Diagnostic Value of Exercise Electrocardiography and Thallium Myocardial Scintigraphy in Patients Without Previous Myocardial Infarction: A Bayesian Approach


SUMMARY The clinical value of combining exertional ECG and postexertional thallium (²⁰¹TI) scintigraphy was assessed in 160 patients (130 men and 30 women) suspected of having coronary artery disease (CAD) who underwent a coronary arteriography. Based on sex and history, the patients were subdivided in two groups with different prevalences of CAD: Group 1 (high prevalence of CAD = 90%) included 98 men with typical angina pectoris (AP) and group 2 (low prevalence of CAD = 18%) included 32 men and 30 women with atypical AP.

Compared with the exertional ECG, myocardial scintigraphy was more sensitive (87% vs 74%) and more specific (89% vs 70%) for the diagnosis of CAD. The combination of the ECG and scintigraphic data was useful if both tests gave concordant results: 100% of true positives (n = 67) and 84% of true negatives (n = 43). In case of discordant results (n = 50), no firm diagnostic conclusion could be made due to the many false-positive (27%) and false-negative (25%) scintigrams.

These results are easier to interpret when the prevalence of CAD is taken into account. According to Bayes' theorem, abnormal exercise results confirm CAD when the prevalence is high and normal results rule out CAD when the prevalence is low; also, a normal response to exercise has no predictive value when the prevalence is high. When the prevalence is low, an abnormal ECG or thallium has low predictive value but concordant abnormal responses are highly predictive for CAD (100% of true positives).

EXERCISE myocardial perfusion scintigraphy with thallium-201 is useful for detecting myocardial ischemia due to coronary artery disease (CAD) and seems more reliable than the exertional ECG.1-9

In symptomatic patients, the characteristics of the complaints are important and, from a well-taken history, one can evaluate the likelihood of CAD.6-12 Several reports on exertional ECG have indicated that the diagnostic information provided by the test was largely determined by the prevalence of the disease within the population.9, 13-17

This study was undertaken to assess the diagnostic value of exercise thallium scintigraphy and its combination with exertional ECG; in order to analyze the influence of the prevalence of CAD, the patients were subdivided in groups according to the information provided by the history. The prevalence of CAD is almost 100% after an acute myocardial infarction, so patients with a history of infarction were excluded.

Material

One hundred sixty patients, 130 men and 30 women, suspected of CAD but without evidence of a previous myocardial infarction, were studied. They underwent a multistage maximal exercise test 1 to several days before the arteriographic study. These patients were studied because of the presence of chest pain. Before the exercise test, the patients were carefully questioned by the same physician. From the clinical history, the complaints were subjectively judged to be typical or atypical of angina pectoris (AP). As in a previous study,9 this judgment was based on the location, quality and radiation of pain, the precipitating factors and the relief of pain with rest and/or nitroglycerin. The chest pain was considered typical AP when it had all characteristic features. The pain was considered atypical AP when it had no feature of AP or some but not all suggestive features.

Patients who had valvular heart diseases, cardiomyopathies, previous coronary bypass surgery, bundle branch block, ECG signs of left ventricular hypertrophy and who were under digitalis therapy were excluded; the β blockers were always interrupted 3 days at least before the exercise test.

Methods

The exercise tests were performed on a bicycle ergometer with an initial work load of 20 W for 1 minute; the exercise intensity was subsequently increased by 20 W every minute until the patient ex-
experienced a typical anginal pain or until subjective exhaustion. An isolated important depression of the ST segment was never a reason for discontinuing the exercise test.

Three orthogonal leads (X, Y and Z of the Frank system) were constantly monitored and recorded on paper every minute during the exercise and the first 5 minutes of the recovery. A 20-second ECG sample was recorded on a digital magnetic tape at the end of every minute, at rest, during the exercise and during the first 5 minutes of the recovery. These digitized ECG samples were later averaged and analyzed by computer (Modcomp II/25) using an adapted version of the program of the Thorax Centrum in Rotterdam. After rejecting all premature beats, a representative QRS complex is obtained by averaging at least 12 QRS complexes and quantitative measurements are made at 10-msec intervals before the beginning (PR) and after the end (ST segment) of the QRS complex. The amount of ST-segment depression during maximal exercise was measured 80 msec after the end of QRS with the PR interval (30 to 10 msec before QRS onset) as reference level; a horizontal ST depression of 0.1 mV or more below the resting ST-segment level was considered abnormal.

Thallium (2 mCi) was injected 1 minute before the end of the exercise test; 5-6 minutes after peak exercise, myocardial imaging started with a Searle Pho Gamma V camera using a high-resolution, parallel-hole collimator. Images (250,000 counts) were obtained in the anterior, left anterior oblique (LAO) 45° and LAO 65° positions; myocardial imaging was always completed 50 minutes after peak exercise. Reequilibration myocardial scintigrams were not obtained in all patients, and thus, were not included in the present study. Analog Polaroid images without computer processing were independently analyzed by two observers unaware of the angiographic data. In case of discrepancy (7% of the studies), the images were reanalyzed by the two observers, whose common agreement was retained.

Selective coronary arteriography was performed using a percutaneous transfemoral approach and as many injections were made in the left and right coronary arteries to provide adequate films. The angiographic study always began with left ventricular injection in the right anterior oblique position.

The coronary arteriogram was considered abnormal in presence of a reduction of 50% in diameter of at least one coronary vessel.

The following statistical values were calculated:

Sensitivity = true positives/true positives + false negatives.

Specificity = true negatives/false negatives + false positives.

% of true positives (predictive value of a positive test) = true positives/true positives + false positives.

% of true negatives (predictive value of a negative test) = true negatives/true negatives + false negatives.

Statistical analysis of the data was performed using the t test and the McNemar’s test for paired data. No complication occurred as a result of the present study.

Results

The ECG and thallium data collected during exercise are presented in table 1. The prevalence of CAD was 90% in men with typical AP and varied from 0-35% in the other subgroups.

Considering all 160 patients (table 1 and fig. 1), the thallium scintigraphy was more sensitive (87% vs 74%; p < 0.01) and more specific (89% vs 70%; p < 0.025) than the exercise ECG; the frequency of true-positive (92% vs 80%) and true-negative responses (81% vs 62%) was also higher for the thallium scintigraphy.

The maximal heart rate (HR) of the false-negative ECG responders (138 beats/min, range 102-182 beats/min) is lower (p < 0.001) than the maximal HR

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**Table 1. Data Provided by History and Maximal Exercise Testing in 100 Patients Without Previous Myocardial Infarction**

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th></th>
<th></th>
<th>Women</th>
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<tbody>
<tr>
<td></td>
<td>Typical AP</td>
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<td>All</td>
<td>Typical AP</td>
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<td><strong>n</strong></td>
<td><strong>CAD (%)</strong></td>
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<td>100</td>
<td>32</td>
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<td>130</td>
<td>72</td>
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<tr>
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<tr>
<td>ECG +</td>
<td>71</td>
<td>93</td>
<td>7</td>
<td>43</td>
<td>78</td>
<td>88</td>
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<tr>
<td>Ti +</td>
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<td>8</td>
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<td>86</td>
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<tr>
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<td>25</td>
<td>8</td>
<td>52</td>
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<tr>
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<td>2</td>
<td>100</td>
<td>63</td>
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<td>60</td>
<td>19</td>
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Abbreviations: AP = angina pectoris; CAD = coronary artery disease; Ti = thallium scintigraphy; + = abnormal response; – = normal response.
of the true negative ECG responders (160 beats/min, range 110–195 beats/min). A similar but smaller difference (p < 0.05) appears when the false-negative thallium responders (151 beats/min, range 132–187 beats/min) are compared with the true-negative thallium responders (163 beats/min, range 105–192 beats/min). However, the maximal HRs of the false-negative ECG and thallium responders are, except for one, situated within the range of the maximal HR of the true-negative ECG and thallium responders.

The four combinations of thallium and ECG data are compared with the information provided by thallium alone and ECG alone in figure 2. The association of an abnormal thallium with an abnormal ECG always indicates the presence of significant coronary lesions (100% of true positives) and it is slightly superior to an isolated abnormal thallium (92%) or ECG (80%). The frequency of true positives is much lower when the thallium and ECG data are conflicting but in such cases, an abnormal thallium has better predictive value than an abnormal ECG (73% vs 25%).

A normal scintigram with a normal ECG indicates the absence of disease in 84% of the patients, which is slightly superior to a normal scintigram alone (81%) or ECG alone (62%); when the ECG and thallium data are conflicting, a negative thallium has a better predictive value than a normal ECG (75% vs 27%).

The prevalence of CAD within each group of patients clearly influences the frequency of true-positive and true-negative responders (table 1); this observation is illustrated on figure 3, which is a comparison of the data collected in 98 men with typical AP (prevalence of CAD = 90%) to the data of the 62 other patients (prevalence of CAD = 18%). In men with typical AP, an abnormal response to exercise has a high predictive value (thallium, 99%; ECG, 93%; thallium and ECG, 100%), but in this group the predictive value of a normal response to exercise is low (thallium, 45%; ECG, 19%; thallium and ECG, 40%). When the prevalence of the disease is low (men with atypical complaints and women) a normal response to exercise has an excellent predictive value (thallium, 96%; ECG, 90%; thallium and ECG, 97%) in these patients, an abnormal response to exercise is poorly predictive (thallium, 60%; ECG, 35%) except when both tests give abnormal results (thallium and ECG, 100%). When thallium and ECG data are conflicting the presence or absence of CAD cannot be adequately predicted except in men suffering from AP, in whom an abnormal thallium associated with a normal ECG keeps an excellent predictive value (94%).

Discussion

Several reports indicate that, for the diagnosis of CAD, thallium myocardial scintigraphy is superior to the exertional ECG.1–8 These observations are confirmed by our findings, which also indicate a greater sensitivity (87% vs 74%) and specificity (89% vs 70%) for thallium scintigraphy. The ECG data reported here for the entire group are less satisfactory than in a previous study from our laboratory7 in which in 192 symptomatic patients without myocardial infarction, the sensitivity and the specificity of the exertional
ECG were 91% and 70%, respectively. This discrepancy is likely explained by the use of only three orthogonal leads instead of the 12 conventional ECG leads and because we considered only the horizontal depression of the ST segment, while many other computerized systems do not take into account the slope of the ST-segment and/or use heart-rate-dependent criteria.\textsuperscript{19, 21, 22}

When interpreting the response to a diagnostic exercise test, one must take into account both the ECG response and the myocardial scans. When the results of both tests are in agreement, as in 110 patients (69%) of the present study, an abnormal response clearly indicates the presence of CAD (100% of true positives) and a normal response strongly suggests the absence of CAD (84% of true negatives). In a similar population (no myocardial infarctions), Turner et al.\textsuperscript{4} reported a predictive value of 85% for both abnormal tests and a predictive value of 79% for both normal tests; these less satisfactory results may be partly explained by the use of submaximal target heart rate.

When the data provided by the thallium scintigraphy conflict with the results of the exercise ECG (50 patients; 31% of the group), the interpretation of the response to the test should be analyzed very cautiously because many of the responses are false positive or false negative; in this situation, thallium scintigraphy is more reliable than exercise ECG; still, no firm conclusion can be drawn (27% of false-positive and 25% of false-negative scintigrams).

It has been known for years that the probability of CAD can be accurately predicted from the history. A previous myocardial infarction is practically always attended in men by significant coronary lesions;\textsuperscript{6, 7, 9} this is also true in women, with a few exceptions.\textsuperscript{8, 23}

The patients with a previous myocardial infarction have therefore been excluded from the present study because in such patients the goals of maximal exercise testing are to measure the physical work capacity and to predict the severity and the extent of CAD.\textsuperscript{24-25}

Complaints of typical AP strongly suggest in men the presence of significant CAD and our data (90% of CAD) confirm those of other larger series.\textsuperscript{7, 9} Reciprocally, in men, CAD is unlikely when the complaints are not characteristic of AP (16% of CAD). This pretest estimation of the likelihood for CAD can be refined still further when the age is taken into account, and when the patients are subdivided in atypical AP, no anginal chest pain and asymptomatic.\textsuperscript{11} In symptomatic women, the situation is different because CAD has a lower prevalence (±50%) in the presence of typical anginal complaints\textsuperscript{8, 10} and only 35% of the women with typical anginal complaints had significant coronary lesions in this study. In women with atypical complaints, CAD is very unlikely\textsuperscript{8, 10} and it was never observed in our small sample of 13 women.

More recently, several reports over exercise ECG have indicated that the presence of angina is not a clear influence on the frequency of false-positive and false-negative responders.\textsuperscript{8, 14, 17} In agreement with the Bayes' theorem, the false-positive responses are frequent when CAD is unlikely while false-negative responses are common when CAD is likely. We have therefore divided our patients in two groups on the basis of the data provided by the history. Group I had

\textbf{Figure 3. Influence of the prevalence of coronary artery disease on the incidence of true-positive and true-negative responses to maximal exercise testing in patients suspected of having coronary artery disease.}
a high CAD prevalence (88 of 98, 90%) and included the men with typical AP. Group 2 had a low CAD prevalence (11 of 62, 18%) and included the men with atypical complaints and all women. Pooling together men and women in the same group is justified by data indicating that, by itself, sex does not influence the sensitivity or the specificity of the exertional ECG.4–10

As far as exertional ECG is concerned, our data confirm that false-positive ECG responses are frequent (13 of 20, 65%) when the pretest likelihood for CAD is low, while false-negative ECG responses are common (22 of 27, 81%) when CAD is likely from the history (men with typical AP).

A major finding of our study is that the results of thallium scintigrams are also influenced by the prevalence of CAD within the studied population. False-positive scintigrams are common (six of 15, 40%) when CAD has a low prevalence, while false-negative scintigrams are frequent (11 of 20, 55%) when CAD is likely from the history. Conversely, an abnormal thallium scintigraphy confirms the presence of CAD (77 of 78; 99% of true positives) when the complaints are characteristic of AP; in this group, a positive myocardial scan has a slightly better predictive value than an abnormal ECG (66 of 71, 93% of true positives). Also in patients with a low prevalence of CAD, the predictive value of a normal scintigraphy (45 of 47, 96%) is excellent and slightly superior to the predictive value of a normal ECG (38 of 42; 90%).

These results confirm the theoretical speculations of Hamilton et al.29,30 Moreover, this Bayesian approach remains valid when both tests give negative results: 60% (six of 10) of false-negative responders in a high-prevalence group. In patients with a low prevalence for CAD, the combination of both positive tests has an unexpectedly high predictive value (six of six, 100%), and our data confirm previous reports.31–33 Our findings are not in real disagreement with the Bayes’ theorem, as the post-test calculated likelihood for CAD in these patients with both abnormal tests and an 18% prevalence of CAD is 81%. This frequency calculated from our own sensitivity and specificity data is not very different from the 100% frequency observed in a limited sample of six patients. These conclusions should be tested on larger populations with a very low prevalence of CAD.

We conclude that the thallium scintigraphy is a reliable noninvasive method for the diagnosis of CAD and that its results should be analyzed together with the data provided by the exertional ECG. The diagnostic value of these exercise tests is, however, determined by the prevalence of CAD within the studied population. These noninvasive methods are very useful when the results confirm the clinical diagnosis based on the history. When the ECG and/or thallium data are conflicting with the pretest clinical judgment, the diagnosis remains largely uncertain and the management of the patients will depend on the judgment of the physician; in these puzzling circumstances, the additional information provided by a third diagnostic test, for instance the radionuclide exercise ventriculography, must be evaluated.

Acknowledgment

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