Diagnostic Value of History and Maximal Exercise Electrocardiography in Men and Women Suspected of Coronary Heart Disease

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SUMMARY Coronary arteriographic data have been compared in 278 patients (231 males and 47 females) with the ECG response to a maximal exercise test and with the history (myocardial infarction — MI, typical or atypical angina pectoris — AP). The sensitivity and specificity of exercise ECG were similar in males and females. False negative ECG responses were frequent in males (40%) and false positive ECG responses were frequent in females (38%). This difference between sexes was essentially due in our patients to the higher prevalence of CHD in males (80%) than in females (43%).

In the absence of a previous MI, a history of typical AP was associated with coronary heart disease (CHD) in 94% of males and 62% of females. Atypical AP was rarely associated with CHD (18% in males; 11% in females). When typical AP was associated with an abnormal exercise ECG, CHD was highly probable in males (98%) and present in 75% of females. In presence of atypical AP with a normal exercise ECG, CHD was unlikely in males (11%) and in females (8%).

We conclude that exercise ECG has limited value for the diagnosis of CHD. In men with typical AP, exercise ECG often confirms the diagnosis but a negative ECG exercise does not rule out CHD because of the high incidence of false negative responses. In males and females with atypical AP, an abnormal response to exercise is difficult to interpret owing to a high incidence of false positive responses.

EXERCISE ELECTROCARDIOGRAPHY (ECG) is a well-established method for the diagnosis of coronary heart disease (CHD). Its value has been differently assessed from correlative studies with arteriographic data and the validity of exercise ECG has more recently been questioned especially in women. Clinically, however, the results of an exercise test are never interpreted without taking into account the patient's history and complaints. The purpose of the present study was to estimate the actual contribution of exercise ECG to the overall diagnosis of CHD and thus to define its advantages and limitations. The patient's history and the ECG recorded during a test of maximally tolerated exercise were compared with the angiographic findings in a group of 278 patients.

Material

Of the 278 patients that were studied, 231 were males (mean age 48 years, range 27–65) and 47 were females (mean age 49 years; range 33–64). This group included a series of patients from January 1971 to November 1975 who had a coronary arteriographic study and within one month prior to the arteriography underwent a maximal exercise test. The majority of the exercise tests were performed one to five days before the coronary arteriography. Those patients with bundle branch block, valvular heart disease and those receiving digitalis less than three weeks before the exercise test were excluded.

The reasons for having these patients undergo exercise tests and coronary arteriography were: 1) the diagnosis of CHD in patients with complaints of typical or atypical angina pectoris (AP); 2) the presence of typical or atypical AP in patients with a previous well-documented acute myocardial infarction — MI (table 1).

Methods

The exercise tests were performed on a bicycle ergometer with a constant pedaling rate of 50 rpm. The initial workload was 20 watts for a duration of one minute. The exercise intensity was then increased by 20 watts every minute. The patients were asked to exercise until the onset of typical AP or until their complete subjective exhaustion. In order to prevent fainting after the discontinuation of exercise, the patients continued to pedal at 50 rpm but at no workload for a duration of 3 to 4 minutes. In three instances, the exercise test was interrupted by the supervising physician: twice for the appearance of an important ST-segment elevation with widening of the QRS complex and once for a ventricular tachycardia. Ventricular tachycardia was observed immediately after exercise in four additional cases but never required electrical defibrillation. No other major complications were observed.

Before the exercise test, the patients were carefully questioned by the supervising physician and their charts were reviewed. From the clinical history, the complaints were subjectively judged to be typical or atypical of AP; this judgment was based on 1) the location, quality and radiation of pain, 2) the precipitating factors and 3) 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 features of AP or some features suggesting AP but not definitely so. When the supervising physician could not classify the pain into one of these two groups, the pain was arbitrarily considered atypical AP. A diagnosis of previous MI was based on characteristic resting ECG and/or on a characteristic history with positive enzymatic findings.

A twelve lead ECG was recorded at rest in supine and in sitting position; the limb electrodes were attached to the torso, V₄, V₅ and V₆ precordial leads were constantly monitored during exercise on an oscilloscope and recorded.
on paper every minute. A twelve lead ECG was recorded during exercise every five minutes, at the maximal exercise level and at the third and sixth minute of the recovery. Expiratory gases were usually collected during the last minutes of exercise and analyzed as previously reported.18

All ECG records were analyzed independently from the arteriographic data by one of the authors. The ECG were visually analyzed and the amount of ST-segment depression or elevation was measured in every lead at the J point with the PR level used as zero reference. The ST-segment abnormalities already present at rest were subtracted from the observed changes. The ECG response to exercise was considered as abnormal in presence of: 1) a horizontal or downsloping ST depression ≥ 0.1 mV for at least 0.08 sec; 2) an elevation of the ST segment ≥ 0.1 mV. The ECG abnormalities were usually observed during exercise and were most marked at the maximal exercise level. Only five of the 214 abnormal ECG responses were observed only after exercise. The mean maximal heart rate was 150 per minute in men and in women.

The coronary arteriography was performed through the femoral artery using preshaped catheters.19 The angiographic studies always began with a left ventricular injection in the right oblique anterior position. As many injections as necessary were made in the left and right coronary arteries to provide adequate films. The major complications of this procedure were two acute MI with no death. An anterior MI occurred at the end of the procedure in a patient with a 75% stenosis of the LAD and a poor distal bed; a patient with a 75% stenosis of the RCA developed an inferior MI 6 hours after the procedure. All films were independently reviewed by one of the authors. The coronary arteriography was considered abnormal in presence of a decrease of 50% in diameter of at least one coronary vessel; C+ = absence of significant coronary lesion; E+ and E− refer to an abnormal and normal ECG response to exercise.

The data concerning every patient were keypunched on ribbons and analyzed by computer using a Computer Conversational Statistical System (CCSS). The following parameters were calculated:

- **sensitivity** = true positives/true positives + false negatives
- **specificity** = true negatives/true negatives + false positives
- **true positives** = true positives/true positives + false positives
- **false positives** = false positives/true positives + false positives
- **true negatives** = true negatives/true negatives + false negatives
- **false negatives** = false negatives/true negatives + false negatives

Statistical analysis of the data was performed using the Chi-square test and the Student’s t-test.

Informed consent was obtained from every patient.

### Results

In the present group of patients, CHD was more frequent in men than in women (80% versus 43%; \( P < 0.001 \); table I).
All patients with a history of MI had significant CHD. In the absence of a previous MI, symptoms of typical AP were associated with significant CHD in 94% of the men and 62% of the women ($P < 0.01$); these percentages were slightly but nonsignificantly higher in the patients who experienced typical AP during the exercise test itself (96% in men and 71% in women). When the complaints were atypical, CHD was present in 18% of the men and 11% of the women.

The maximal heart rate (HR) was always lower in patients with a history of typical AP since the exercise test was often interrupted for the onset of AP (table 1); the latter was observed in 71% (105/147) of the men and 54% (15/28) of the women with a history of typical AP. In men with a history of atypical AP, the mean maximal HR was 151 in those with a previous MI and 165 in those without a previous MI ($P < 0.001$); these HR correspond to 89% and 96% of the predicted maximal HR. In women with a history of atypical AP, the mean maximal HR was 162 which corresponds to 93% of the predicted maximal HR.

In all 278 patients (231 men and 47 women), the sensitivity of ECG during maximal exercise was 86% (176/204) and the specificity 70% (52/74). The sensitivity and specificity of exercise ECG were slightly higher in men than in women (table 1). False negative ECG responses were more frequent in men (40% vs 19%; $P < 0.10$) while the false positive ECG responses were more frequent in women (38% vs 7%; $P < 0.001$). Among the men without a previous MI, false negative responses were frequent (56%) when typical AP was present; false positive responses were frequent in men (67%) when the complaints were atypical. It is apparent from table 1 that the differences existing between sexes and those among a given sex are related to differences in the prevalence of CHD. In our patients, when CHD was uncommon (women; men or women without AP) the false positive responses were frequent and when CHD was frequent (men; men with AP) the false negative responses were frequent.

The false positive responders (table 1; fig. 1) had in both sexes a significantly higher maximal HR than the true positives responders (165 vs 144 in men, $P < 0.001$; 172 vs 136 in women, $P < 0.001$). In men and in women this difference is largely due to the fact that the true positive responders include many patients with typical AP and a low maximal HR; the majority of the men with a false positive response belong to the group of patients with a history of atypical AP and in this group, the maximal HR of false positive responders is slightly less than that of true positive responders (164 versus 168).

The false negative responders (table 1; fig. 1) had in both sexes a significantly lower maximal HR than the true negatives responders (156 vs 166 in men, $P < 0.001$; 142 vs 153 in women, $P < 0.001$).

Since significant coronary lesions were seen in all patients with a history of MI, exercise ECG has a limited diagnostic value in this subgroup. Therefore the diagnostic value of exercise ECG in the patients without a previous MI will now be examined.

In these patients (table 2), when typical AP is associated with an abnormal ECG response to exercise, 98% (86/88) of the men and 75% (15/20) of the women have significant CHD. When atypical complaints are associated with a normal ECG response to exercise, only 11% (4/35) of the men and 8% (1/13) of the women have significant coronary lesions. In the presence of a discrepancy between history and exercise ECG (abnormal ECG with atypical complaints or normal ECG with typical AP), 42% (10/24) of the men and

### Table 2. Correlation between Exertional ECG, History and Arteriographic Data in Patients without Previous Myocardial Infarction

<table>
<thead>
<tr>
<th>Presence of CHD</th>
<th>History of typical AP</th>
<th>Exertional ECG</th>
<th>All patients</th>
<th>Patients with AP during the test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td></td>
<td>N %</td>
<td>N %</td>
</tr>
<tr>
<td>Yes</td>
<td>Abn</td>
<td>15/20</td>
<td>95/95</td>
<td>95/95</td>
</tr>
<tr>
<td>Abn</td>
<td>1/6</td>
<td>1/6</td>
<td>1/6</td>
<td>1/6</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td></td>
<td>N %</td>
<td>N %</td>
</tr>
<tr>
<td>Yes</td>
<td>Abn</td>
<td>15/20</td>
<td>95/95</td>
<td>95/95</td>
</tr>
<tr>
<td>Abn</td>
<td>1/6</td>
<td>1/6</td>
<td>1/6</td>
<td>1/6</td>
</tr>
</tbody>
</table>

Abbreviations: Abn = abnormal; NI = normal.

### Table 3. Type of ECG Response to Exercise and Arteriographic Data

<table>
<thead>
<tr>
<th>ECG response to exercise</th>
<th>Number of diseased vessels (stenosis $\geq 50%$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Normal</td>
<td>35</td>
</tr>
<tr>
<td>ST depression $\geq -0.1$ mV</td>
<td>12</td>
</tr>
<tr>
<td>ST elevation $\geq +0.1$ mV</td>
<td>9 (3)*</td>
</tr>
<tr>
<td>Normal</td>
<td>17</td>
</tr>
<tr>
<td>ST depression $\geq -0.1$ mV</td>
<td>9</td>
</tr>
<tr>
<td>ST elevation $\geq +0.1$ mV</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

*The numbers in parentheses indicate the patients with ST elevation who had also a significant ST depression in another reciprocal lead.

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**Figure 1.** The filled circles indicate the mean; the vertical bars are placed at ±1 standard deviation and the arrows indicate the range. The numbers refer to the number of cases in each group. 
TP = true positive; FP = false positive; TN = true negative; FN = false negative.
These correlations are not significantly different in the patients who experienced typical AP during the exercise test.

ECG abnormalities during exercise were not significantly related to the number of diseased vessels (table 3). Of the men with single vessel disease 79% (37/47) had an abnormal exercise ECG vs 90% (60/67) of those with triple vessel disease. In patients with a previous MI, however, ST-segment changes with exercise were more frequent in those with three vessel disease (31/35; 89%) than in those with single vessel disease (9/14; 64%; P < 0.05).

In men (table 3) ST-segment elevation during exercise was not frequent, but when present was highly specific for CHD (30/30; 100%). The majority (23/30; 77%) of these patients had a prior MI; among the seven other patients, four suffered from variant angina pectoris. The occurrence of ST-segment elevation during exercise was often accompanied by impaired left ventricular function (table 4). After an MI, the onset or aggravation of ST-segment elevation during exercise was associated in 21 of 23 cases (92%) with an akinetic or dyskinetic left ventricular segment.

The degree of the ST-segment depression also influences the data (table 5). A 100% specificity was noted for a 0.4 mV depression of the ST segment but this finding had a very low sensitivity.

Discussion

It is important to discuss first whether or not the exercise tests performed by the patients were really maximal. The mean maximal HR of men (150) and women (150) correspond to ± 85% of their predicted maximal HR; this rather low percentage of the predicted maximal HR is essentially due to the inclusion of patients with a history of typical AP. Many of these patients experienced typical AP during the exercise test and the latter prevented their predicted maximal HR from being reached. The patients without previous MI and with complaints of atypical AP reached 93% (women) and 96% (men) of their predicted maximal HR, which indicates that the intensity of the exercise was sufficient to elicit near-maximal to maximal HR. In patients with a previous MI but atypical AP, the maximal HR was lower (± 85% of the predicted maximal HR); similar values of maximal HR have been observed previously in such patients.21 It should be remembered that all our patients were instructed to exercise until the onset of symptoms or until subjective exhaustion and that they all cooperated very well. From a clinical point of view, the exercise tests were therefore really maximal since the patients were unable to exercise further; this raises the question whether or not predicted values of maximal HR measured in completely asymptomatic subjects are applicable to patients referred for symptoms of atypical AP.

Many previous reports correlating exercise ECG with coronary arteriography included a significant number of patients with a history of MI as well as a small and variable percentage of women. The sensitivity (86%) and specificity (70%) of exercise ECG observed in all patients in our study are in general agreement with previous studies using similar methods.1,2,7,8 Our data, as well as those of others,22-14 clearly indicate, however, that the diagnostic value of exercise ECG varies according to the history and the sex of the patients.

Patients With a Previous MI

In our group of men, a history of MI was always associated with significant coronary lesions.22 Our data in women do not allow any valid conclusion because this subgroup was too small. The existence of myocardial infarction with normal coronary arteries has been documented in women.23

ST-segment changes with exercise in post-MI patients were more frequent in patients with three vessel disease than in those with single vessel disease (89% vs 64%; P < 0.05) and they were more frequently recorded in patients with residual AP (90% vs 71%). These data may help explain the poorer prognosis of post-MI patients with an abnormal ECG response to exercise.21

The onset or the aggravation of an ST-segment elevation during exercise was observed in 23 patients with a history of MI; 21 of these patients (92%) had akinetic or dyskinetic left ventricular segments. This association already mentioned by others22-24 is of clinical importance and appears to be more specific than the association between the persistence of an ST-segment elevation on the resting ECG and the presence of left ventricular asynergic zones.25-28

Patients Without a Previous MI

In men, the clinical diagnosis correlated very well with the arteriographic data since 94% of those with typical AP had significant CHD while 82% of those with atypical complaints had normal coronary arteries. In women, the clinical diagnosis is much less reliable since only 62% of the women with typical AP had significant CHD. No satisfactory explanation has yet been offered for angina-like symptoms with normal coronary arteries in women although their prognosis appears to be good.29-32 The occurrence of AP during the exercise test itself had no more diagnostic value than the presence of a history of typical AP.

Our data in patients with typical AP are practically identical with those previously reported by others in larger groups of men and women.21,28,29 The prevalence of CHD in

**Table 4. ST-Segment Elevation during Exercise and Left Ventriculography (N = 231 men)**

<table>
<thead>
<tr>
<th>Left ventriculography</th>
<th>All patients</th>
<th>Patients with a previous MI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>Normal</td>
<td>6/108 (5.6)</td>
<td>1/13 (7.7)</td>
</tr>
<tr>
<td>Hypokinesia</td>
<td>2/48 (4.2)</td>
<td>1/20 (5.0)</td>
</tr>
<tr>
<td>Akinesia</td>
<td>10/44 (22.7)</td>
<td>9/30 (30.0)</td>
</tr>
<tr>
<td>Diskinesia</td>
<td>12/22 (54.5)</td>
<td>12/21 (57.1)</td>
</tr>
</tbody>
</table>

17% (2/12) of the women have significant CHD (table 2). These correlations are not significantly different in the patients who experienced typical AP during the exercise test.

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**Table 5. Influence of the Degree of ST-segment Depression during Maximal Exercise (213 men)**

<table>
<thead>
<tr>
<th>ST-segment depression</th>
<th>N</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>False positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 0.1</td>
<td>154</td>
<td>86%</td>
<td>74%</td>
<td>7</td>
</tr>
<tr>
<td>≥ 0.2</td>
<td>120</td>
<td>67%</td>
<td>84%</td>
<td>7</td>
</tr>
<tr>
<td>≥ 0.3</td>
<td>79</td>
<td>45%</td>
<td>92%</td>
<td>5</td>
</tr>
<tr>
<td>≥ 0.4</td>
<td>42</td>
<td>25%</td>
<td>100%</td>
<td>0</td>
</tr>
</tbody>
</table>

*Eighteen patients with isolated ST-segment elevation during exercise have been excluded.*
our patients with atypical AP appears to be low since other studies have indicated a prevalence of CHD varying from 26 to 46%;23, 29, 30 in these studies, the patients with chest pain but whose clinical diagnosis was "normal or probably normal" were considered separately from those with atypical AP, which was not done in the present study due to the smaller number of patients. When the patients quoted by Welch et al.24, 29, 30 as normal, probably normal and atypical AP are pooled together, their prevalence of CHD is 12% in women and 18% in men, which is similar to our findings.

In patients without previous MI, the sex does not significantly influence the sensitivity (91% in males; 89% in females) nor the specificity (74% in males; 63% in females) of exercise ECG. Sketch et al.11 also reported equal sensitivity and specificity in men and women. The lower sensitivity (51% in males and 45% in females) observed by these authors could partly result from their lower maximal heart rate.

False positive and false negative results are strongly influenced by the sex. False positive results were frequent in women (38%) and rarely observed in men (7%) while false negative results were frequent in men (40%) and much less frequent in women (19%). Sketch et al.11 made similar observations but offered no satisfactory explanation for their findings. It should be recalled here that the significance of a diagnostic test depends not only on its accuracy but also on the prevalence of the disease in the population under study. When a disease is frequent many false negative results are observed; conversely, when a disease is rare, many false positive results are observed.14, 26 The differences between sexes have therefore to be examined taking into account the prevalence of CHD, which in the present population is low in women and high in men (43% vs 80%; P < 0.001). This difference is largely responsible for the difference in the relative frequency of false positive and false negative results.

The influence of the prevalence of the disease is also clearly apparent when men and women are considered separately. As previously observed,4 false positive results were more frequent (67%) in the men with atypical complaints (low prevalence of CHD); they were practically absent (2%) in the men with typical AP (high prevalence of CHD). Conversely, false negative responses were frequent (56%) in men with typical AP (high prevalence of CHD) and unfrequent (11%) in men with atypical complaints (low prevalence of CHD). The same trend has also been observed in women although the number of cases is smaller. It is interesting to note that 80% of false positive responses were observed in women with atypical complaints (very low prevalence of CHD).

The aforementioned explanation fits very well with our data and probably helps to explain the very high incidence of positive responses observed in so-called "healthy middle-aged" women.24, 26 Assuming a prevalence of CHD of 10% in such women, and applying our values of sensitivity (89%) and specificity (63%) in women without MI, one can calculate that 42.2% of all women tested would have a positive response to exercise. The calculated result is close to the published results.24, 26 Among these positive responses, 70% would be falsely positive.

In both sexes, the false positive responses are associated with significantly higher maximal HR than the true positive responses while the false negative responders have lower maximal HR than the true negative responders. These findings are difficult to interpret correctly due to the small numbers of both false positive and false negative responses and to the wide range of maximal HR in all groups (fig. 1). The latter precludes a consideration of the maximal HR as a major factor directly responsible for the false positive responses in men or for the false negative responses in women. In women, it is tempting to incriminate the high maximal HR as being responsible for the false positive responses but the maximal HR was above 175 (highest value observed in true positive responses) in only three instances. In men, the negative ECG responses were always falsely negative when the maximal HR was below 135; this may help explain only four of the 24 (17%) false negative responses. It can therefore be concluded that very low or very high maximal HR possibly play a role in a few cases of false negative responses in men or false positive responses in women but that this factor is probably not a major one due to the many cases where its role cannot be incriminated.

The combination of history and exertional ECG allows a better diagnostic approach to patients suspected of CHD. In men, the diagnosis of CHD is highly probable when both history and exercise ECG are positive (98% of true positive) while it is unlikely when atypical complaints are associated with a normal ECG response to exercise (89% of true negative). When there is a discrepancy between history and exercise ECG, it is not possible to establish in men a reliable diagnosis without performing coronary arteriography. In such cases, the probability of having CHD varies from 33 to 56%, which is in agreement with previously published series.1, 2, 30

In women, the diagnosis of CHD should be considered only when typical complaints are associated with an abnormal ECG response to exercise. In such cases, coronary arteriography should be performed since 25% of these women have normal coronary arteries. In other conditions, namely a discrepancy between the history and the exercise ECG, or when both are negative, the presence of CHD is very unlikely in women.

Finally, the significance of the degree of ST-segment depression should be mentioned. The more the ST segment is depressed, the more likely is the presence of significant CHD. Very abnormal responses to exercise are indeed highly specific but they are infrequently observed.1, 5, 30

We conclude from the present study that exercise ECG has a limited value for the diagnosis of CHD. In men with typical AP, exercise ECG most often confirms the diagnosis but a negative ECG response does not rule out the diagnosis of CHD. In men with atypical complaints, exercise ECG is difficult to interpret owing to the numerous false positive responses. In women, the diagnosis of CHD cannot be established reliably from the history nor from the ECG response to exercise; when the complaints are atypical, exercise ECG has no value in women because of the numerous false positive responses.

Acknowledgment

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