. These angiographic studies demonstrate that patients with chest pain represent a spectrum with a varying disease prevalence dependent on age, sex, and quality of symptoms. Furthermore, the severity of disease can differ within each subset.

Exercise Test Results

Typical Angina Pectoris

The pretest risk of coronary disease was 0.86 in men with typical angina pectoris. The use of 14 leads significantly increased sensitivity compared with an isolated V₅ lead (p < 0.005). A positive test predicted coronary disease in all patients regardless of lead system used: the post-test risk for a patient with typical angina pectoris and a positive exercise test was 1.00. Detry and colleagues²⁸ have reported a post-test risk of 0.98 in a similar group of patients.

The pretest risk for multivessel disease in this group was 0.56. Figure 1 shows that when 14 ECG leads were used, the post-test risk increased to 0.81 if the test were positive and treadmill work time were ≤ 360 seconds. The post-test risk for multivessel disease was increased by 0.30 when ST-segment depression ≥ 2 mm occurred. A negative test using 14 ECG leads and treadmill work time > 540 seconds ruled out three-vessel disease in 95% of cases. These results demonstrate that important diagnostic information can be obtained in this subset of patients by considering the lead system, depth of ST-segment depression, and the duration of exercise.

Probable Angina Pectoris

The pretest risk for coronary disease was 0.65 in this group of patients. The use of 14 leads significantly increased sensitivity (p < 0.005) compared to lead V₅. A positive test increased the post-test risk to 0.82 using 14 leads and decreased the risk of coronary disease to 0.30 when all leads were negative. In this subset of patients, exercise testing with 14 leads had the greatest diagnostic impact.

The pretest risk of multivessel disease was 0.47. The post-test risk of multivessel disease was 1.00 in all 15 men who had a positive test and a treadmill work time ≤ 360 seconds (fig. 2). A negative test using 14 ECG leads and treadmill work time > 540 seconds ruled out three-vessel disease in all cases. McNeer and coworkers²⁹ have reported that three-vessel disease was absent in 89% of 248 patients with a negative test in 12 leads and treadmill work time > 540 seconds. Their series was slightly different from ours since they included patients with an abnormal resting ECG and those with previous transmural myocardial infarction.

The data obtained in this and other studies²⁴, ²⁵ depict how exercise-test results in men with typical and probable angina pectoris can be used to help determine which patient may benefit from a coronary arteriogram. A negative test in 14 leads associated with a treadmill work time > 540 seconds reduces the chance of three-vessel disease to 5–10%. The likelihood of multivessel disease in a patient with a positive test and a treadmill time ≤ 360 seconds is approximately 90%.

Men with Nonspecific Chest Pain

The pretest risk for coronary disease was 0.28 in this clinical subset. A positive test increased the post-test risk of coronary disease to 0.58 using lead V₅ or 0.45 using 14 leads. Although the post-test risk increased the chances of having coronary disease by as much as 0.30, only slightly more than half of the patients had coronary disease. There was no clear advantage to recording bipolar leads CC₅, CM₅, and CL in addition to the standard 11-lead ECG in this group. Although we did not observe an increased incidence of false positive results in this subgroup by using a slowly upsloping ST-segment depression ≥ 2 mm at 0.08 seconds after the J point, it would seem wise not to use this criteria in a subgroup of patients with a low disease prevalence since it could lead to an excess of false positives. By increasing the criteria for a positive test to 2 mm or more horizontal or downsloping ST-segment depression, the predictive value of a positive test result increased from 0.45 to 0.57 using 14 leads. Of the 14 leads, lead CC₅ had the highest predictive value for coronary disease (0.83) when positive. Treadmill work time was less useful in this subgroup of patients since most were not limited by angina pectoris.

Since exercise testing with 14 leads only predicts coronary disease 45% of the time when positive, other clinical parameters and noninvasive tests should be used when evaluating individual patients with nonspecific chest pain. Among these, age and number of coronary risk factors as shown in the coronary risk handbook²⁸ could be useful. Among noninvasive tests, cardiac fluoroscopy for coronary calcification,⁰⁶, ⁰⁷ a positive thallium scan at rest or during exercise,⁰⁸, ⁰⁹ or a positive displacement cardiokymograph (CKG) which can measure exercise-induced changes in ventricular wall motion using an electromagnetic field¹⁰, ¹¹ may be potentially useful but all require further evaluation in this subgroup of patients. A fourth noninvasive test which seems promising and merits further study in patients with nonspecific chest pain is radionuclide cineangiography performed during supine exercise-stress testing. Borer and colleagues¹² have studied 11 patients with coronary disease whose ejection fraction decreased or remained the same during exercise-induced ischemia in contrast to 14 age-matched controls whose ejection fraction increased. Whichever test or combination of tests is used, it should be remembered that three-vessel disease and proximal left coronary lesions are uncommon in these patients. If the clinical situation requires an absolute diagnosis and an expensive battery of noninvasive tests, the sum of the costs of the noninvasive tests should be balanced against the cost and small risk of a coronary arteriogram.
Likelihood Ratios

Several investigators\textsuperscript{6-7} have generated likelihood ratios and probability curves from exercise-test papers dealing with symptomatic patients undergoing coronary arteriography. Extrapolation from these probability curves give a quantitative estimate of the chance of disease when the exercise test is positive or negative according to the prevalence of disease in the population examined. One assumes from these curves that differences in clinical populations are caused only by different prevalences of disease.

The Bayes theorem states that the post-test risk of coronary disease equals the pretest risk (prevalence) \times the likelihood ratio.\textsuperscript{8} The likelihood ratio is a numerical value expressing the probability that a given test result is true and is derived from sensitivity and specificity. In table 4, we have shown that the prevalence of coronary disease (pretest risk) was 0.77 in men with typical and probable angina. Thus, before performing an exercise test a patient with anginal symptoms had 77 chances of having disease and 23 chances of not having disease (the odds are 77 to 23). The likelihood ratio for coronary disease when the test was positive in one of 14 leads was 3.58. This increases the odds to 77 \times 3.58 or 276 to 23 that coronary disease will be present. Thus, the predictive value of a positive test is 276/276 + 23 or 0.92, an increase of 0.15 over the pretest risk. The predictive value of a positive result in men with nonspecific chest pain could be obtained by extrapolating from our results in men with typical or probable angina. The pretest risk in men with nonspecific chest pain was 0.28. The likelihood ratio of an abnormal test was 3.58 in men with typical and probable angina pectoris. Thus, 28 \times 3.58 = 276/100 + 72 = 0.58, an increase of 0.30 over the pretest risk. In table 2, we have shown that the predictive value of a positive test in men with nonspecific chest pain is 0.45 using 14 leads, not 0.58. This difference occurs because a positive exercise test is more frequent in men with three-vessel disease than men with single-vessel disease.\textsuperscript{4, 19-23} We have shown that men with nonspecific chest pain as a group have less severe disease and in particular less three-vessel and proximal left anterior descending disease than men with typical or probable angina pectoris. Exercise testing is less sensitive in men with nonspecific chest pain (table 2) which results in a lower predictive value for a positive test than results extrapolated from men with typical and probable angina pectoris. The likelihood ratios for these clinical subsets are different (table 4). Clearly, predictive statements regarding exercise testing in different populations should take into account both prevalence and the fact that likelihood ratios can change when the diseased populations are not comparable. Likelihood ratios are also affected by the lead system used and the ECG criteria for positivity.

When the severity of disease in a particular group of patients is similar to that observed in one of our three clinical subsets, an accurate estimate of the predictive value of a positive or negative exercise test can be made using the Bayes theorem. The probability of coronary disease being present in a patient (pretest risk) is estimated. The likelihood ratio for the lead system employed can be obtained from table 4. The post-test odds of coronary disease being present or absent can then be derived from the formula, pretest risk \times likelihood ratio, giving quantitative information which can be used to make appropriate clinical decisions.

Exercise testing using 14 ECG leads has its major diagnostic impact in men with typical or probable angina. A positive or negative test in conjunction with treadmill work time is highly predictive of the presence or absence of multivessel disease, thus potentially identifying a population of patients at high and low risk for coronary events. Appropriate criteria for positivity in this subset of patients are 1) horizontal or downsloping ST-segment depression \geq 1 mm, 2) ST-segment elevation \geq 1 mm, and 3) a slowly upsloping ST-segment depression \geq 2 mm at 0.08 seconds after the J point in any lead.

In men with nonspecific chest pain, false positives are frequent and the use of multiple leads can increase the false positive rate. In this group of patients, only a single lead such as CM\textsubscript{6} is necessary. If a multiple-lead system is used in selected patients, the predictive value of each of the leads used should be applied to obtain maximal diagnostic information. Appropriate criteria for positivity in this subset would be horizontal or downsloping ST-segment depression \geq 1 mm, or ST-segment elevation \geq 1 mm at 0.08 seconds after the J point. Ancillary techniques using cardiac fluoroscopy, radioactive thallium-201, displacement CKG, and radionuclide cineventriculography could improve the predictive potential of exercise-test results in this subgroup and merit further investigation.

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