Exercise test, history, and serum lipid levels in patients with chest pain and normal electrocardiogram at rest: Comparison to findings at coronary arteriography

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In several clinical and pathologic studies[1-5] the electrocardiogram (ECG) taken at rest was found to predict atherosclerotic heart disease in a disappointingly low proportion of cases. The same was discovered in practically all studies relating the ECG to findings at coronary arteriography[6-10]; in our own material the ECG taken during rest was found to be normal in as many as 51 per cent of the patients with angiographically proved obstructive coronary artery disease.[6,10]

In order to derive more diagnostic information from the electrical activity of the heart, exercise tests are widely employed. For this purpose Master's[14] two-step test has been used universally for many years. However, judging from the literature, there is a growing inclination to use graded exercise tests (GXT) with maximal or submaximal work load instead. While the GXT would seem more promising from a theoretical standpoint, there is still a relative lack of published data to substantiate this supposition. We have examined the results of a GXT and a modified Master's two-step test in data from 96 patients with chest pain and a normal ECG taken at rest. The results were compared to findings at coronary arteriography.

The purpose of this study was to gain better information relative to: (1) the diagnostic value of the two exercise tests, (2) the discriminative value of commonly applied criteria, (3) the diagnostic information which can be derived from various diagnostic parameters (exercise tests, history, and serum lipid levels*) singly and jointly.

Material, methods, and criteria

Patient material. From the total data of more than 1,000 selective coronary arterio-

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*Vectorcardiograms were also taken in all cases. However, since a selection was made of patients with a normal ECG, the results of the vectorcardiographic studies were not included.

grams (CAG's) performed in our department, a series of 96 patients, all recently studied because of chest pain, was selected. Requirements for inclusion in this series were: (a) the ECG taken at rest had to be essentially normal (cases with slight atypical repolarization disturbances or slight intraventricular conduction disturbances, however, were not excluded); (b) no other cardiac abnormalities than those related to ischemia should be present. There were 11 women and 85 men; ages ranged from 30 to 63 years (mean age, 46.2 ± 6.2 years).

Coronary arteriography (CAG). All patients underwent selective coronary arteriography following Sones' technique,[16] with the use of multiple left and right anterior oblique projections. The 5 inch field of an interchangeable 5 and 9 inch Philips image intensifier, linked with a cine-pulse unit, was employed. Recordings were made on 35 mm. film with a speed of 60 frames per second.

Classification of the severity of arterial disease was made according to the severest narrowing in any of the major branches (right coronary artery, main left coronary artery, anterior descending and circumflex branches). The following arbitrary grading system was used: Grade 0, normal; Grade 1, vascular wall irregularities causing narrowings of less than 50 per cent of the lumen diameter; Grade 2, more than 50 per cent narrowing but no occlusion; Grade 3, total occlusion.

Graded exercise test (GXT). Digitalis preparations were withheld for 3 weeks prior to the test. No antianginal drugs (including beta-blocking agents) were administered on the day of testing; a light breakfast was allowed.

A calibrated bicycle ergometer was used. Exercise was begun with a work load of 15 watts and was augmented in steps of 15 watts every 90 seconds until any of the following appeared: (1) angina pectoris, (2) inability of the patient to continue, (3) ischemic S-T depressions $\geqslant$ 0.2 mv., (4) heart rate exceeding 170 beats per minute, (5) repetitive ventricular extrasystoles, and (6) atrioventricular conduction disturbances.

Extremity electrodes were placed as described by Mason and Likar[11]; 6 precordial electrodes were placed in standard positions, careful attention was paid to electrode attachment and skin preparation.

Recordings were made throughout the entire procedure with an 8 channel ink-jet recorder (Elema Mingograf 81) with paper speeds of 25 and 100 mm. per second and an amplitude calibration of 1 mv. per centimeter. A special switching network allowed rapid, successive registration of two groups of 6 leads.

The test was considered to be positive if an ischemic S-T segment depression[12,13] $\geqslant$ 0.1 mv. was observed in any lead. The diagnostic value of other responses was also studied.

The double two-step test. A double two-step test according to the method of Master[14] was performed in 91 patients of this series. The set of exploring leads recommended by Master was replaced by a single lead as described by Yu and Soffer.[15]

History. The patient's history was taken in the usual way; in addition questionnaires were used which were filled out by the patient himself. Typical angina pectoris was considered to be present if the localization of the pain included some area of the left hemithorax and if the following criteria were fulfilled: (1) the pain had to be provoked by physical effort, (2) the pain might, in addition, be precipitated by emotions, cold, and sexual intercourse, and (3) the pain should not occur without explicit inducement. The criteria appeared to have optimal discriminative value in previous association studies,[6,10] in which the agreement with the CAG could not be improved by taking into account other features such as radiation, quality, and duration of the pain. Chest pains, which did not meet these criteria were listed as atypical.

Laboratory methods. The serum cholesterol was determined according to the method of Rappaport (sulfosalicylic acid and acetic anhydride), and the serum beta-lipoprotein was determined with the beta-L test (Hyland); the length of the precipitate column was taken as a measure for the beta-lipoprotein content. Fasting specimens were used.

Statistical methods.[6,10,17] The various diagnostic parameters (exercise tests, history, and serum lipids) were considered as "predictors" concerning the presence or absence of obstructive coronary artery disease. The

CAG was considered to represent the reality. Only binary statements (yes-or-no) were admitted.

In order to display conveniently the relation between prediction and reality in the entire series, use was made of contingency tables (Table I). In the table, a_1 through a_4 represent the number of correct-positive, false-negative, false-positive, and correct-negative predictions, respectively. For each parameter the fraction correct-positive predictions of the total number of positive cases $(\frac{a_1}{a_1 + a_2})$ and the fraction correct-negative predictions of the total number of negative cases $(\frac{a_4}{a_3 + a_4})$ was calculated.

The fact that two figures are required to characterize the relation between prediction and reality makes the comparison of the diagnostic performance of different parameters less perspicuous. Therefore, in addition a single association index was calculated, for which purpose the "index of merit" (T) devised by Kuipers[17] was applied:

$$T = \frac{a_1}{a_1 + a_2} + \frac{a_4}{a_3 + a_4} - 1$$

It follows that T ranges from 0 (no association) to 1 (perfect association).

Standard deviations were also calculated:

$$s^2 \ (T) = \frac{[4p(1-p)]^{-1} - T^2}{\sum_i a_i} \quad \text{in which}$$

$$p = \frac{a_1 + a_2}{\sum_i a_i}.$$

Results

Coronary arteriographic findings. Application of our grading scale in the 96 patients yielded the following distribution: Grade 0, 41 patients; Grade 1, 11 patients; Grade 2, 22 patients; Grade 3, 22 patients. Thus there were 52 subjects in whom the coronary arteries were either normal or showed only slight narrowings (Grades 0 and 1). These subjects were considered to have a negative CAG.

In the other 44 patients (Grades 2 and 3) the CAG was classified as positive. A total of 24 occlusions was noted in the 22 patients of Grade 3, the localization being as follows: right coronary artery, 14; anterior descending artery, 7; and circumflex branch, 3.

Table I. *Contingency table;* a_1 *through* a_4 *represent the numbers of correct-positive, false-negative, false-positive, and correct-negative predictions, respectively*

		Prediction	
		+	−
Reality	+	a_1	a_2
	−	a_3	a_4

Graded exercise test (GXT).

RESPONSES AND RELATION TO THE CAG. The positive (ischemic) and negative (nonischemic) responses and the distribution over the 4 grades of the CAG are presented in Fig. 1.

In 29 subjects an ischemic response (sagging, 10; horizontal, 19) was noted. In 26 of these patients the CAG was positive (more than 50 per cent narrowing, Grades 2 and 3); in the other 3 patients the CAG was negative (Grades 0 and 1).

The remaining 67 patients had a negative GXT. This was associated with a positive CAG in 18 subjects and a negative CAG in 49 patients. Among the 18 false-negative responders there were 6 patients (out of 7 in the total material) with isolated obstruction of the right coronary artery; in the remaining 12 patients the arteriographic abnormalities were basically the same as in the 26 correct-positive subjects.

The responses observed in the subjects with a negative GXT were the following: no change or junctional depression < 2 mm., 55 patients; junctional depression $\geqslant 2$ mm., 9 patients; repetitive ventricular extrasystoles, 3 patients. Of the 9 patients with a junctional depression of 2 mm. or more, only 3 had a positive CAG; in 1 of the 3 with repetitive ventricular extrasystoles, the CAG was also positive. Thus, in both categories the number of the posi-

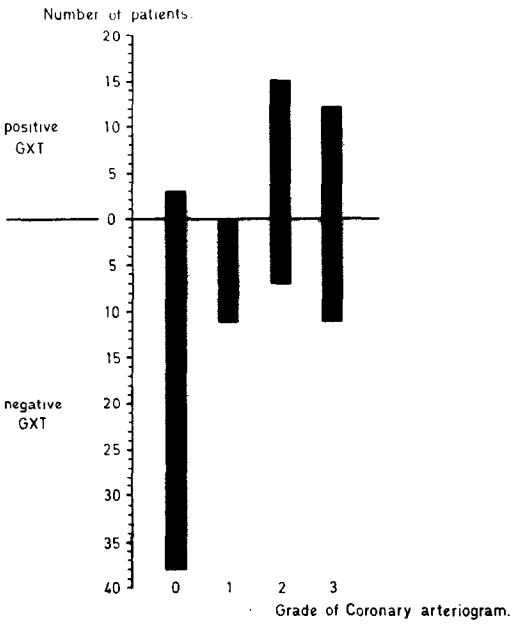

Fig. *1.* Results of the graded exercise test (*GXT*). Distribution of positive and negative cases over the 4 grades of coronary arteriogram.

tive CAG's was below the a priori probability and these criteria had to be considered as nondiscriminative.

THE INDEX OF MERIT. From the results described in the preceding paragraph the contingency table (Table II) can easily be derived. It follows that the correct-positive fraction $= \frac{26}{44} = 0.59$, and the correct-negative fraction $= \frac{49}{52} = 0.94$. The index of merit $= 0.53$ ($\pm$ 0.08).

LOCALIZATION OF ISCHEMIC S-T CHANGES. In the 29 positive responders a total of 84 ischemic S-T segment changes was detected (Table III). There were 6 patients in whom ischemic changes occurred in the extremity leads (I, II, III, aV_L, or aV_F). However, in all these patients ischemic responses were also noted in the precordial leads, which actually appeared even earlier than those in the extremity leads. With regard to the precordial leads, it appeared that ischemic changes in Leads V_3 and V_4 were invariably associated with ischemic changes in Leads V_5 or V_6. In other words, recording of Leads V_5 and V_6 only would have sufficed to detect all positive cases! It might be expected that in patients showing ischemic

Table II. *Relation between coronary arteriogram and graded exercise test**

		GXT		
		+	−	*Total*
CAG	+	26	18	44
	−	3	49	52
Total		29	67	96

*Correct-positive fraction: $\frac{26}{44} = 0.59$. Correct-negative fraction: $\frac{49}{52} = 0.94$. Index of merit: $\frac{26}{44} + \frac{49}{52} - 1 = 0.53$ ($\pm$ 0.08).

changes in Leads II, III, or aV_F, the vascular supply to the diaphragmatic wall of the myocardium (provided by the terminal branches of the right and the circumflex arteries) was impaired. In 4 of the 6 patients at least one of these branches was involved (Table IV). However, severe lesions of the anterior descending artery were also present in 4 subjects, and since isolated obstructions of the right coronary artery yielded in all but one case a negative GXT, it seems that positive responses in the extremity leads were rather an expression of diffuse coronary disease.

WORK LOAD AND WORK PERFORMANCE. The mean maximum heart rate and maximum work load in the 44 patients with a positive CAG are shown in Table V. The maximum work load and the maximum heart rate were not higher in the correct-positive responders than in the false-negative responders. In the 3 patients with a false-positive response the maximum work load had not been excessively high (ranging from 90 to 120 watts). It can be calculated that in the correct-positive cases the mean total work performed at GXT was 2,189 kg.m.

Two-step test. In 91 subjects a two-step test was performed. Ischemic S-T changes occurred in 17 subjects; in 13 of these the CAG was positive, and in 4 the CAG was negative. In the remaining 64 subjects no changes or junctional depressions of less than 2 mm. were observed. Of the latter category, 26 patients had a positive CAG and 48 had a negative CAG. Table VI

Table III. *Total number of ischemic S-T segment changes in separate leads observed in 29 subjects at GXT*

Lead	*I*	*II*	*III*	*aV$_L$*	*aV$_F$*	*V$_3$*	*V$_4$*	*V$_5$*	*V$_6$*	*Total*
Number*	0	6	5	0	6	1	15	25	26	84
Percentage†	0	17.5	14.5	0	17.5	3	52	86	90	

*Number of ischemic S-T segment changes in separate leads.
†Percentage of the 29 patients detected if only this lead were recorded.

Table IV. *Patients with pathologic S-T changes in Leads II, III, or aV$_F$. Relation to the grade and localization of the coronary obstructions*

Patient	*Grading of separate branches**				
	Left coronary artery				*Right coronary artery*
	Main	*Anterior descending*	*Circumflex*		
			Main	*Obtuse margin*	
1	1	3	0	2	3
2	0	3	0	0	0
3	0	2	1	0	3
4	2	2	2	0	1
5	0	0	0	0	0
6	1	0	0	2	2

*0, normal; 1, 0 to 50 per cent narrowing of lumen diameter; 2, more than 50 per cent obstruction but not total; 3, occlusion.

Table V. *Maximal heart rate and maximal work load by GXT in the 44 patients with a positive CAG*

	No. of patients	*Maximal heart rate (beats/min.)*	*Maximal work load (watts)*
Positive GXT	26	127(±20)	88(±21)
Negative GXT	18	143(±30)	115(±25)

represents the contingency between the two-step test and CAG. It follows that the correct-positive fraction = 0.33, the correct-negative fraction = 0.93, and T = 0.26 (± 0.10).

GXT versus two-step test. From the indices of merit it appears that the GXT discriminated better between a pathologic and a normal coronary system than did the two-step test. The difference resulted from a higher correct-positive fraction by the GXT. In 13 subjects with positive CAG the prediction by the GXT was correct, whereas the two-step test yielded a false-negative result.

Table VII shows that the maximum work load in these 13 subjects had not been higher than in the other correct-positive responders (who had a positive two-step test); the mean total work performed was 1,989 kg.m.

Conversely, subjects in whom coronary

obstructions were correctly predicted by the two-step test but not by the GXT were not encountered.

The history. According to our criteria, 50 patients had a history of typical angina pectoris and 46 patients had atypical chest pain. The relation to the CAG was as follows: correct-positive fraction = 0.84, correct-negative fraction = 0.75, T = 0.59 (± 0.08).

The serum lipids. As for the history, the bisection between normal and abnormal was made in retrospect. It appeared that the optimal cutting points were somewhat higher than the upper limits of normality by the laboratory standards, namely, serum cholesterol 280 mg. per 100 ml. and serum β-lipoprotein 3 mm.; this was in agreement with previous observations.[6,10]

SERUM CHOLESTEROL. Correct-positive fraction = 0.52, correct-negative fraction = 0.76, T = 0.28 (± 0.10).

SERUM β-LIPOPROTEIN. Correct-positive fraction = 0.89, correct-negative fraction = 0.48, T = 0.37 (± 0.09).

Joint predictive value. The association for the diagnostic methods which were included in this study with the CAG are summarized in Table VIII. When arranged according to the magnitude of the index of merit, the order is: history, GXT, serum β-lipoprotein, serum cholesterol, and two-step test. It was expected that a combination of diagnostic parameters would yield a better result than the parameters singly. Therefore, the three methods which showed the highest indices of merit together with a high degree of

Table VI. *Relation between CAG and two-step test**

		Two-step test		*Total*
		+	−	
CAG	+	13	26	39
	−	4	48	52
Total		17	74	91

*Correct-positive fraction = 0.33. Correct-negative fraction = 0.93. Index of merit = 0.26 (± 0.10).

Table VII. *Twenty-six patients with positive coronary arteriographic findings and positive GXT divided according to whether the two-step test was positive or negative. Relation to maximal work load and maximal heart rate*

	No. of patients	*GXT test*		*Two-step test*
		Maximal heart rate (beats/min.)	*Maximal work load (watts)*	*Maximal heart rate (beats/min.)*
Positive GXT and positive two-step test	13	129 (±21)	96 (±20)	126(±13)
Positive GXT and negative two-step test	13	125 (±18)	83 (±21)	121(±23)

Table VIII. *Discriminative skill of diagnostic methods which were included in this study*

Method	*Correct-positive fraction*	*Correct-negative fraction*	*Index of merit*
History	0.84	0.75	0.59(±0.08)
GXT	0.59	0.94	0.53(±0.08)
Serum β-lipoprotein	0.89	0.48	0.37(±0.09)
Serum cholesterol	0.52	0.76	0.28(±0.10)
Two-step test	0.33	0.93	0.26(±0.10)

mutual independency, i.e., history, GXT, and serum β-lipoprotein, were studied in combination. First the subjects in whom these 3 parameters were concordant (all being either positive or negative) were singled out. In 30 patients (31 per cent of the total patients) such a combination was encountered; the prediction was positive in 15 of these and negative in the other 15. In this group the association with the CAG was excellent; there was only one patient in whom the prediction was false-positive, and there were no patients with a false-negative diagnosis (Fig. 2). The index of merit was as high as 0.93.

In 34 subjects the statement by history and GXT were concordant, but the serum β-lipoprotein level was at variance. If these subjects are added to the previous 30 patients, the number of patients in whom the statements by GXT and history were in agreement amounts to 64 (Fig. 2). For this category the correct-positive fraction and the correct-negative fraction were 0.85 and 0.97, respectively, and T = 0.82. In the remaining 32 subjects, in whom the statements by GXT and history were contradictory, the highest index of merit was obtained, if the decision was based on the serum β-lipoprotein level. In other words, for the entire group of 96 patients an optimal association with the CAG was gained if the diagnosis was made according to 2 or 3 concordant parameters. The result of this procedure is represented by Table IX. It follows that the correct-

Table IX. *Contingency table for the entire group of patients if the decision is made on the basis of 3 independent parameters (history, GXT, and serum β-lipoprotein)**

		2 or 3 methods		*Total*
		+	−	
CAG	+	36	8	44
	−	7	45	52
Total		43	53	96

*Correct-positive fraction = 0.82. Correct-negative fraction = 0.85. Index of merit = 0.67.

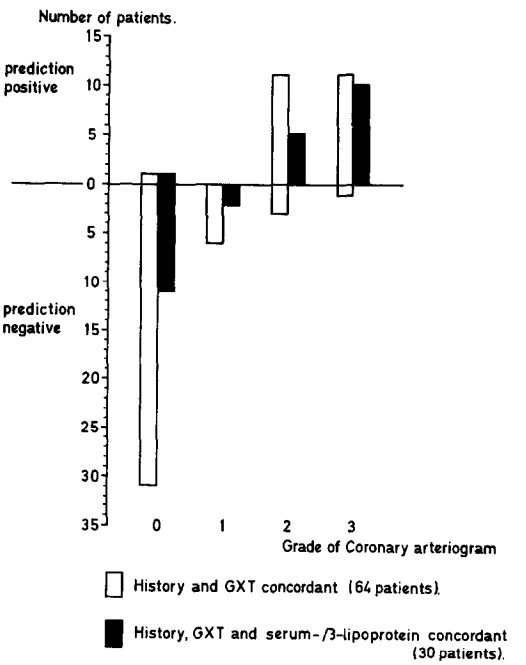

Fig. 2. Patients in whom the statements by either *GXT* and *history* or *GXT*, *history*, and *serum β-lipoprotein* level were concordant. Distribution of positive and negative cases over the 4 grades of coronary arteriogram.

Table X. *Results of GXT and comparison to coronary arteriographic findings by different authors*

Author	*No. of patients*	*Correct-positive fraction*	*Correct-negative fraction*	*Index of merit*
Kassebaum, Sutherland, and Judkins[18]	68	0.51	0.96	0.47(±0.11)
Mason et al.[19]	84	0.77	0.89	0.66(±0.08)
Roitman, Jones, and Sheffield[20]	46	0.80	0.87	0.67(±0.12)
This report	96	0.59	0.94	0.53(±0.08)

positive fraction = 0.82, the correct-negative fraction = 0.85, and T = 0.67.

Discussion

In order to be able to compare our findings to the results obtained by other investigators, we have applied the same statistical calculations to studies dealing with the relation between coronary arteriography and the GXT (Table X). It appears that our results are in good agreement with the findings reported in the literature.

In our material the diagnostic performance of the GXT was significantly better than that of the two-step test ($p < 0.01$). The difference resulted from a higher fraction correct-positive prediction.

A review of the literature revealed no comparative exercise test studies, with the use of the coronary arteriogram as a reference. However, more correct-positive responses by the GXT were also reported by Mason and co-workers,[19] Sheffield, Holt, and Reeves,[21] and Bellet and Roman,[22] in patients with a clinical diagnosis of angina pectoris.

One might suppose that in our material the GXT compared favorably to the two-step test because more leads were employed. However it seems unlikely that this could be the only explanation. First, in 86 per cent of the positive cases by the GXT an ischemic response was found in Lead V_5; if only this lead were recorded the GXT would still score definitely higher than the two-step test. Second, in the above mentioned studies,[19,21,22] the GXT yielded more positive diagnoses than the two-step test, although multiple leads were used in both. Therefore the difference has to be explained mainly by either the maximum work load or the total work performed. In the subjects with a correct-positive GXT but a false-negative two-step test, the mean maximum work load and total work performed were 83 watts and 1,989 kg.m., respectively. It has been calculated that the (maximum) work load in the two-step test is approximately 75 watts.[23] Consequently, the total work performed in three minutes is 1,440 kg.m. Thus the total work performed appears to be the most influential factor. Although the diagnostic gain from GXT appeared to be considerable in our series of patients who all had a normal ECG at rest, it should be noted that the test failed to show ischemic changes in 41 per cent of the patients who had marked coronary artery disease disclosed by the CAG. Comparison of these false-negative subjects to the correct-positive responders revealed that the first group comprised a relatively high proportion of patients with isolated obstruction of the right coronary artery while the maximum work load, the total work performed, and the maximum heart rate were almost the same in both categories. It would seem, therefore, that inferior wall ischemia is especially difficult to detect. Application of less rigid criteria for a positive GXT (junctional depressions and repetitive ventricular extrasystoles) did result in a small increase of the number of correct-positive diagnoses but at the same time entailed a substantial number of false-positive predictions, and consequently lowered the index of merit. It is of interest that a positive GXT corroborated by a positive history or, conversely, a negative GXT in conjunction with a negative history yielded a diagnostic accuracy which was definitely superior to the discriminative skill of the parameters singly. If the serum β-lipoprotein content was also in agreement, the prediction was almost perfect. In 34 per cent of the patients the GXT and the history were discordant; in this group the diagnostic accuracy could be enhanced by leaving the decision to the serum β-lipoprotein content, nevertheless, in the total data the association with the CAG remained far from optimal. It may be hoped that inclusion of more diagnostic parameters will eventually permit further differentiation in such cases. The material presently available is still too limited and too much influenced by selection to warrant definite statistical conclusions, but we feel that there is an indication that continuing multidimensional studies are of great importance in selecting patients for coronary arteriography and that these investigations may constitute a rational basis for epidemiologic studies.

Summary

In a series of 96 patients with chest pain, and a normal ECG at rest, the results of a GXT, the history, and the serum lipid

levels were compared to the findings at coronary arteriography. In addition, in 91 subjects a modified two-step test was performed.

To characterize quantitatively and in one number the relation to the coronary arteriogram, use was made of the index of merit (T) which ranges from 0 to 1. The following indices were found: history, 0.59; GXT, 0.53; serum β-lipoprotein, 0.37; serum cholesterol, 0.28; and two-step test, 0.26.

In 30 subjects the statements of the history, the GXT, and serum β-lipoprotein were concordant. In this category the agreement with the coronary arteriogram was excellent (T = 0.93).

In 64 subjects the statements by the history and the GXT were concordant, but the serum β-lipoprotein level was at variance. For this group T = 0.82. For the entire series the best result was obtained if the decision was made according to two or three identical statements, which resulted in an index of merit of 0.67.

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