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A comparison of methods of analysing exercise tests for diagnosis of coronary artery disease

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SUMMARY The diagnostic accuracy of the following methods of analysing exercise tests were evaluated: (*a*) the cumulative area of ST segment depression during exercise normalised for workload and heart rate (exercise score); (*b*) discriminant analysis of electrocardiographic exercise variables, workload, and symptoms; and (*c*) ST segment amplitude changes during exercise adjusted for heart rate. Three hundred and forty five men without a history of myocardial infarction were studied. One hundred and twenty three were apparently healthy. Less than half (170) had coronary artery disease. All had a normal electrocardiogram at rest. A Frank lead electrocardiogram was computer processed during symptom limited bicycle ergometry. The accuracy of the exercise score (*a*) was low (sensitivity 67%, specificity 90%). Discriminant analysis (*b*) and ST segment amplitude changes adjusted for heart rate (*c*) had excellent diagnostic characteristics (sensitivity 80%, specificity 90%), which were little affected by concomitant use of β blockers. Both methods seem well suited for diagnostic application in clinical practice.

In 1977 a system for computer assisted interpretation of exercise electrocardiograms was introduced in our hospital. This system used ST segment amplitudes and ST segment slopes adjusted for heart rate, and was more accurate than visual interpretation of the exercise electrocardiogram.[1] Since then, various other complex diagnostic analyses have been described that include not only electrocardiographic variables but also other exercise variables.[2-4] Hollenberg *et al* proposed a treadmill exercise score that measures the cumulative area of ST segment depression during exercise normalised for workload.[2,5] In 116 men with a high likelihood of coronary disease this score had a sensitivity of 85% and a specificity of 91%.[2] Among 45 men with a low likelihood of coronary disease but with a positive test according to conventional interpretation, the score identified the one who had coronary artery disease and produced no false positive responses.[5] Detry *et al* developed a discriminant function that correctly classified 83% of a study population of 370 men without previous myocardial infarction.[3] Detrano *et al* recently assessed the relative value of ST segment slope, R wave amplitude, and ST amplitude adjusted for heart rate and R wave amplitude in 303 patients without previous infarction and concluded that simple adjustment of ST segment changes for exercise induced heart rate gave the best diagnostic accuracy.[4] Claims that these techniques enhance the diagnostic accuracy of exercise electrocardiography have not yet been confirmed in an independent series of patients. We examined the merits of these approaches in men without a previous myocardial infarction.

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Patients and methods

STUDY POPULATION

We studied 345 men. None of them had a prior myocardial infarction or was taking digitalis. All had a normal electrocardiogram at rest. The study group included 222 men consecutively referred between January 1978 and May 1983 for evaluation of chest pain, who performed a symptom limited exercise test and subsequently underwent coronary angiography. Symptoms were classified according to the criteria of the Coronary Artery Surgery Study register.[6] Left ventriculography and coronary angiography were

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Table 1 *Electrocardiographic and exercise variables of the various diagnostic exercise analyses*

Analysis	*ST amplitude*	*ST slope*	*R wave*	*HR*	*Workload*	*Angina*
HR adjusted ST and slope[1]	ST_{20}, ST_{80} (X)	ST_{20-80} (X)		+		
Exercise score[2 3]	J point (X and Y)	ST_{20-60} (X and Y)	+	+	+	
Discriminant function[4]	ST_{60} (X)	ST_{20-60} (X)		+	+	+
HR adjusted ST amplitudes[5]	ST_{80} ex-ST_{80} rest (X)			+		

HR, heart rate; ex, peak exercise.
ST_{20}, ST segment amplitudes at 20 ms after J.
X and Y, Frank leads X and Y.

performed within three months of the exercise test. The presence of a diameter stenosis of at least 50% in one or more major coronary arteries was regarded as evidence of coronary disease. Angiograms were interpreted by two experienced cardiologists without knowledge of the exercise test results. Ninety five patients with coronary disease and 21 patients with normal angiograms were taking β blockers at the time of the exercise test.

The other 123 men were studied in the Kaunas-Rotterdam Intervention Study. In this World Health Organisation project, a representative sample of men in Rotterdam was screened for the presence of coronary risk factors.[7] A subgroup volunteered to participate in the exercise study. They were without symptoms and none of them was taking cardiac medication.

EXERCISE TEST

The men performed a symptom limited exercise test while sitting on a bicycle ergometer. The workload was increased by 10 or 20 W until moderate symptoms appeared or until exhaustion occurred. The men continued to cycle at a low load for four minutes after peak exercise. The corrected orthogonal Frank lead electrocardiogram was recorded with the chest electrodes attached at the level of the fifth intercostal space. The electrocardiogram was computer processed as described elsewhere.[8] In short, the electrocardiogram was sampled for 20 seconds with the man sitting at rest, every minute during exercise, and during a six minute recovery period. The sampling frequency was 250 Hz. After rejection of abnormal complexes or those showing excessive baseline drift, an average representative complex was calculated.[9] The baseline level was defined as the mean signal amplitude for 5–3 samples (20–12 ms) before the QRS complex. All amplitudes were measured relative to this baseline. Measurements included heart rate, R wave amplitude, J point amplitude, and ST segment amplitudes every 20 ms intervals between the J point and 100 ms after J in leads X and Y. ST_{20} is the ST amplitude 20 ms after J.

The following diagnostic analyses, outlined in table 1, were evaluated:

(*a*) ST segment measurements adjusted for instantaneous heart rate.[1] The diagnostic accuracy of the combination of ST_{20} and ST_{80} in Frank lead X, corrected for heart rate, was re-evaluated.

(*b*) A modification of the treadmill exercise score as described by Hollenberg *et al.* This score quantifies the electrocardiographic response to exercise by measuring the cumulative area of ST segment amplitude during exercise and recovery in leads V5 and aVF, which is then normalised for QRS amplitude and for workload—by dividing the ST segment sum by the product of the duration of exercise (in minutes) and the fraction of the maximal

Table 2 *Results of discriminant analysis of exercise variables in 345 men without previous myocardial infarction for coefficients derived by Detry et al[3] and for those obtained in the present study*

	Detry et al[3]			*This study*		
		*Discriminant score**			*Discriminant score**	
Exercise variables	*Coefficient*	*CAD*	*Normal*	*Coefficient*	*CAD*	*Normal*
Heart rate (beats/min)	0·02	2·79	3·55	0·02	2·28	3·00
ST_{60} lead X (mV)	3·78	−0·53	−0·11	7·00	−0·78	0·21
Angina (yes: 1, no: 2)	0·78	1·09	1·56	0·92	1·28	1·53
Workload (W)	0·004	0·59	0·90	0·004	0·46	0·67
ST_{20-60} slope lead X (mV/s)	0·16	0·10	0·44	0·21	0·09	0·46
Intercept	−5·04	−5·04	−5·04	−4·38	−4·38	−4·38
Overall discriminant score†		−1·00	1·30		−1·05	1·49

CAD, coronary artery disease.
*Calculated as the product of the coefficient and the mean value of the variable.
†Calculated as the sum of the item-specific scores; this score can be regarded as the discriminant score of the average patient.

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predicted heart rate (MPHR) achieved.[2 5 10] We modified the original method by using Frank leads X and Y instead of standard leads V5 and aVF and by limiting the electrocardiographic measurements in the recovery period to six minutes after peak exercise instead of 10 minutes. The ST segment slope was calculated from ST segment amplitudes at 20 and 60 ms, because this was the most informative slope in our study population. The slope measurements in the original publication were not specified. The maximal predicted heart rate (MPHR) was calculated 220 − age. Mean R wave amplitude values obtained in the present study population were entered as R in the formula:

$$\text{Exercise score} = \text{area (J point + ST slope) lead X} \times \bar{R}/R \text{ lead X} + \text{area (J point + ST slope) lead Y} \times \bar{R}/R \text{ lead Y} \div \text{exercise duration} \times \text{fraction of MPHR}$$

(*c*) The discriminant function (D) described by Detry *et al* and presented in table 2.[3]

(*d*) The electrocardiographic method of Detrano *et al*.[4] Changes in ST amplitude were adjusted for heart rate in Frank lead X only:

$$(ST_{80}\text{ exercise} - ST_{80}\text{ rest})\text{ lead X} \div \text{heart rate adjusted ST} = \text{exercise heart rate} - \text{resting heart rate}$$

STATISTICAL ANALYSIS

We used univariate analysis with unpaired Student's *t* test for continuous variables and Fisher's exact test for discrete variables. Stepwise discriminant analysis was performed with the BMDP 7M statistical package. The sensitivity and specificity of the various electrocardiographic variables and of the different diagnostic analyses and their sub-elements were presented as receiver operator characteristic curves (sensitivity *v* specificity).[11 12]

Table 3 *Clinical and angiographic data of 345 men without previous myocardial infarction*

History	No	Age (yr) Mean	Range	CAD No (%)
Typical angina	124	52	28–69	111 (90)
Atypical angina	63	50	30–66	43 (68)
Non-anginal pain	35	46	22–68	16 (46)
Volunteers	123	47	19–64	— —

CAD, coronary artery disease.

Results

Table 3 shows the details of the study population. Of the 170 patients with coronary disease, one had left main disease, 53 had three vessel disease, 64 two vessel disease, and 52 single vessel disease. The mean ejection fraction of the patients with coronary disease was 64% (range 37–83). The other 52 men with symptoms had normal coronary arteries or no significant lesions at angiography. Angiography was not performed in the 123 men without symptoms. A follow up of 9 years (SD 9 months) confirmed that they did not have heart disease. Six of them had died; whereas the number of deaths expected in a random sample of Dutch men of similar age would have been 12.[13]

No complications occurred during exercise testing. Table 4 shows the relevant exercise variables. Patients with coronary disease reached lower maximal workload and lower peak heart rate and ST segment amplitudes in leads X and Y were significantly more negative than in the other men. Patients with normal angiograms had intermediate mean exercise values, although their individual electrocardiographic variables fell within the ranges of the healthy subjects.

Table 4 *Exercise test data in 170 patients with coronary disease (CAD), in 52 patients with normal coronary angiograms (No CAD), and in 123 symptom free men. Measurements are given at peak exercise unless otherwise indicated. All data, except angina, are given as mean (SD)*

	CAD (n = 170)		No CAD and healthy men (n = 175)		No CAD (n = 52)		Healthy men (n = 123)	
Max workload (W)	115	(33)**	168	(43)	156	(46)*	173	(41)
Angina (%)	103	(61)**	7	(4)	7	(13)	—	
Max heart rate (beats/min)	120	(22)**	158	(24)	143	(28)*	165	(18)
R wave lead X at rest (μV)	1304	(423)	1369	(451)	1358	(483)	1374	(439)
ST_{60} lead X (μV)	−112	(79)**	30	(92)	−7	(62)*	44	(97)
ST_{80} lead X (μV)	−92	(100)**	117	(139)	45	(92)*	144	(144)
ST_{20-60} slope lead X (μV/s)	0·43	(0·93)**	2·16	(1·37)	1·54	(0·94)*	2·41	(1·44)
R wave lead Y at rest (μV)	547	(328)	654	(396)	681	(416)	643	(389)
ST_{60} lead Y (μV)	−46	(63)**	10	(66)	−16	(55)*	21	(67)
ST_{80} lead Y (μV)	−31	(76)**	51	(92)	2	(69)*	70	(92)
ST_{20-60} slope lead Y (μV/s)	0·43	(0·62)**	1·28	(0·84)	0·97	(0·70)	1·40	(0·87)

*p = < 0·02 No CAD *v* healthy men.
**p = < 0·001 CAD *v* all men with normal tests.

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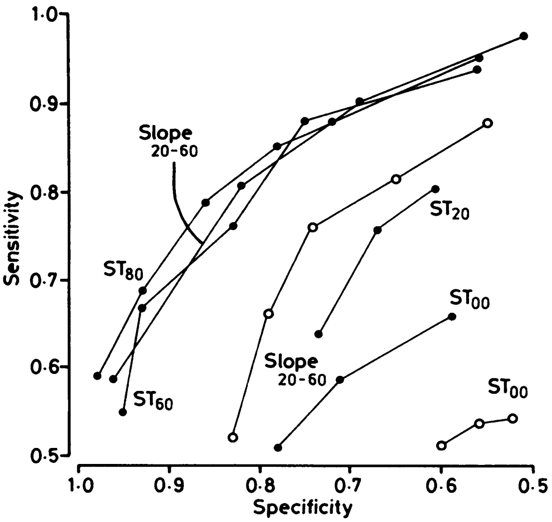

Fig 1 *Sensitivity and specificity for the prediction of coronary disease of ST_{00} in Frank leads X (solid circles) and Y (open circles), ST_{20}, ST_{60}, and ST_{80} in lead X, and ST_{20-60} slope in leads X and Y in 345 men without previous myocardial infarction.*

ST_{60} and ST_{80} in lead X had a sensitivity of 70% and a specificity of 90% for the prediction of coronary disease. The ST_{20-60} slope in lead X had similar diagnostic value (fig 1). The diagnostic accuracy of ST_{20} was lower, while values for ST segment measurements at 40 and 100 ms in lead X were intermediate (not illustrated). Other electrocardiographic variables used in the various formulas, such as J point amplitudes in leads X and Y and ST_{20-60} slope in lead Y were inaccurate indicators for the presence or absence of coronary disease (fig 1).

The diagnostic yield of ST segment measurements adjusted for instantaneous heart rate was good (sensitivity 74%, specificity 90%) in the study population as a whole (fig 2, table 5). These measurements, however, were less reliable in the 116 men who were treated with β blockers (95 men with coronary disease and 21 men with normal angiograms) (table 5).

The diagnostic accuracy of the exercise score was low, even in patients not taking β blockers (fig 2, table 5). Conventional ST segment measurements in lead X were more powerful predictors. To determine the strong and weak components of the exercise score, the various elements of the original formula were analysed. When only the numerator of the equation, the cumulative J point depression and ST segment slope, was evaluated the test's accuracy increased. In contrast, addition of the maximum predicted heart rate or achieved workload to the denominator of the equation reduced the diagnostic value of the test (table 5).

The sensitivity and specificity of the discriminant function developed and described by Detry *et al*[3] were quite high (fig 2). This analysis also proved to be accurate in patients taking β blockers, although the sensitivity was higher at corresponding levels of specificity in patients who were not taking these drugs (table 5). The coefficients of the discriminant function in this series of patients were calculated by stepwise discriminant analysis with the same variables as used by Detry *et al.* Table 2 shows the derived coefficients and table 5 the sensitivity and specificity of this analysis. ST segment amplitude was more important in this "optimised" equation, and the differences between the coefficients of the two discriminant functions related to ST_{60} were statistically significant.

The sensitivity of the ST segment changes adjusted for heart rate was high at all levels of specificity (fig 2, table 5). The results of the analysis were not affected by the use of β blocking agents during exercise. The sensitivity and specificity of the test were poor when the unadjusted difference between ST segment measurements at peak exercise and at rest were evaluated. The subsequent correction of the ST segment changes for R wave amplitude only improved this component of the test's yield at high levels of specificity (table 5).

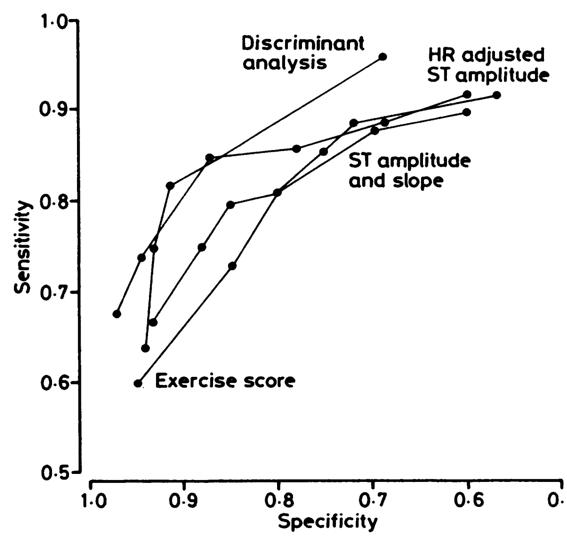

Fig 2 *Sensitivity and specificity for the prediction of coronary disease of changes in ST segment adjusted for instantaneous heart rate,[1] of exercise score,[2 5] and of discriminant function according to Detry et al [3] and of changes in ST amplitude adjusted for heart rate as proposed by Detrano et al [4] in 345 men.*

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Table 5 *Sensitivities (%) at fixed specificity for various diagnostic analyses of exercise tests and their components*

	Specificity (%)			
	80	85	90	95
HR adjusted ST amplitudes and slope[1]:				
All patients	82	79	74	58
Patients with β blockers	73	64	63	43
Patients without β blockers	84	81	76	68
Exercise score[2 5]:				
All patients	82	73	67	60
Patients with β blockers	74	68	66	58
Patients without β blockers	78	70	63	53
ST area measurements only	91	84	71	55
Area/% MPHR	68	61	44	29
Area/minutes in test	77	67	56	40
Discriminant function according to Detry *et al*[3]:				
All patients	88	86	84	50
Patients with β blockers	89	82	71	66
Patients without β blockers	91	89	84	54
Present discriminant analysis	95	92	91	78
HR adjusted ST segment changes[4]:				
All patients	84	82	78	73
Patients with β blockers	81	81	80	77
Patients without β blockers	81	78	76	64
ST_{80} max—ST_{80} rest	80	73	65	56
Correction for R wave amplitude	80	73	70	61

HR, heart rate; MPHR, maximum predicted heart rate.

Discussion

The success of apparently promising new diagnostic techniques is often found to be limited when they are applied to other populations.[14] Inappropriate selection of patients and biased evaluation of the test and disease state are the usual causes of such failures[15]; the contribution of different stress test protocols or electrocardiographic techniques is less crucial.[16] We studied patients with a broad range of coronary disease: men without coronary disease who were apparently very healthy, and men with symptoms who did not have important coronary disease. Figure 3 shows that the results of the exercise test were related to the severity of coronary disease.

Discriminant function analysis of exercise variables and ST segment amplitude changes adjusted for heart rate seemed to be the best predictors of the absence or presence of obstructive coronary disease. Both analyses had a sensitivity between 70% and 80% at a specificity level of 90%. The diagnostic accuracy was highest with the discriminant function according to Detry *et al*.[3] The coefficients obtained in the present study resembled the original values reported by Detry *et al*[3] although the weight given to ST segment changes in our equation was higher. The relative importance of the various exercise variables in the discriminant analyses became apparent when the mean exercise variables of the two patient groups were entered in the two equations (table 2). Heart rate at peak exercise, ST_{60} in lead X, and the appearance of angina during exercise were the most important variables, as they were in other studies.[17-19] Although exercise tolerance is a major indicator of prognosis in patients with known coronary disease,[20] workload was not an important factor in the diagnosis of coronary disease by either function in patients without a previous myocardial infarction and normal left ventricular function. The use of anginal symptoms during exercise in the discriminant function may not be appropriate because bayesian probability analysis relies on the mutual independence of variables; angina may have already been used to calculate the pre-test risk of coronary disease.[21]

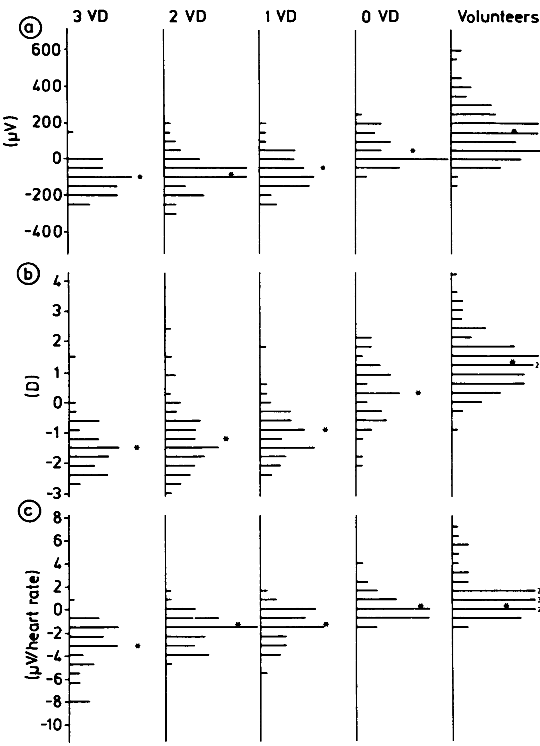

Fig 3 *Exercise variables ST_{80} in lead X for values obtained with the discriminant function according to Detry et al[3] and for ST segment amplitudes adjusted for heart rate in 345 men with three vessel disease (VD), two vessel disease, single vessel disease, patients with normal findings at angiography (No CAD), and volunteers. (a) Distribution of ST_{80}. (b) Discriminant function according to Detry et al.[3] (c) ST segment amplitude adjusted for heart rate. A complete column represents 20 subjects. The asterisk indicates the mean in that group. Note the overlap between the various groups, in particular between 1 VD and 2 VD. Patients with three vessel disease showed the most abnormal results and volunteers the most normal results.*

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The adjustment of ST segment amplitude for heart rate in the manner proposed by Detrano *et al*[4] yielded similar diagnostic results—a sensitivity of 78% at a specificity level of 90%. This is remarkable because we evaluated ST segment changes in Frank lead X only. The processing of the electrocardiographic variables by computer and the exclusion of data from women in this study probably account for this excellent result.[22 23]

Surprisingly, the method with the lowest diagnostic accuracy was the exercise score. But in theory some features of this score are appealing. Its use of the cumulated changes in J point and ST segment slope during the full test period seems to be attractive, because this will reduce errors inherent in single measurements at peak exercise. On the other hand, the test score was adversely affected when there was low exercise capacity not caused by cardiac factors or when other disorders precluded normal exercise capacity. Such conditions are common in middle aged patients with symptoms and to some extent could explain the relatively poor performance of the exercise score in this study. In addition, exercise capacity, which was a relatively unimportant variable in the discriminant analyses, was included in the exercise score. Also, the J point amplitude in the numerator of the equation was not the most accurate of the various electrocardiographic variables studied. The results of another study in which ST segment measurements were taken at 80 ms after J instead of at the J point were also disappointing.[24] There were important differences between the exercise score in this study and its original description by Hollenberg *et al*. Although the tests in both studies were symptom limited and the workload was increased in stages in both, the two methods cannot be directly compared; we used bicycle ergometry and they used a treadmill.

Earlier, we reported a sensitivity of 84% and a specificity of 88% when ST measurements at 20 and 80 ms and instantaneous heart rates in Frank lead X were combined. In the current population, the diagnostic accuracy of the method was lower (sensitivity 74%, specificity 90%): in addition, the usefulness of the method was strongly influenced by the use of β blockers during exercise, which makes it less reliable than the other methods tested.

In the current comparison of various diagnostic approaches to exercise tests in men with a normal electrocardiogram at rest, the most complex technique considered, the discriminant function as described by Detry *et al*, was the most accurate. The simplest analysis, the adjustment of the ST segment amplitude changes for heart rate, came second. Neither method was affected by the use of β blockers during exercise. Because the workload contributes little to the strength of the discriminant analysis, both techniques rely most on the same haemodynamic and electrocardiographic variables—heart rate and ST segment depression. These variables were also associated with the presence or absence of coronary disease in other studies, even when clinical variables were taken into account.[25] Thus discriminant analysis and ST segment changes adjusted for heart rate are both good methods for the diagnosis or exclusion of coronary artery disease in men. When computer facilities are not available, measurement of ST amplitude adjusted for heart rate is the most appropriate choice of analysis.

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