False suspicion of coronary heart disease: a 7 year follow-up study of 36 apparently healthy middle-aged men

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ABSTRACT Latent coronary heart disease was suspected in 115 of 2014 apparently healthy middle-aged men after a baseline cardiovascular survey. One hundred five of these men underwent angiography and 36 were found to have normal coronary arteries (group 1). A 7 year follow-up survey revealed that: (1) three had died of sudden cardiac death, (2) four had received a diagnosis of cardiomyopathy, (3) one had developed aortic dilatation/aortic regurgitation since the baseline survey, (4) they all had a significantly more rapid decline in their physical performance and maximal heart rate levels from the time of the baseline survey to follow-up than did randomly selected normal controls (group 2), and (5) thallium study results were normal in both groups (27 and 26 patients), but technetium ventriculography revealed a subnormal increase in ejection fraction during exercise (< 5% units) in 14 of 27 group 1 subjects and in 4 of 26 group 2 subjects. Thus, incipient heart disease may be present in subjects in whom coronary angiographic examination has removed a previous suspicion of coronary heart disease.


EXERCISE ELECTROCARDIOGRAPHIC (ECG) testing is valuable in the evaluation of patients with chest pain and as a screening procedure in apparently healthy subjects.1–6 In addition to the ST segment response, important information is obtained through the study of parameters such as maximal heart rate obtained, level of exercise reached, blood pressure response, and symptoms or signs that develop during the test.1, 6–8

According to Baye’s rule, the extrapolation of the prognostic value of positive exercise test results in patients with clinical symptoms or signs of coronary heart disease (CHD) to asymptomatic, apparently healthy subjects is unwarranted. A high proportion of such subjects have normal coronary arteries,4, 9, 10 and little is known of the long-term prognostic impact of positive stress tests.

This study reports the clinical course of a group of middle-aged, apparently healthy men with positive stress test results during the time period of a cardiovascular survey, but in whom coronary angiography revealed normal findings. The report covers a follow-up period of 6 to 9 years (average 7 years).

Material and methods

During the years 1972 through 1975, 2014 apparently healthy men from 40 to 59 years old underwent examination for the cardiovascular disease survey. The main aim, as reported in detail elsewhere, was to search for CHD that previously was neither diagnosed nor suspected.7, 10 According to the selection/inclusion criteria, none of the survey participants had any suspected CHD or other heart disease, none used drugs known to influence resting/exercise ECG results, and all were free from other specified diseases.7, 10 The examination programs for the baseline and follow-up studies are given in table 1.

Men fulfilling any of the criteria listed in table 2 were considered to have suspected latent CHD and were asked to undergo coronary angiographic examination to confirm or exclude this diagnosis.

According to the survey findings, the patients were subdivided into groups as shown in figure 1. Of 115 with suspected latent CHD, 109 gave their informed consent for coronary angiography. The 105 satisfactory angiograms that were obtained showed that 69 subjects had pathologic and 36 had normal coronary arteries. The clinical reasons that latent CHD was suspected in these 36 men are listed in table 2. Thirty-three had completely normal coronary arteries, and three had minor, hemodynamically insignificant irregularities.

For the purpose of this study, performed 6 to 9 years after the one described above, the “angionegatives” were assigned to group 1, and the men participating as control subjects (group 2) were selected as follows. Each time one of the men from group 1 was examined, the next man to be examined was designated a normal control subject, provided he belonged to the normal...
TABLE 1  
Baseline and follow-up examination programs*  
(1) A comprehensive case history (including WHO angina questionnaire and New York Health Insurance Plan Survey questionnaire on angina)  
(2) Full clinical examination and spirometric studies.  
(3) A panel of blood tests (an intravenous glucose tolerance test [IVGTT], and insulin response to the IVGTT)  
(4) Phonocardiography, resting electrocardiogram, and near-maximal bicycle exercise electrocardiographic test  
(5) X-ray film of heart and lungs  
(6) Platelet function studies* and study of coagulation factors*  
(7) Selective coronary angiography in men with strong suspicion of latent CHD after informed consent  
(8) Isotope studies of myocardial perfusion and left ventricular function at rest and during exercise*  
(9) Echocardiography*  

Tests not labeled B, C, or D were performed in all individuals during both surveys.  
 Studied in all, but only during the baseline survey.  
 Studied in subgroups during baseline study.  
 Studied in subgroups only during follow-up examination (and in particular in all group I and II subjects; see text).  

group during the baseline study (figure 1), had not had a coronary event during the follow-up period, had a normal second exercise ECG, and did not use cardioactive drugs. The additional radionuclide studies (see below) were done in 27 of the men from group I (for various nonmedical reasons it could not be done in the remaining five still alive), and we therefore selected 27 normal controls. One of these was later excluded because he developed angina pectoris 6 months after the second study, even though all findings during the follow-up were normal.  

Exercise testing. Exercise testing was performed as reported elsewhere,7,10 and the technique was identical during the survey and the exercise testing with respect to thallium scanning. Approximately 98% of all exercise tests both at the baseline and follow-up were performed by the same investigator, and all tests were performed by using the same calibrated, electrically braked Elema bicycle. End points of the exercise tests were angina, ST depression of 3 mm or more, severe dyspnea, fatigue/exhaustion, arrhythmias, or any combination of these factors. Chest-lead CH7,2 were recorded during and immediately after exercise and 12-lead ECGs were recorded before and for 1, 2, 3, and 5 min after exercise. A positive exercise test result was defined as one in which ST depression was 1.5 mm or more 0.08 sec from the J point in CH7,2, or 1 mm or more in leads I, II, aVF, aVL, or V5,7, irrespective of whether the ST segment was upward or downward sloping or horizontal.7,10 During the base-

TABLE 2  
Criteria for a diagnosis of latent CHD during the baseline survey of 2014 apparently healthy men 40 to 59 years old and criteria/combinations of criteria fulfilled in 36 men with normal coronary angiograms  

Criteria  
Positive WHO questionnaire on angina pectoris ( = Q +)  
Angina pectoris during near maximal bicycle exercise ECG test ( = A +)  
Positive exercise ECG during exercise ( = D +)  
Positive exercise ECG after exercise ( = P +)  
Resting ECG finding of an 1.1-type Minnesota Code  

Findings among the 36 anginegative men  
Q + n  = 2  
A + n  = 2  
D + n  = 2  
Q + A + n  = 2  
D + P +  
Q + A + P +  
Q + D + P +  
Q + A + D + P +  

n  = 25  
(n  = 1)  
(n  = 1)  
(n  = 1)  

Positive exercise ECG with or without angina pectoris, n = 30  
Angina pectoris as the sole CHD-indicating finding, n = 6  

Criteria for a diagnosis of latent CHD during the baseline survey of 2014 apparently healthy men 40 to 59 years old and criteria/combinations of criteria fulfilled in 36 men with normal coronary angiograms  

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Findings among the 36 anginegative men  
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A + n  = 2  
D + n  = 2  
Q + A + n  = 2  
D + P +  
Q + A + P +  
Q + D + P +  
Q + A + D + P +  

n  = 25  
(n  = 1)  
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study subjects with ST depression induced by hyperventilation or by an orthostatic test were excluded from the angiographic study, as reported previously.7

**Radionuclide procedures.** 201Tl (60 MBq) was injected into the antecubital vein when peak load was reached and 90 sec before termination of the exercise test. Immediately after exercise and 5 hr later images were obtained in three views by collecting 200,000 counts per image. Cardiac scintigrams were obtained with a GE scintillation camera (Maxicamera 400 T) with a hardware 2:1 zoom. The camera was interfaced to an Intertechnique cine 330 data system.

Radionuclide ventriculography (multiple gated acquisition ventriculography, MUGA) was performed at equilibrium after in vivo labeling of erythrocytes with 900 MBq 99mTc-pertechnetate and with the same equipment used during the thallium studies. The detector was located in the 40 degree left anterior projection. The detector was adjusted to maximize separation of left from right ventricle. Counts of 1,500,000 were stored in a list mode together with an ECG R wave physiologic trigger. After acquisition at rest the gated-pool study was repeated in exactly the same left anterior oblique position 30 sec after the subjects had immersed one hand into ice cold water in every second subject from both groups. Whether or not this cold pressor test MUGA (CP-MUGA) was performed, a symptom-limited exercise test as described above was performed by all patients while supine, the scintigrams were recorded beginning when the limiting load was reached. Thus, one-half the subjects underwent three and one-half only two MUGA tests. The details on the isotope techniques applied have been described previously.11

In five angionegative men sufficiently severe symptoms developed during follow-up to warrant a second complete left and right heart catheterization. In four of these a myocardial biopsy was also performed.

**Statistical analysis.** Student's t test and the chi-squared test were used to study possible statistically significant differences between groups. A two-tailed p < .05 was regarded as statistically significant.

**Results**

During the 7 year follow-up period three angionegative men died from cardiac causes. Two of them developed signs of heart failure before sudden death, and the third died suddenly without previous symptoms. Furthermore, five men had symptoms sufficiently severe to warrant a second invasive study. In four of these increased left ventricular end-diastolic pressure (LVEDP) was observed both before and after ventriculography (i.e., LVEDP > 12 mm Hg before and > 20 mm Hg after ventriculography). All four had myocardial biopsy results consistent with the diagnosis of cardiomyopathy,12,13 and all had a cardiac index in the lower normal range. The fifth man restudied had developed a mild aortic valve incompetence and marked aortic and left ventricular dilatation (table 3A). In addition, one subject who did not want to be restudied had developed increasing, incapacitating angina pectoris, and one showed signs of severe, localized ischemia, without other signs of heart disease, during CP-MUGA (table 3B).

The exercise test data from the two groups are listed in table 4. The baseline physical work performance and maximal heart rate were significantly lower among the group 1 than among group 2 subjects. At follow-up, 31 subjects from group 1 showed a significantly more pronounced drop in maximal heart rate (p < .05) and possibly also in physical performance than the normal subjects (.05 < p < .10). Twelve group 2 subjects and 24 group 1 subjects had a decrease of 1 min or more in exercise time at follow-up compared with at baseline (p < .05). These differences could not be explained by our having selected a particularly fit group of normal controls. Thus, analysis of the baseline exercise data in the 1832 group 2 subjects (figure

**TABLE 3A**

<table>
<thead>
<tr>
<th>Seven year follow-up findings in 36 angionegative men related to baseline study indicators of possible latent CHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>**Baseline indicators (n)</td>
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AP+/− = angina pectoris present or not present; exercise ECG +/− = pathologic exercise ECG or not.

^aMUGA response to exercise: a = increase by ≥ 5%; b = by 0% to 4% units; c = decrease by 1% to 9%; d = by ≥ 10%. ND = not done.

^bSevere perfusion defect and regional dyskinesia in one man during CP test.
TABLE 3B
Summary of 7 year follow-up findings in 36 angionegative men

<table>
<thead>
<tr>
<th>Finding (n)</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite cardiac pathology (8)</td>
<td>Cardiac deaths (n = 3) and pathologic findings on heart catheterization/myocardial biopsies (n = 5) during follow-up period</td>
</tr>
<tr>
<td>Probable cardiac pathology (2)</td>
<td>Decrease in EF during exercise by ≥ 10%</td>
</tr>
<tr>
<td>Questionable data (1)</td>
<td>Increasing, incapacitating angina in one man not restudied (refused)</td>
</tr>
<tr>
<td>Coronary artery spasm (1)</td>
<td>Pronounced ischemia in the LAD tributary during CP test, normal perfusion during exercise</td>
</tr>
<tr>
<td>Possible cardiac pathology (6)</td>
<td>Decrease in EF during exercise by 1% to 9% and normal thallium scans</td>
</tr>
<tr>
<td>Normal findings (6)</td>
<td>Normal thallium scans and EF increase during exercise by 1% to 5%</td>
</tr>
<tr>
<td>Normal findings (12)</td>
<td>Normal thallium scans and EF increase in response to exercise by ≥ 5%</td>
</tr>
</tbody>
</table>

1) indicated an age-related drop in maximal heart rate and work performance by 0.75 beats/year and 120 kpm/year, respectively. This implies that men from group 2 showed a drop in work performance and maximal heart rate of a magnitude that would be predicted for a 7 year follow-up period.

Apart from the exercise test result virtually no difference was apparent between the two groups in physiologic and biochemical parameters such as blood lipids, body dimensions, blood pressure, spirographic values, heart size, and smoking habits (data not shown). Three of the patients in group 1 had completely normal exercise ECGs at follow-up, whereas the remaining 28 tested had the same (or more pronounced) pathologic findings indicated in table 2.

Resting ejection fraction (EF) according to MUGA was normal in both groups of subjects at rest (table 5). During exercise EF increased somewhat less in group 1 than in group 2 (p = .06). As shown in figure 2, six group 1 subjects had a drop in EF during exercise; this is in contrast to the group 2 subjects in whom this did not occur. Eight subjects in group 1 (including the four with pathologic myocardial biopsies/increased LVEDP) and four of those in group 2 showed an EF response of less than 5%. As shown in figures 3 and 4 the response of EF to exercise was homogeneous in group 2 and the response in group 1 was widely scattered.

The CP-MUGA test did not allow discrimination between the groups, and in a high proportion of cases the EF dropped during CP in both groups (data not shown).

The thallium scans during exercise were normal in all but one group 1 subject. He showed a considerable drop in EF during CP, and obtained a major filling defect in the left anterior descending coronary artery tributary during the test. The drop in EF was caused by a regional dyskinesia in this area. Otherwise, we could not detect any regional abnormalities in the contraction pattern of the left ventricle during any of the tests.14 A blinded restudy of the baseline angiograms

TABLE 4
Exercise test data from baseline and 7 year follow-up study in groups 1 and 2

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline examination</th>
<th>Follow-up examination</th>
<th>Levels of significance for group differences</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1 (A, n = 36)</td>
<td>Group 2 (B, n = 26)</td>
<td>A vs B A vs C B vs D C vs D</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>56.7 ± 5.4</td>
<td>55.2 ± 5.9</td>
<td>NS</td>
</tr>
<tr>
<td>Observation time (yr)</td>
<td>6.5 ± 0.6</td>
<td>6.7 ± 1.2</td>
<td>NS</td>
</tr>
<tr>
<td>MHR (beats/min)</td>
<td>159.6 (164.1) ± 13.9</td>
<td>172.8 ± 9.6</td>
<td>C A A C</td>
</tr>
<tr>
<td>MBP (mm Hg)</td>
<td>217 ± 26</td>
<td>218 ± 23</td>
<td>NS NS NS NS</td>
</tr>
<tr>
<td>TW (kpm)</td>
<td>9816 (10,654) ± 4129</td>
<td>12092 ± 3816</td>
<td>A B A A</td>
</tr>
</tbody>
</table>

MHR = maximal heart rate; MBP = maximal blood pressure during exercise; TW = total work performed.

Values are mean ± SD. Values in parentheses represent baseline MHR and TW for the 31 who performed the follow-up exercise test.

*p < .05; p < .01; p < .001; NS = not a significant group difference (p > .10).

Second exercise test performed in 31 group 1 subjects.
TABLE 5
EF at rest and during exercise among men with a false-positive exercise ECG and among healthy control subjects of similar age

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Angio-negative (n = 27)</th>
<th>Normal negative (n = 26)</th>
<th>Level of significance for differences between angio-negative and normal subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting EF</td>
<td>67.1 (27)</td>
<td>68.5 (26)</td>
<td>NS</td>
</tr>
<tr>
<td>SD</td>
<td>8.0</td>
<td>7.0</td>
<td></td>
</tr>
<tr>
<td>Exercise EF</td>
<td>70.4 (27)</td>
<td>77.2 (26)</td>
<td>( p &lt; .05 )</td>
</tr>
<tr>
<td>SD</td>
<td>11.7</td>
<td>7.2</td>
<td></td>
</tr>
<tr>
<td>Resting CP test EF</td>
<td>68.2 (13)</td>
<td>73.2 (14)</td>
<td>( p = .06 )</td>
</tr>
<tr>
<td>SD</td>
<td>7.6</td>
<td>6.9</td>
<td></td>
</tr>
</tbody>
</table>

NS = not significant (\( p > .10 \)).

showed identical results, i.e., completely normal coronary arteries were observed in 33 and minor irregularities in three subjects. Apart from a positive exercise ECG during the second test, no other abnormalities were found in the latter three men; specifically, none had developed symptoms or resting ECG signs indicative of CHD.

Echocardiographic examination revealed no signs of valvular disease in any of the men reported in this study, and in particular no mitral valve prolapse was apparent.

Discussion

Coronary angiography was performed prospectively during the baseline study of apparently healthy men in order to confirm or refute the suspicion of CHD that existed after the survey examination. Of the 115 patients suspected to have CHD, 109 underwent angiography (four were excluded for various reasons). Sixty-nine were found to have significant CHD, and 36 had normal coronary angiograms. Since no other available data suggested heart disease, these 36 were considered to have healthy hearts. However, the 7 year follow-up has disclosed too many cardiac events to warrant adherence to this primary conclusion. For example, three men had died from cardiac causes, two of them possibly from cardiomyopathy, and five had de-

![Figure 2](http://circ.ahajournals.org/)

**FIGURE 2.** EF at rest and during near maximal exercise in four men with proven cardiomyopathy (□), 23 angionegative men (●), and 26 normal (○) middle-aged men.
developed symptoms that necessitated a second invasive investigation after some years. Although all five also had normal coronary arteries at the second study, increased LVEDP indicated cardiac dysfunction in all, and myocardial biopsy results suggested cardiomyopathy in four.

Significant myocardial disease had thus developed in eight of the 36 angionegative men at follow-up. Furthermore, less conclusive data suggest that a considerable proportion of the remaining subjects might not be considered to have completely healthy hearts for the following reasons: (1) The angionegative men as a group obtained a significantly lower maximal heart rate and work performance during the baseline study.

FIGURE 3. Directional change in work performance from baseline to follow-up examination (ordinate) in relation to directional change of EF during exercise (abscissa). Arrowheads present follow-up values for work performance and exercise values for EF. □ = men with proven cardiomyopathy; ● remaining angionegative men studied.

FIGURE 4. Directional change in work performance from baseline to follow-up examination (ordinate) in relation to directional change of EF during exercise (abscissa). Arrowheads represent follow-up values for work performance and exercise values for EF.
than the randomly selected control group. (2) The heart rate and work performance of subjects in group 1 declined more between the first and second exercise tests. (3) The isotope studies indicated a mild-to-moderate aberration in left ventricular function in several of the angionegative men. However, despite normal thallium scans and normal EF at rest in all subjects, the exercise MUGA showed an increase in EF of less than 5% in 14 of 27 group 1 subjects in contrast to four of 26 group 2 subjects, and in six subjects from group 1 (and in none of the subjects in group 2) EF dropped below resting values during exercise. An increase in EF of 5% or more is said to represent the normal response to exercise.\textsuperscript{15-17} These MUGA-determined differences could not be explained by differences in heart or left ventricular size,\textsuperscript{16} and local changes in contractility could not be found. These isotope findings are to some extent similar to data reported recently in patients with chest pain and normal coronary angiograms. However, these studies have been in symptomatic patients, whereas the majority of our subjects were asymptomatic. Moreover, a high proportion of the above-mentioned patients were women.\textsuperscript{19, 20}

Our results are in contrast to the commonly accepted view that the finding of normal coronary arteries in individuals with suspected CHD carries an excellent prognosis.\textsuperscript{21-25} There are several possible explanations for these discrepancies, such as differences in age and sex distribution between groups, differences in symptoms, and differences in the intensity of the search for confounding conditions that might explain a positive exercise test result. We have only dealt with carefully selected men within a restricted age range; before the survey all subjects with known or suspected heart disease were excluded, as were subjects using drugs known to influence resting or exercise ECG.\textsuperscript{7, 10} Before accepting an exercise ECG as pathologic, orthostatic changes or those induced by hyperventilation were also ruled out, and an M mode echocardiogram had confirmed normal valvular movements. The great majority of our patients had a pathologic exercise ECG as the sole pathologic finding, and our follow-up study is therefore essentially a study of the long-term implications of a positive exercise ECG in men with normal coronary arteries (table 2).\textsuperscript{7, 10}

To what extent differences in subjects, methods, and length of follow-up account for differences in results is uncertain. However, our study seems to be unique in the use of coronary angiography prospectively as a diagnostic aid in apparently healthy subjects with positive exercise ECGs. Besides, follow-up studies usually do not include repeated exercise testing. Instead, much of the information on the clinical course in patients with normal coronary arteries is obtained through questionnaires, telephone contact, or through the patients’ physicians.\textsuperscript{21-25} It is conceivable that important information may be lost in such studies.

Our results indicate that even when normal coronary arteries are found, one should be cautious in labeling a positive exercise ECG as false, since it may be an early sign of heart disease. In the light of the follow-up findings, it is tempting to speculate on whether the baseline clinical findings in this series — i.e., a pathologic exercise ECG with or without angina pectoris in the presence of normal coronary arteries — may be an early sign of cardiomyopathy in a number of cases. This seems probable based on results in three of our patients who died and the five who were restudied angiographically. The significance of the MUGA and exercise test results can only be determined by further follow-up. The underlying causes for the positive exercise ECGs and/or angina are obscure. However, it is known that coronary artery dilatory capacity is reduced in some cases of cardiomyopathy, and some patients with angina and normal coronary arteries produce lactate during pacing.\textsuperscript{26-29} No search for these more subtle myocardial functional changes was made in this study, and the relevance of such findings is therefore unknown to us.

We are not aware of prospective studies in which attempts to define early development of cardiomyopathies have been made. Once patients are referred for diagnostic evaluation because of definite symptoms, congestive cardiomyopathy deteriorates rapidly.\textsuperscript{30, 31}

Some of our suggestions are based on the contrasts between the angionegative and the normal subjects, and the applicability of these conclusions depends on having a repeatable technique and a control group free from bias. By definition, all subjects in group 2 were survivors, whereas three from group 1 had died. Otherwise our selection criteria, and the very high response rate of 92%\textsuperscript{8} to the follow-up study, strongly indicate that the findings in our control subjects should be reasonably representative of what happens to healthy, middle-aged men over a 7 year period.

In conclusion, normal coronary arteries in patients with suspected CHD do not exclude incipient heart disease. Since the majority of our men underwent angiography solely on the basis of a pathologic exercise ECG, an ST depression in the absence of angina pectoris should not be considered an innocuous finding even when unexplained by drugs, functional disorders, or other conditions known to influence the ST segments during exercise.\textsuperscript{1, 4} Although the short-term
mortality was low in our subjects, long-term prognosis may be poorer than average in the light of the increased cardiac morbidity and the subnormal response to exercise and isotope studies found in several of the angino-
negative men.

References
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