False Positive Diagnostic Tests and Coronary Angiographic Findings in 105 Presumably Healthy Males

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SUMMARY Among 2014 presumably healthy males aged 40–59 years coronary heart disease (CHD) was suggested in 115 in the presence of one or more of the following criteria: 1) a WHO-questionnaire on angina pectoris positive on interview, 2) typical angina during a near maximal bicycle exercise test, 3) a positive exercise ECG during and/or post exercise, 4) a Minnesota Code 1.1 on a resting ECG. Diagnostic coronary angiography was offered to all 115 CHD-suspect cases. Six refused angiography and four others were excluded.

IN CLINICAL MEDICINE it is hazardous to extrapolate from findings in one population to another population if the two are selected in different ways, and particularly so from the findings in hospitalized patients to the population in general.

The aims of the present study are: 1) to define the prevalence of previously undetected coronary heart disease (CHD) among presumably healthy males aged 40–59 years by means of predetermined criteria, and 2) to validate these criteria by means of coronary angiography in individuals fulfilling one or more of these criteria.

Material and Methods

The base population of approximately 2000 males represents working, presumably healthy males, coming from five preselected firms or state agencies in Oslo, Norway. All men with known CHD, other heart disease, hypertension under treatment, diabetes mellitus, malignancy, disorders of the locomotive system preventing a near-maximal bicycle exercise test and miscellaneous disorders (advanced pulmonary disease, renal disease, liver disease, etc.) were excluded. Of the eligible men 86% came for the examination which included a comprehensive case history, complete physical examination, laboratory tests, lung function tests, X-ray of the heart, phonocardiogram, resting ECG and exercise and post exercise ECGs during a near maximal bicycle exercise test (on an electrically braked Elema bicycle). In the case history the World Health Organization questionnaires (WHO-Q; see appendix) on angina pectoris was included, and this was checked according to accepted procedures.

All came for the examination at 7:30 a.m. after at least 12 hours' fasting.

The exercise test was a step-wise test with a duration of six minutes on each load, starting with 600 Kpm (~100 watts) in all but 2% (who because of poor physique started with 300 Kpm ~50 watts). Increments were made by 300 Kpm. Of the remaining 105, thirty-six had less than 50% obstruction of any major coronary artery (34.3%). Eighteen (17.1%) had single, 25 (23.8%) had double and 26 (24.8%) had triple vessel disease. In 62 of the 69 with pathologic angigrams at least one obstruction ≥75% was found. Eighty percent of the cases with proven CHD were ≥50 years. All CHD-suggestive criteria had approximately the same diagnostic performance regardless of age, i.e., approximately one false positive/two true positives. Except for one retroperitoneal hematoma no complications to angiography occurred.

Before the test a resting, supine and sitting 12-lead ECG was taken as well as a resting chest-head ECG on the bicycle (CH_1, 2, 3 and 6 minutes on the first load, at 2, 4 and 6 minutes on all other loads as well as immediately before the break of the test. CH-leads were then followed in the immediate 30 seconds post exercise, sitting on the bicycle and at 1 minute resting, supine. At 2, 3 and 5 minutes post exercise standard 12-lead ECGs were recorded. Additional ECGs were taken according to oscilloscopic findings. Common precautions were taken during the test, and unless specific symptoms or signs contraindicated continuation, each subject was asked to continue until at least 90% of maximal predicted heart rate (MHR) was reached. If the individual seemed fit after a MHR of 90% + 10 beats was reached on one load, a usual increment of 300 Kpm was made, and the test was continued until symptoms or signs necessitated break or until a full load of 6 minutes was reached. The tests were, however, always stopped before complete exhaustion.

All ECGs were coded according to the Scandinavian Modification of the Minnesota Code (MC). All individuals with a definitely pathologic or borderline exercise ECG (see below) had a repeat exercise test performed within two weeks. Repeat exercise tests were also performed in individuals who fulfilled other CHD-suggestive criteria as well as in individuals with illnesses and/or electrolyte aberrations during the first test. During the survey all pathologic and borderline ECGs (including the repeat ECGs) were read by two of the authors, and a joint decision was made concerning the necessity for further examination. In the rare cases where disagreement still existed after a thorough examination and discussion of the ECGs, the exercise ECG was defined as negative.

After finishing the survey all ECGs were read and reread blindly by two of us. In all who came for angiography the same ECG-conclusion was reached as was reached during the survey. However, seven additional cases were read as definitely pathologic on the second occasion. These seven cases have not been examined further, and as the diagnosis was made after completion of the survey, they have not been counted as CHD-suggestive cases. These criteria for a suspect CHD were used: 1) a resting
ECG-code of MC 1.1-type, 2) a positive WHO-Q on interview (i.e., not solely on filling-in), 3) typical angina pectoris during the exercise test, 4) a positive exercise ECG during and/or post exercise.

The following criteria for a positive exercise ECG have been used: a) A horizontal or downward sloping ST-segment \( \geq 1.5 \text{ mm} \geq 0.08 \text{ seconds} \) from the J-point in CH\( _{2,3} \), or a \( \geq 1.0 \) mm ST depression in I, II, aV\(_{L}\), aV\(_{R}\), V\(_{5,7}\). Reference level was PR-(Q)-line. b) An ST depression which was upward sloping from the J-point, but which regardless of slope, was \( \geq 1.5 \) mm below the isoelectric line \( \geq 0.08 \) seconds from the J-point in CH\( _{2,3} \), or \( \geq 1.0 \) mm below the isoelectric line in I, II, aV\(_{L}\), aV\(_{R}\), V\(_{5,7}\).

For the sake of simplicity "a" has been labelled 4.1 ischemic type = 4.1 i and "b" 4.1 slowly ascending type = 4.1 s.9

If one or more of the above mentioned criteria were present, each individual was told that a strong suspicion of CHD existed, and he was offered a coronary angiogram for the evaluation of this problem. They were all thoroughly informed about the procedures, risks and possible benefits, and in all who later came for coronary angiography an informed consent was obtained.

If an ST depression was present in the resting, supine ECG, additional 1.5 (or 1.0 in standard 12 lead ECG) mm ST depression in the exercise ECG had to be present for a test to be called positive. We have disregarded ST abnormalities of the vasoregulatory type during the exercise test.7 In individuals with positive exercise recordings the time from break to "normalization" of the ECG had been noted. "Normalization time" is defined as the time (in seconds) taken from break of the test until the ST segment no longer fulfills the criteria for positivity.

Coronary angiography was performed within 2–3 months of the first examination in all but four cases.

Coronary Angiography

On each of the two days preceding angiography the patients were given 1.0 g acetylsalicylic acid orally. Within half an hour of the procedure 0.6 mg atropline sulphate was given subcutaneously. Nitroglycerin 0.5 mg was administered after the local anesthesia was given, and every 20 minutes thereafter.

Selective cine coronary angiography was performed according to Judkins.8 Left and right anterior oblique and left lateral projections were used, with additional projections when needed, the patients being rotated in a cradle (Rotacor, Cordis Corporation). The contrast material was Isoopaque Coronar (metrizoate meglumine [Na/Ca/J] [58/911/370 mg/ml]). Preshaped catheters were used (Ducor, Cordis Corporation), and injections were made by hand pressure. Cine recordings were made by a 35 mm Arriflex camera with image intensifier, running at 75 frames/second. In order to assess the necessity for additional projections, immediate preliminary studies of the angio-films were made with a video tape recorder (OD-X 40 Old Delft, Holland).

The degree of stenosis of the coronary arteries was assessed by comparing the diameter of the stenotic area with the prestenotic part in at least two projections. All measurements were made by the two angiographers with the help of a Tagarno 35, 3 film analyzer (Tagarno, Denmark). For an angiogram to be called positive an obstruction of a major coronary artery \( \geq 50\% \) had to be present (significant obstruction). An obstruction of \( \geq 25\% \) but less than \( 50\% \) has been called minimal disease, while a less than \( 25\% \) obstruction was considered normal. Only lesions of the main arteries and their major secondary branches were considered.

All angiograms were read blindly on two separate occasions at least three months apart. After the second reading had been made the first readings were reconsidered, and a consensus was easily made in most cases. In cases of major disagreement the angiograms were scrutinized on a third occasion, and these findings were used as the final recordings.

Significant obstructions of one, two or three major coronary arteries and/or their major branches have been labelled one, two and three-vessel disease.

The time from insertion of the first catheter into the femoral artery to the extrusion of the last catheter was measured with a stopwatch, mean catheterization time being 16.30 minutes (SD 4.30 minutes, range 9.10 minutes – 35.00 minutes).

The patients were hospitalized 1–3 days before the procedure and all but one left the hospital the day after angiography. A meticulous search for complications was made, in particular looking for possible cerebral embolism, myocardial infarction, bleeding from the femoral artery, thrombosis and early or late arrhythmias.

Statistical Methods

Tests of significance used were t-test and Chi-square, applied through the Biomedical Programs 1F and 3D.

Results

In all, 2014 men (mean age 49.8 years, SD 5.5 years) were examined according to the protocol, of whom 115 (5.7%) fulfilled one or more CHD-suggestive criteria. Six refused angiography, while 109 gave their consent. Four were excluded later; two because they were found to have slight aortic valve disease, and two because of inability to perform the angiography by the femoral approach due to occluded iliac arteries. The study thus comprises 105 individuals, 91.3% of those eligible for angiography.

Table 1 shows the distribution of arterial obstructions related to age. Thirty-three (31.4%) had normal coronary angiograms, three (2.9%) had minimal disease of one or more vessels, 18 (17.1%) had one vessel disease, 25 (23.8%) had two vessel disease and 26 (24.8%) had three vessel disease. At least one significant obstruction was found in 3/9

<table>
<thead>
<tr>
<th>Age</th>
<th>Normal coronary angiogram</th>
<th>1VD</th>
<th>2VD</th>
<th>3VD</th>
<th>m(_{1})</th>
<th>m(_{2})</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 – 44</td>
<td>6(2)*</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>9</td>
<td>396</td>
</tr>
<tr>
<td>45 – 49</td>
<td>4</td>
<td>3</td>
<td>4</td>
<td>4</td>
<td>15</td>
<td>572</td>
</tr>
<tr>
<td>50 – 54</td>
<td>14</td>
<td>5</td>
<td>10</td>
<td>7</td>
<td>36</td>
<td>520</td>
</tr>
<tr>
<td>55 – 59</td>
<td>12(1)*</td>
<td>10</td>
<td>9</td>
<td>14</td>
<td>45</td>
<td>419</td>
</tr>
<tr>
<td>60 – 65</td>
<td>36(3)*</td>
<td>18</td>
<td>25</td>
<td>26</td>
<td>105</td>
<td>1907</td>
</tr>
</tbody>
</table>

*Individuals with minimal disease only.
\(m_{1}\) = total number studied by angiography in each age group.
\(m_{2}\) = total number not studied by angiography in each age group.
patients in age group 40-44, 11/15 in age group 45-49, 22/36 in age group 50-54 and 33/45 in age group 55-59. The distribution of correct vs false positives is similar above and below 50 years.

Our criteria thus have a false positive score of approximately 1/3 in all age groups. There is a significantly higher number of individuals with CHD in the higher age groups.

Table 2 summarizes the indications for coronary angiography in the various age groups. Twenty had a positive WHO-Q, 23 had angina during the exercise test, 85 had a positive ECG during and 79 a positive ECG post exercise. Only two had a Minnesota Code 1.1.

Table 3 shows the angiographic findings with reference to the various diagnostic criteria taken singly. Each criterion obtained approximately the same proportion of significant obstructions, namely two correct positives/one false positive.

During exercise the distribution of slowly ascending pattern vs ischemic pattern (4. 1 s codes vs 4. 1 i codes) was similar in the different angiographic subgroups. Hence the two patterns had similar diagnostic performance during exercise. After exercise a significantly higher number of individuals had a 4. 1 i response than during exercise. The 4. 1 i pattern was significantly more often related to CHD than the 4. 1 s pattern (P < 0.01).

Table 4 presents the diagnostic performance of the various combinations of criteria found. For the sake of simplicity the two individuals with a MC 1.1 have been omitted, leaving 103 cases. In several of the subgroups the numbers are very small, but it is seen that false positives exist in almost all subgroups, even in one individual who presented with all four indications for coronary angiography. Sixteen had a single criterion, ten of whom had positive and six a negative angiogram. Seventy-five had two criteria; 48 had a positive and 27 a negative angiogram. Seven had three criteria and two of these had normal angiograms while one of five with four criteria had a normal coronary angiogram. Statistical analysis indicates that no single criterion or combination of criteria were superior to the others in this group.

In 75 of the 103 cases presented in table 4 a positive ECG during and/or post exercise was the only clue to a diagnosis of CHD. Angina with or without ECG changes was present in the remaining 28 cases. Thus angina during exercise tests and/or a positive WHO-Q had a poor sensitivity in this material. The data in table 4 also indicate that the presence of angina was no more reliable than the exercise ECG only.

Table 5 shows the distribution of vessels affected singly or in combination. Disregarding minimal disease, in all but ten cases the left anterior descending artery (LAD) was involved. In all but seven cases (five with one vessel disease and two with two vessel disease) at least one obstruction ≥75% was found. However, the number of individuals with the latter response during exercise is small.

Complications to Angiography

Three individuals had a transient vaso-vagal reaction. Two technical failures occurred due to obstruction or obstructive lesions of both iliac arteries (both had bilateral intermittent claudication), and these two individuals have been excluded from the material. In one of these an attempt to advance the catheter past the obstruction caused a partial perforation of the left common iliac artery, and a retroperitoneal hematoma occurred which was treated conservatively without sequelae. His claudication was unchanged after discharge from the hospital, and he is doing well ap-

<table>
<thead>
<tr>
<th>Table 2. CHD-suspect Criteria in the Different Age Groups</th>
<th>Age groups</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive WHO questionnaire on angina</td>
<td>40-44</td>
<td>45-49</td>
</tr>
<tr>
<td>Angina pectoris during exercise test</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Positive exercise ECG</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Positive postexercise ECG</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>Minnesota Code 1.1 in resting ECG</td>
<td>7</td>
<td>11</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 3. Relation Between the Various CHD-suspect Criteria and Coronary Angiographic Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication for angiography</td>
</tr>
<tr>
<td>Positive WHO questionnaire on angina</td>
</tr>
<tr>
<td>Angina during exercise test</td>
</tr>
<tr>
<td>Positive exercise 4.1-s*</td>
</tr>
<tr>
<td>ECG 4.1-i*</td>
</tr>
<tr>
<td>Positive postexercise 4.1-s*</td>
</tr>
<tr>
<td>ECG 4.1-i*</td>
</tr>
<tr>
<td>Minnesota Code 1.1 in resting ECG</td>
</tr>
</tbody>
</table>

*Codes according to the Scandinavian Modification of the Minnesota Code.

<table>
<thead>
<tr>
<th>Table 4. Distribution of CHD-suspect Criteria and Combination of Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Criterion*</td>
</tr>
<tr>
<td>Q</td>
</tr>
<tr>
<td>A</td>
</tr>
<tr>
<td>D</td>
</tr>
<tr>
<td>P</td>
</tr>
<tr>
<td>Q</td>
</tr>
<tr>
<td>QD</td>
</tr>
<tr>
<td>QAD</td>
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<tr>
<td>QAP</td>
</tr>
<tr>
<td>QDP</td>
</tr>
<tr>
<td>QD</td>
</tr>
<tr>
<td>QADP</td>
</tr>
</tbody>
</table>

*Q = Positive questionnaire on angina pectoris; A = Angina pectoris during exercise test; D = Positive exercise ECG during exercise; P = Positive exercise test post exercise.
proximately two years later. No instance of myocardial infarction or serious rhythm disturbances occurred, nor peripheral embolism, thrombosis or clinically detectable hematomas.

**Discussion**

The rational use of various symptoms and signs in the diagnosis of CHD must be based on the knowledge of their sensitivity, specificity and validity. However, most of our knowledge concerning various criteria is based on findings in symptomatic, hospitalized populations. It may be hazardous to extrapolate from such populations to the general population, and even from a population in one country to a seemingly similar population in another. Very little is known about the validity of the accepted CHD-criteria in the general population, which still ought to be known for the sake of progress in our understanding of CHD-epidemiology and for the sake of prevention. Our data indicate the following:

Detectable CHD increases by age, nearly 4/5 of our cases being above 50 years. There is no significant difference in the proportion of correct vs false positive cases above and below 50 years.

Epidemiological research has mostly to rely on such crude estimates of CHD as questionnaires. We have included the WHO-Q on angina pectoris, partly because it is widely adopted and partly because, as far as we can see, it has never been validated by coronary angiography in the general population. Twenty of the men studied by angiography (1% of the presumably healthy base population) had angina pectoris according to the WHO-Q although they had never reported their complaints to any physician. The presence of normal angiograms in seven of this group indicates that the commonly held view that this questionnaire is insensitive but fairly specific may be unwarranted in the general population.

Of the 23 who experienced angina during the exercise test, 17 had significant obstructions. In the group studied by angiography this sign had a sensitivity of 17/69 (24.6%) and a specificity of 30/36 (83.3%). This is an acceptable specificity but a poor sensitivity. However, the occurrence of typical angina and negative coronary angiograms has been reported repeatedly.

We have seen only two papers dealing with the relation between pathologic exercise ECGs and coronary angiography in more or less asymptomatic individuals. The work of Froelicher et al., however, included several individuals accepted for flying programs, and most of their cases were referred from a large base population because of pathologic resting ECGs and/or borderline or pathologic Master’s two-step tests. The work of Borer et al. is also highly biased as it only comprises individuals with significant hypercholesterolemia. Females are included, and probably only part of their study population had not sought medical advice. A different exercise protocol was used in their work, and the age limits indicate that the mean age was lower than in our investigation. With this criticism in mind these papers suggest a poorer validity of exercise ECGs than we have found. Our exercise and post-exercise ECGs have a diagnostic score of some 65% despite our inclusion of ST changes of the slowly ascending pattern. Perhaps one of the reasons may be a different age composition. Although there was no significant difference in distribution of true and false positives above and below 50 years in our material, six of nine CHD-suspect individuals in the youngest five year age-group were false positives.

Of our material is not a random sample of the general population, and we do not know what sort of bias may have been introduced by our mode of selection. However, as 86% of the eligible men came for the examination and 91% of the 115 men with suggestive signs of CHD had high-quality angiograms, our data ought to be fairly representative of this particular population. Still our figures represent minimal figures of CHD, and only follow-up may indicate the number of false negatives in the total material.

A study like this can only validate the various criteria for a diagnosis of CHD. By means of coronary angiography we may easily and reliably pick up the true and false positive cases. However, for the assessment of sensitivity and specificity in the general population we would have to perform coronary angiography in completely asymptomatic individuals without ECG signs of CHD. Such an approach is
Our exercise ECGs were positive in 85 cases, of whom 16 had a 4.1 i and 69 a 4.1 s pattern. Twenty-nine (31.1%) of these 85 had normal coronary angiograms with a distribution of four 4.1 i and twenty-five 4.1 s patterns. In the 69 with positive angiograms the distribution of 4.1 i and 4.1 s in one vessel disease, two vessel disease and three vessel disease was 2/13, 5/15 and 5/16, respectively. There is thus astonishingly no significant difference in diagnostic score between the more pathological 4.1 i and the less pathological 4.1 s when these criteria are applied to our in-exercise tracings. Seventy-eight percent (78.5) of the angio-positive and eight-six percent (86.1) of the angio-negative cases had a 4.1 s pattern during exercise.

Post exercise a significantly higher number had 4.1 i than during exercise (table 3), namely 32 4.1 i and 47 4.1 s vs 16 4.1 i and 69 4.1 s during exercise (P < 0.001). The 4.1 i pattern is also significantly more often related to CHD than 4.1 s post exercise (P < 0.01). The assumption that 4.1 s is a less pathologic response thus seems to hold true post exercise while no difference was seen during exercise in our group. The more rapid normalization of the 4.1 s pattern in the angio-negative cases seen in this material must also be taken into consideration when judging the significance of particular ECG-responses as signs of suggestive CHD.

While most workers in this field use a ≥1.0 mm horizontal ST depression as the sole sign of ischemia, 13, 16-25 we have included the slowly ascending ST pattern, as have Ellestad and Wan26 and McHenry et al.27 If we had used 4.1 i as the sole ECG-criterion we would have obtained a considerable decrease in sensitivity without a concomitant increase in specificity. Of our 69 patients with positive angiograms 58 had a positive exercise ECG during and/or post exercise (table 4). This constitutes a sensitivity of 84%. Only 11 cases were picked up by the other criteria, which emphasizes the importance of the exercise ECG in the early detection of CHD. In fact, 48 of these 58 cases had a positive exercise ECG as the sole sign.

We have disregarded ST abnormalities of the vaso-regulatory type as it has been postulated that such changes are related to normal coronary angiography.7 This is at variance with the statement of Froelicher et al.19 This important question therefore remains unsettled.

Froelicher et al.19 suggest that a 50% obstruction as a sign of ischemic heart disease is too strict, and they suggest that far less advanced obstructions may limit flow during exercise due to inhibition of coronary vasodilatation. As far as we know this is purely speculative, although a "flitter effect"28, 29 might explain such an occurrence. The opposing view is that an obstruction does not limit flow until at least 70% of the vessel is obstructed.28, 29 Our data are at variance with the suggestions of Froelicher et al., and rather corroborate the latter view. Only three of our 105 individuals had minimal disease, and the finding of these few cases may have been purely fortuitous. Also, only five with one vessel disease and two with two vessel disease had significant obstructions in the range of 50-75%, i.e., 62 of the 69 angio-positive cases had at least one obstruction ≥75% in a major coronary artery or a main secondary branch. This of course does not imply that lesser obstructions are unimportant.


Appendix

London School of Hygiene Cardiovascular Questionnaire

Section A. Chest Pain on Effort

1. Have you ever had any pain or discomfort in your chest?
   Yes No

2. Do you get it when you walk uphill or hurry?
   Yes No Never hurry

3. Do you get it when you walk at an ordinary pace at the level?
   Yes No

4. What do you do if you get it while you are walking?
   Stop or slow down Carry on

5. If you stand still, what happens to it?
   Relieved Not relieved

6. How soon?
   10 minutes or less
   More than 10 minutes

7. Will you show me where it was?
   Sternum (upper or middle)
   Sternum (lower)
   Left anterior chest
   Left arm
   Other

8. Do you feel it anywhere else?
   Yes No

9. Did you see a doctor because of this pain (or discomfort)?
   Yes No

10. If yes, what did he say it was?

Diagnostic Criteria of Angina Pectoris

1. Yes

2 or 3 Yes

4. Stop or slow down

5. Relieved

6. 10 minutes or less
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