DIAGNOSTIC AND PROGNOSTIC IMPLICATIONS OF EXERCISE TESTING IN CORONARY ARTERY DISEASE

Over de interpretatie van inspanningsonderzoek

PROEFSCHRIFT

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To the memory of my father

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CHAPTER 1

INTRODUCTION

The clinical indications for exercise testing as a diagnostic and prognostic tool in the assessment of patients with ischemic heart disease have gradually evolved since Master introduced the two-step exercise test in 1929 (1). New information from correlations between electrocardiographic and angiocardiographic data, the use of exercise test results for prognostic stratification in patient subsets and the role of other non-invasive methods which supplement the information obtained from exercise testing have markedly enhanced the clinical utility of the test.

Exercise testing is currently most useful in the evaluation of patients in whom the origin of their chest pain must be elucidated, in patients with ischemic heart disease in whom the prognosis is to be assessed and in patients in whom the efficacy of antianginal therapy or revascularization procedures is to be measured. Although some physicians have become disillusioned with the diagnostic accuracy of the exercise test, the procedure remains an important, as well as relatively inexpensive technique in the routine assessment of patients with suspected or documented chronic heart disease of various causes.

Since the main application of exercise testing is in patients with ischemic heart disease, this review of the status of the exercise test and the interpretation of exercise test results will be restricted to this patient group.

Exercise protocol and report

Historically, most attention has been given to the exercise electrocardiogram. However, other information that can be obtained during the test is of equal diagnostic and prognostic importance, such as exercise duration, symptoms during exercise and heart rate and blood pressure responses. Clearly, in 1988 as well as in 1929, it is inappropriate to report a diagnostic stress test just in terms of "positive" or "negative". An adequate report must contain a summary of the history of the patient, present symptoms, current medication, as well as a description of the electrocardiogram at rest. The exercise procedure should be described comparing the actual exercise tolerance with the expected performance of a normal subject of similar sex, age and body size. The reasons for termination of exercise should be stated, as well as symptoms at the time and workload at which they began, their type, severity, and duration after cessation of exercise. Heart rate and blood pressure should be reported at rest, at the onset of symptoms, at peak exercise and after approximately six minutes in the recovery period. The description of the electrocardiogram should contain the leads which were used, as well as the occurrence of

any arrhythmias and changes in the QRS complex and the ST segment. Finally, a conclusion relative to the clinical questions which prompted the execution of the test should be formulated in unequivocal terms. Thus, what historically began as a purely electrocardiographic evaluation, has now become an integrated but still simple evaluation of the cardiovascular system.

Exercise protocols

Clinical exercise tests are best performed on a calibrated bicycle ergometer or a treadmill (2,3). The older type of step tests are outdated, since they do not permit quantitation of the performed workload. The choice of either a bicycle ergometer or a treadmill is made on basis of personal preference or local custom of the population to be tested. In general, normal subjects reach similar levels of heart rate and oxygen uptake with both techniques (4). Virtually anyone can be exercised on a treadmill, while some skill and experience is required for the bicycle. On the other hand, the body position on the bicycle ergometer is more stable and results in fewer motion artefacts in the electrocardiogram. The actual workload performed is obviously dependent on physiologic and ambulatory circumstances; body weight is an important factor on the treadmill, but workload performed on a bicycle ergometer is independent of this variable because of the sitting position of the individual.

Exercise should start at a low workload, with stepwise or continuous increments in load according to a fixed protocol. A large number of treadmill protocols has been described. In the most widely used method, developed by Bruce, the grade or the slope and speed of the treadmill are altered at the end of each three minute stage (5). Variations of this protocol alter the speed of the treadmill, with similar levels of slope, or maintain a constant speed at increasing degrees of slope (6,7). The protocol used by Weld in patients recovering from myocardial infarction employs two stages with a low treadmill slope prior to the first stage of the Bruce protocol (8).

Many laboratories which use a bicycle ergometer increase the workload by 10 or 20 Watts per minute. For adult male subjects the metabolic requirements, in terms of total body oxygen consumption, during a protocol with 20 Watts per minute workload increments are equivalent to the Bruce protocol (4).

For most purposes and in most subjects, exercise can be continued until symptoms develop. It is a fallacy to terminate exercise when 70% or 85% of the age predicted "maximal" heart rate is reached. Firstly, heart rate response in normal subjects is highly variable (9). Although the mean peak value at each age can be predicted by the equation 220 minus age, or 200 minus age/2, the standard deviation is large and approximates 10 beats per minute; thus, 95 percent of the patients will reach values between 20 beats below and 20 beats above the predicted mean value. Furthermore, maximum heart rate reached by patients with severe disease is considerably lower than heart rates recorded from normal subjects (10). Thus, when achieved heart rate level is used to terminate exercise, patients with severe disease may be often stressed to their maximum, while healthy subjects or patients with lesser degrees of disease will unnecessarily be prevented from exercising up to their

true capacity. Finally, the heart rate response to exercise may be altered by medication such as beta-blockers, some calcium antagonists and specific sinus node inhibitors (11-16).

It has therefore been suggested to cease all medication several days before the exercise test. Although this may be useful for certain scientific studies, it is not practical in daily routine. Particularly, in patients with chest pain syndromes, (un)stable angina may develop when beta-blockers, nitrates or calcium antagonists are withdrawn. If it is assumed that the interpretation of a test is significantly hampered by medication, for example in case of a normal response in a patient with chest pain using beta-blockers, the medication can gradually be withdrawn and the test repeated. However, most patients with angina will develop symptoms and electrocardiographic changes, albeit at a higher workload, in spite of their use of anti-anginal drugs (13-16).

Recording of the electrocardiogram

It is essential to record a high quality electrocardiogram during exercise. Adequate electrocardiographic quality can be achieved in virtually all patients with a correct combination of skin preparation, electrodes, cables and signal amplifiers (17). The selection of the lead system may depend on the purpose of the investigation. For monitoring of heart rate and arrhythmias only, as for instance in sports medicine, any bipolar chest lead will suffice. A single lead system could also be used in patients with suspected coronary disease and a normal electrocardiogram at rest. Precordial ST segment depression will be missed in only 10 % of these patients when a bipolar lead from the right infraclavicular region to V_5 (CS_5) is employed (18,19). In patients with a previous myocardial infarction, a single lead system is inadequate, and a combination of three "pseudo" orthogonal leads such as standard leads V_2, V_5 and aVF or truly orthogonal leads such as the Frank system or a standard 12 lead electrocardiogram is preferred in this group (6,20,21).

Computer processing of electrocardiograms

In order to facilitate the interpretation of the electrocardiogram during exercise the noise level and motion artefacts must be reduced. Computer supported signal averaging and further processing of the electrocardiographic signal markedly improve the quality of the electrocardiogram. Optimal results can only be obtained by simultaneous analysis of multiple leads, since precise definition of QRS onset and QRS end requires a combination of leads (22,23). The diagnostic performance of visual reading versus computer assisted electrocardiographic interpretation during exercise has demonstrated improved diagnostic performance of the latter in most studies (24-28). Readers interested in the applications of computer analysis of exercise electrocardiograms are referred to reviews on this subject (29,30). In addition to improvement of the electrocardiographic interpretation by quantitative analysis, the computer system can be used to regulate the bicycle or treadmill

according to one or several predefined protocols, to start and stop the electrocardiographic writer at appropriate times and to generate a summary report of the test.

Risk of exercise testing

Stress testing is a safe diagnostic procedure. A survey of 712,285 mostly asymptomatic subjects tested in three German speaking countries reported only 17 deaths (31). Non-fatal ventricular fibrillation occurred at a rate of one per 7,000 tests; non-fatal myocardial infarction at a rate of one per 70,000 procedures. Higher complication rates are observed in hospitals or other institutions where symptomatic cardiac patients are tested: mortality amounted to about four per 10,000 tests in the United States, but fatality was confined to patients with known coronary artery disease (32). Mortality related to exercise testing at the Thoraxcenter amounted to three patients during the past sixteen years in which nearly 24,000 exercise tests were performed.

Clearly, patient selection remains the best method to reduce the risk of stress testing. General contraindications include the presence of untreated, life-threatening arrhythmias, advanced atrioventricular heart block, critical aortic stenosis and myocarditis (33). Also, the test should definitely be postponed in subjects with recently worsened angina or suspected angina at rest. Postinfarction patients with angina or overt signs of heart failure should not be referred for a predischarge test. Blood pressure should be measured at regular intervals during the test and exercise must be terminated promptly whenever a decrease in systolic blood pressure, pallor or signs of physical exhaustion are observed (34).

Diagnostic considerations

For most physicians, the exercise test is the initial noninvasive investigation in the evaluation of patients with chest pain and much effort has been devoted to study its reliability for this purpose. In spite of this attention, the extent to which electrocardiographic stress testing improves diagnostic accuracy as compared to routine clinical examination has remained uncertain for a long time.

Generally speaking, the "efficacy" of a diagnostic test is its ability to indicate the presence or absence of a disease. Unfortunately, diagnostic exercise electrocardiography shares a characteristic inherent to probably all tests: they are virtually never perfect in the detection or the exclusion of a given disease; that is, a certain proportion of persons with the disease in question will have normal test results ("false negatives"), and conversely, some of those without the disease will yield abnormal test results ("false positives"). The percentages of false negatives and false positives for any given tests are encompassed in the concepts of "sensitivity" and "specificity". Sensitivity is simply defined as the percentage of those persons with a given disease testing positively, whereas specificity is defined as the percentage of those without the disease testing negatively. Sensitivity thus answers the question:

"If the patient has the disease, how likely is he/she to have a positive test?" and specificity answers the question: "If the person does not have the disease, how likely is he/she to have a negative test?". Few tests, however, have simple binary outputs and thus can not be labeled as just positive or negative. Instead, most, including exercise electrocardiography, yield a continuous scale of outcome values, of which one of several can be selected as a cut off point to differentiate subjects with and without disease. If one selects a cut off point that makes the test very sensitive to detect as many patients with actual disease as possible, the number of false-positive diagnoses unavoidably increases; in other words, the more sensitive a given examination, the less specific it becomes. This inverse relationship between test sensitivity and specificity can be graphically represented by a receiver operator characteristic (ROC) curve (35). An example of such a curve is illustrated in Figure 1.

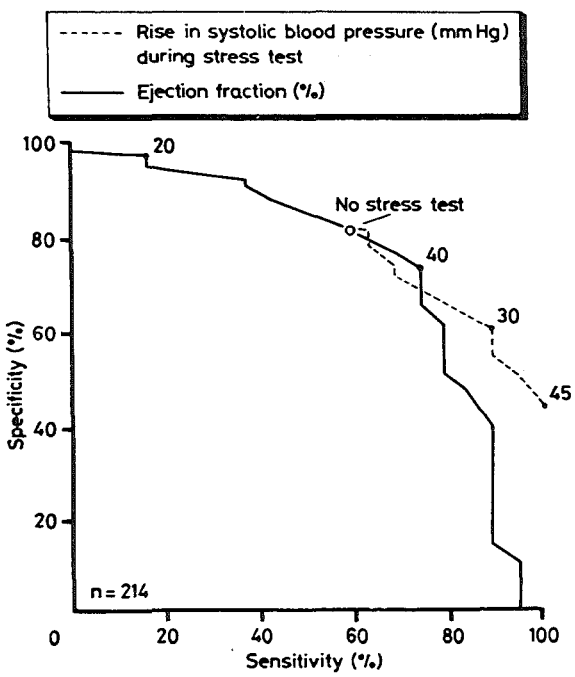

Figure 1 Specificity vs sensitivity for late mortality of exercise testing (contraindications or change of systolic pressure during the test) and radionuclide ventriculography. (From ref 36, reproduced by permission of the publisher)

Since the original evaluations of a test are usually expressed in sensitivity and specificity, it is obvious that the calculation of those indices is of primary importance. However, it should be appreciated that the values attained for these indices can be severely distorted by two types of problems or bias: the selection of patients included in a study and bias in associating the test result and the state of the disease (37).

Bias in selection of patients

Ransohoff and Feinstein predicted that when a diagnostic test is evaluated under biased circumstances, initially high values for sensitivity and specificity will fall as the indications for testing - and therefore the patients referred for testing - stabilize (37). A population of "referrals" with a high probability of disease will have an proportionally higher frequency of abnormal responses, and the specificity of the test will be reduced as a result of this selection, known as *pretest referral bias.*

The *post test referral bias*, the preferential selection of positive test responders, is a second factor which contributes to the declining specificity of many tests when subsequently applied in other study populations. Initial reports of high sensitivity and specificity soon establish a correspondingly high level of confidence in the test, and an abnormal test response becomes a powerful decision criterion for further analysis (38). It is easy to see where this practice could lead if carried to the extreme: if only positive responders were to be referred for further analysis, the test would appear to be 100 percent sensitive, since all patients with disease would have a positive test, and 0 percent specific, since all those without disease would also have a positive test. Thus, to assess a test's true ability to exclude a diagnosis or to establish the presence of disease, sensitivity and specificity should be examined in a broad range of patients with and without the disease. Features like extent and location of the disease and severity of symptoms can significantly affect sensitivity in the diseased group. In the comparative group of nondiseased subjects, the challenge is to discover false positive results in those with similar features as the patients, for example in symptomatic subjects. The comparison of two populations near the two extremes of a response spectrum should be avoided: the preferential selection of "the sickest of the sick" versus the "wellest of the well" can be minimized only by validation of the test in broadly representative populations of subjects with and without the disease.

Bias in associating the test result and disease

Erroneous statistical associations may also give the test a falsely high diagnostic efficacy if determinations of test result and the status of the disease as present or absent or not made independently. Of this type of bias, the following subcategories can be recognized:

Work-up bias. The result of a positive test may affect the subsequent work up needed to establish the diagnosis of a disease that would otherwise be undetected.

Work up bias will not lead to overdiagnosis, but to underdiagnosis in patients with a negative test result. For instance, the absence of symptoms or ST segment depression during exercise may incorrectly lead to the conclusion that coronary disease is absent.

Diagnostic review bias can occur if the result of the test affects the subjective review of the data that establish the diagnosis. This bias can be avoided by "blind" interpretation of the data used to establish the diagnosis.

Test review bias arises when the test is performed after the establishment of the diagnosis; knowledge of the diagnosis may affect the subjective interpretation of the test. Further, performance of the test after a conclusive diagnosis has been reached will influence its completion by the subject under study.

Once a diagnostic test has been evaluated so that its characteristics (i.e., sensitivity and specificity) are known, it is possible to formulate probability statements about the presence or absence of disease in a given patient examined by the test. In clinical practice, the question is indeed: "If the patient has a positive test, how likely is he/she to have the disease?" or: "If the patient has a negative test, how likely is he/she not to have the disease?", the predictive values of the test.

When electrocardiographic exercise test results were compared with coronary angiographic findings a decade ago and asymptomatic subjects with an abnormal exercise electrocardiogram were found to be without coronary disease at angiography, considerably controversy over the diagnostic usefulness of exercise testing was fuelled (39,40). Although articles by Detry *et al.* and Simoons emphasized that some of these variations were due to the nature of the population under study (41,42), these factors became better understood when a formal analysis of empirical stress test data was provided by Rifkin and Hood (43). These authors employed the likelihood ratio formulation of Bayes' theorem to express the graphic relation between predictive value of the ST segment response during exercise, and the prevalence, or pre-test risk, of disease in the population under investigation. Bayes' theorem resolves conditional probabilities by stating that the post test probability of the presence or the absence of disease is not only dependent on the characteristics of a given test, but also on the prior probability of disease. Although rather intimidating at first glance, Bayes' formula, when used to predict the probability of disease given a "positive" test, only delineates the ratio of the number of individuals who have the disease and whose test results are positive to the number of all those individuals whose test results are positive (Table 1). Rifkin and Hood also analyzed this relation according to the degree of abnormality of the exercise induced ST segment response. By resolving study results into multiple ranges of ST segment depression rather than simply into "positive" or "negative", the data can be cast in a form that is more appropriate for clinical application in the individual patient.

The validity of application of Bayes' theorem to multiple clinical and exercise test variables depends on the presumptions of mutual statistical independence of these variables in populations of patients with and without the disease as well as on stability of the test properties in patients with varying degrees of severity of disease.

Although these factors can theoretically limit its application, the Bayesian approach proved to be robust even when applied non-conditionally in practice (44,45).

Table 1 Bayes' Theorem

To the clinician interpreting a test result, the posterior probability of disease, or $P(D|O)$, is of principal interest. Its value may be found from Bayes' theorem in terms of the values of P, $P(O|D)$ and $P(O|\overline{D})$, all of which are known quantities. P represents the probability of disease before testing. Sensitivity, $P(O|D)$ and specificity $P(O|\overline{D})$, represent characteristics of the test outcome itself. The posterior probability of disease, therefore, constitutes the revised estimate of risk in a subject based on the knowledge of the test result.

$$P(D|O) = \frac{P \cdot P(O|D)}{P \cdot P(O|D) + (1 - P) \cdot P(O|\overline{D})}$$

Changes of the electrocardiogram during exercise in normal subjects

Electrocardiographic changes during exercise in healthy male subjects have been studied with standard chest lead systems, with corrected orthogonal lead systems, and by body surface mapping (46-49). Several exercise induced changes in the electrocardiogram are directly related to increases in heart rate. With stress, the amplitude of the P-waves increases without major change in its wave form. This is enhanced by superposition of the T wave on the P wave when heart rates exceed 140 beats per minute. At peak-exercise, at rates of 160 beats per minute or more, the P-wave amplitude is on average twice, but in some patients up to five times the resting amplitude. The PQ interval shortens due to increased sympathic activity during the stress.

QRS duration hardly changes with exercise. In one study specifically designed for this purpose, a systemic reduction of QRS duration of a few milliseconds was observed (50). Prolongation of QRS duration is abnormal. At peak exercise QRS forces shift toward the right and superior. Accordingly, Q waves in left precordial leads deepen, R waves in left precordial leads decrease, and S waves become wider and deeper. In standard precordial leads, R wave amplitude increases frequently at intermediate workloads, with heart rates between 120 and 160 beats per minute but intra-individual variation is large (46). R wave amplitude at peak exercise is usually smaller than at rest. Again, the variability in this response is considerable. The situation is more complex when body surface maps are analyzed (48). The position of the maximum amplitude on the chest wall during ventricular depolarization remains

located in the left anterior region, but the precise location of the maximum vector shifted at least one electrode position in seven out of 25 normal subjects studied by Block *et al.* (48). No consistent pattern was observed in the changes of the maximum QRS forces in body surface maps in normal subjects exercised up to a heart rate of 150 bpm during maximum exercise.

The mechanism of the QRS changes during exercise is still unclear. It has been suggested that these are related to a variety of factors, one of which might be the reduction of end-diastolic volume during exercise, the Brody effect (51). Brody postulated that intracavitary blood exerts direct effects on the heart-lead relationship by augmenting normal radial components of myocardial dipoles, at the same time decreasing the tangential components of these electromotive forces. Numerous investigators have attempted to correlate QRS potentials with intraventricular volumes; some have validated Brody's hypothesis (52,53), but others have been unable to confirm the relationship between left ventricular volume and changes in R wave amplitude during exercise (54). Also, R wave amplitude variations proved unrelated to changes in left ventricular volume during experimental myocardial ischemia (55). Other factors, such as changes in lung volume, hematocrit levels and ionic balance can also influence the electrical field (53,56).

The QT interval shortens with exercise but accurate measurements are difficult when T and P waves overlap at higher heart rates. The T wave amplitude varies during exercise but increases sharply immediately after cessation of exercise. ST segment amplitudes 60 msec after the end of QRS remain positive in normal male subjects at heart rates around 140 beats per minute in the left precordial area.

Descriptions of the exercise induced electrocardiographic changes in healthy females have remained limited to the ST segment. In most publications, ST segment depression with exercise was more marked in middle aged females than in their male counterparts (57-59). Changes and variations in P, QRS and ST segment vectors in females will be discussed in more detail in Chapter 2 of this thesis.

Diagnostic electrocardiographic criteria

Exercise induced ST segment changes remain the most widely used and accepted benchmark of myocardial ischemia. The generally accepted boundary between "normal" and "abnormal" is the criterion of horizontal or downsloping ST segment depression of at least 0.1 mV extending at 80 msec after the J point. The probability that a given subject has coronary artery disease will increase if the ST segment shift is deeper, has a downsloping pattern and occurs early during exercise at a low heart rate. Pronounced ST segment depression, for example > 0.2 mV with a downsloping ST segment, is highly (99 percent) specific, but has a low sensitivity for the detection of coronary disease since only about 20 percent of patients with disease will exhibit this response (60).

It has been realized since long that ST segment measurements should be related to changes in heart rate (26), and many attempts have been made to increase the diagnostic yield of electrocardiography using this principle (61,62). Elamin *et al.*

correlated the maximal rate of progression of ST segment depression relative to increases in heart rate (maximal ST/heart rate slope) and claimed 100 percent diagnostic accuracy in 206 symptomatic patients without previous myocardial infarction (61). Others, however, were unable to confirm these findings (63). A modified approach was recently suggested by Detrano *et al.* (64). These investigators assessed the diagnostic yield of the ratio of ST segment amplitude and the increase in heart rate during exercise and reported significant improved diagnostic accuracy relative to conventional measurements in a carefully designed study encompassing 303 patients without prior infarction.

It has been suggested that a high R wave amplitude will require a greater amount of ST segment depression, and low R wave amplitudes smaller ST segment shifts, but the precise "gain factor" correction and its diagnostic worth needs further study (65,66).

Other electrocardiographic variables that may improve the merits of exercise electrocardiography consider the depth of the J point, ST segment slope, exercise duration and peak heart rate achieved with exercise. Hollenberg integrated these variables into a "treadmill exercise score" that appeared to be useful not only in differentiating patients with extensive coronary disease but also in identifying persons with coronary disease in a male population with low prevalence of disease (67,68).

A combination of ST segment depression and ST segment slope measurements was proposed by other authors (69) and the usefulness of these criteria against conventional ST segment changes has indeed been confirmed by some authors (64).

A decrease in R wave amplitude during exercise may reflect the presence of coronary disease according to some studies: however, the variability in this response is so large in normal subjects that the specificity of this parameter is probably too low for diagnostic use (56).

In addition to the changes of the ST segment and QRS complex discussed above, the appearance of U waves during exercise has also been reported to be associated with the presence of coronary artery disease (70). These findings have not been tested by others so far. Analysis of this criterion will be difficult at heart rates over 120 beats per minute when the P and T waves overlap.

Exercise electrocardiography in females

The diagnostic value of exercise testing in females is lower than in males, since it is confounded by a low prevalence of disease and a high incidence of ST segment depression during exercise in apparently normal members of this gender (58,71). Both factors have given rise to many frustrated reports which questioned the value of exercise testing in women. The low prevalence of coronary disease in females has implied that few females were represented in studies that tried to enhance the diagnostic accuracy of exercise testing with inherent problems of subsequent (non)applicability in the female population. The high incidence of ST segment depression in females has prompted Barolsky *et al.* to develop a discriminant

function with a compensatory sex-dependent ST segment factor (59). In an other attempt to increase the yield of the diagnostic exercise test in females, Ilsley *et al.* suggested the combined use of ST segment depression and increase in R wave amplitude with exercise (72).

The diagnostic worth of exercise testing and exercise electrocardiography in males and females will be addressed in more detail in Chapters 3 and 4.

Multivariate analyses

Multivariate techniques have been used to improve the diagnostic yield of exercise testing and to quantify the incremental diagnostic merits of the exercise test for the diagnosis of coronary disease compared with estimated based on clinical variables alone.

Discriminant analysis of exercise data was performed by Detry *et al.* in 387 males without previous infarction (10). With a combination of variables including heart rate at peak exercise, ST segment depression and ST segment slope, workload and symptoms during the test, the authors were able to correctly classify 83% of subjects studied. Other studies employed discriminant analysis or logistic regression analysis of clinical as well as exercise variables in patients without a previous myocardial infarction (73-77). The presence of angina, ST segment depression with exercise, peak heart rate and workload were the most predictive variables in these analyses (Table 2). Surprisingly, chest pain during exercise was an important variable in two investigations only. Clearly, this symptom is of limited diagnostic value in patients known to have typical angina, but it certainly could be of diagnostic use in patients with non-specific or atypical complaints. As a matter of fact, symptoms that were poorly understood during an office visit can be labeled as angina when they appear during the actual test and disappear soon after cessation of exercise.

Table 2 Clinical and exercise variables associated with the presence of coronary artery disease with multivariate techniques in different studies

Variables	Pruvost(73) n=558	Hung(74) n=171	Goldman(75) n=321	Fisher(76) n=1351	Currie(77) n=105
Angina (history)	v	v	v	v	v
Age	v		v	v	
Smoking			v	v	
Cholesterol					v
ST segment depression		v	v	v	v
Heart rate	v	v		v	
Angina during exercise	v			v	
Workload	v				v

Table 3 Estimation of angiographic prevalence of obstructive coronary artery disease in males and females of 50-59 years of age, based on symptoms and exercise test results (data derived from ref. 78). Numbers denote percentages.

		TYPE OF CHEST PAIN		
	Asymptomatic	Nonspecific angina	Atypical angina	Angina
Males				
Pretest probability	10	22	59	92
ST segment depression, mV				
0.0 - 0.04	2	6	25	73
0.05 - 0.09	9	20	57	91
0.10 - 0.14	19	37	75	96
0.15 - 0.19	31	53	86	98
0.20 - 0.24	54	75	94	99
> 0.25	81	91	98	99
Females				
Pretest probability	3	8	32	79
ST segment depression, mV				
0.0 - 0.04	1	2	10	47
0.05 - 0.09	3	8	31	78
0.10 - 0.14	7	16	50	89
0.15 - 0.19	12	28	67	94
0.20 - 0.24	27	50	84	98
> 0.25	56	78	95	99

Definitions:

Angina: *- substernal chest discomfort, precipitated by*
- exertion, emotion or cold
- relieved within 10 minutes after rest or nitroglycerin

Atypical angina: *only two of these characteristics are present*

Nonspecific: *only one characteristic is present*

Example: A 55 year old male with atypical complaints has a pretest probability of coronary artery disease of 59%; when exercise induced ST segment depression of 0.04 mV is observed, post-test probability of disease will decrease to 25%.

A Bayesian approach has also been developed to predict the likelihood of coronary disease in patients without previous myocardial infarction. Diamond and Forrester used data of more than 60,000 patients from the American literature to calculate pre- and post-exercise test probabilities of disease in a given subject, taking into account factors such as age, sex, risk factors, type of chest pain and ST segment changes during exercise (78). The data in Table 3 have been derived from these calculations and pertain to middle aged males and females. It is evident that an exercise test is not very useful to verify the diagnosis of obstructive coronary disease in a 56 year old man with typical angina. Even if there would be no electrocardiographic changes during the test, the likelihood of disease in that subject would still amount to 73 percent, while it is 99 percent in case 0.2 mV ST segment depression occurs with stress. Nevertheless, the test might be used in such a patient to determine his functional impairment. Similarly, the diagnostic value of exercise electrocardiography is low in asymptomatic subjects. The greatest diagnostic merit of exercise testing is obtained with intermediate pre-test likelihood of coronary disease - that is, in male patients with atypical complaints (60). The relative diagnostic contribution of clinical and exercise variables will be discussed in Chapter 5.

ST segment changes and the location of coronary disease

Attempts have been made to relate the degree or the location of ST segment changes during exercise to coronary anatomy. It is obvious that extensive coronary artery disease (three vessel or left main disease) is more likely to be present in a patient who develops large ST segment changes in multiple leads. However, even in patients with single vessel disease there is no clear separation between the leads where ST segment changes appear when either the right coronary artery or the left anterior descending artery are involved (79). Surface mapping has indicated that the ST segment depression is most prominent in the precordium, but the actual position where the largest ST segment depression occurs varies widely, from the level of the third intercostal space to the tenth intercostal space (80). Thus, prediction of the location of coronary disease is inconceivable from standard or even orthogonal electrocardiographic leads.

Supplementary noninvasive testing

Additional noninvasive tests can sometimes be required to confirm or to clarify the diagnosis of obstructive coronary disease. These ancillary techniques include cardiac fluoroscopy, exercise cardiokymography, exercise thallium imaging, exercise radionuclide cineangiography and exercise two-dimensional echocardiography (81-85). Cardiac fluoroscopy and exercise cardiokymography are relatively unknown and impopular tests with unconfirmed diagnostic accuracy. Exercise thallium imaging is now the most widely used additional diagnostic technique. Myocardial uptake of Thallium-201 after intravenous injection during peak exercise is dependent on the distribution of blood flow, and to a lesser extent on myocardial metabolism. Exercise

induced myocardial ischemia can be recognized as a region with abnormal Thallium uptake in the immediate postexercise scintigrams, which recovers completely or in part when delayed images are made, usually three to four hours after exercise. Comparative studies of conventional exercise electrocardiography and Thallium scintigraphy indicate that the latter is more sensitive and more specific for detection of coronary disease (86). Furthermore, Thallium scintigraphy permits to a certain extent separation of subjects with single and multiple vessel disease and detection of the location of significant coronary stenoses (87). The performance of Thallium scintigraphy has been improved by computer assisted quantitative analysis of the images (88). Therefore, Thallium scintigraphy may provide additional diagnostic information when diagnosis remains uncertain after conventional exercise testing.

Prognostic value of exercise testing

Already in 1953, Master *et al.* reported one to six year follow up data on 300 mostly asymptomatic patients who underwent a double two step test (89). The criterion for an abnormal test was ST segment depression of 0.5 mV or more or isoelectric-inverted T waves. Among the 150 patients with an abnormal test, 24 subsequently developed myocardial infarction or unstable angina and 20 died of cardiac causes. Among the 150 subjects with a negative test, only one had a myocardial infarction and none died.

Table 4 Exercise test outcome and coronary artery disease (CAD) mortality in MRFIT (90) and LRC (91)

	n	Age	% Abn test	Follow-up years	Mortality rate#	RR	95% CI
MRFIT	12,866	35-57	12	7	104	3.4*	2.3, 5.1
LRC	3,178	30-79	6	8	133	4.6**	1.8, 11.7

RR = relative risk; CI = confidence interval; abn = abnormal

* *adjusted for age, diastolic blood pressure, serum cholesterol level and number of cigarettes smoked per day*

** *adjusted for age*

\# *total CAD mortality per 10,000 person-years of follow-up*

The relative risk was defined as the risk for CAD mortality of patients with abnormal tests divided by that of patients with normal tests.

The prognostic value of exercise testing in asymptomatic subjects has been studied extensively in recent years. Results of the larger investigations, notably the Multiple Risk Factor Intervention Trial (MRFIT, 12,866 individuals) and the Lipids Research Clinics Mortality Follow-up Study (LRC, 3,178 individuals) indicate that apparently healthy male subjects with exercise induced ST segment depression have a three to five fold increase in subsequent cardiac mortality (Table 4)(90,91). Criterion for abnormality was a computer-read negative ST voltage time integral in MRFIT and a horizontal or downsloping ST segment depression of at least 0.1 mV in the LRC trial. However, both studies comprised study subjects with a higher than average risk profile and actual risk may be lower in subjects without risk factors or in women (92,93). Other studies were too small to detect differences in mortality rates between patients with and without exercise induced ST segment depression and used combined coronary events as endpoints. The results of these studies are less concordant. McHenry and associates observed an abnormal (horizontal or downsloping ST segment depression of at least 0.1 mV) exercise test in 61 of 916 asymptomatic males (94). This response was associated with a 34 percent incidence rate of cardiac events over an average 6.3 years follow-up: however, 86 percent of these events were anginal symptoms and only one of these 61 subjects died. A normal exercise electrocardiographic response was associated with a 5.3 percent incidence of events over the same time period: 56% of these were myocardial infarction and seven subjects in this group died suddenly. These results seem to indicate that an abnormal electrocardiographic response to exercise is a particularly good predictor of subsequent angina rather than of myocardial infarction. Giagnoni *et al.*, on the other hand, found exercise induced ST segment depression to be strongly associated with subsequent myocardial infarction rather than with angina (95). In the Seattle Heart Watch Study, ischemic ST segment depression during exercise was only associated with an increased risk of subsequent coronary disease when, in addition to one of the conventional risk factors, also two of the following exertional parameters were observed: lower than predicted heart rate, low workload or occurrence of chest pain with exercise (96). There is a clear relationship between classical risk factors and exercise induced ST segment depression: in MRFIT, a positive relation between magnitude of ST segment depression with age, total serum cholesterol and diastolic blood pressure was indeed observed (97). Surprisingly, an intriguing inverse relation association between smoking and ST segment depression was found, which could only be explained by the particular selection of subjects in that study. Nevertheless, the LRC trial demonstrated that exercise induced ST segment depression indeed represents an independent risk factor for cardiac related mortality (91).

The prognostic value of exercise test results in patients with known coronary disease was studied by Dagenais *et al.*, who reported a long term follow-up of 107 patients with 0.2 mV ST segment depression with exercise (98). This response was associated with a 26 percent five year mortality. Findings of Podrid *et al.*, on the other hand, were different (99). These authors reported 142 men with coronary artery disease who developed "pronounced" ST segment depression during exercise.

Table 5 Comparison of the prognostic value of various parameters from a pre-discharge exercise test

			ST depression			Angina			PVC			Wmax			Blood pressure		
Study	n	mort	+	-	RR	+	-	RR	+	-	RR	low	norm	RR	abn	norm	RR
Theroux (104)	210	10	17/64	3/146	12.9	7/43	13/167	2.1	7/42	13/168	2.2						
Weld (8)	236	9	7/52	14/184	1.8	7/49	14/187	1.9	7/18	14/218	6.1	20/121	1/115	19.0	8/33	12/195	3.9
Saunamaki*	317*	15*	13/115	26/153	0.7				13/49	34/268	2.1				33/138	14/179	3.1
Madsen (107)	205	16										31/153	1/52	10.5			
Fioretti (108)	300	7	8/133	11/165	0.9	3/61	17/239	0.7	7/63	13/237	2.0	16/144	4/156	4.3	14/88	6/212	5.6
Krone (109)	667	5	7/167	24/500	0.9	10/115	21/552	2.3	6/45	25/622	3.3	22/269	9/398	3.6	10/57	21/610	5.1
Combined	1935	9	52/531	78/1148	1.4	27/268	65/1145	1.8	40/217	99/1513	2.8	89/687	15/721	6.2	65/316	53/1196	4.6

mort = 1-year mortality rate; RR = risk ratio; PVC = premature ventricular complexes; Wmax = highest workload achieved; norm = normal; abn = abnormal

** including 49 subjects >70 years of age of whom 8 had died at 1 year follow-up (ref. 105, 106)*

Their annual mortality was only 1.4 percent, and survival did not correlate with ST segment depression, but with exercise duration. According to other studies, notably data from the CASS registry, combining clinical and exercise variables can be useful to distinguish high and low risk subgroups of patients coronary disease with similar anatomy in predicting cardiac mortality. These observations have emphasized the relevance of the exercise parameters workload as well as ischemic ST segment depression (100,101). Gohlke *et al.* analyzed the additional value of exercise testing in 1034 patients with known coronary anatomy and normal or mildly impaired left ventricular function (102). In various subgroups five year survival was highest in patients with the better exercise tolerance. For instance in patients with double vessel disease, five year survival was 95 percent in those with exercise tolerance greater than 110 Watts while survival was only 81 percent in those who performed less than 90 Watts in supine position.

In patients with a recent myocardial infarction, exercise tests can be performed as an aid in patient management and for prognostic reasons. These tests are safe, provided that the main contra-indications, manifest heart failure and post infarction angina, are rigidly observed. Patients excluded for predischarge exercise testing because of these cardiac contraindications carry the highest risk for mortality in the first year (8). Among all patients admitted to the coronary care unit with a myocardial infarction, the proportion of patients excluded for exercise testing amounted to 45 percent in 24 studies from different institutions (103). In ten reports which provided these data, mortality rate was 21 percent in excluded patients and only 8 percent during similar follow-up in patients who did perform the predischarge exercise test (103). Thus, the use of early exercise tests for assessing prognosis has been limited to patients recovering from an uncomplicated myocardial infarction and the selected nature of these patients complicates the interpretation of the available data. The prediction of prognosis in the first year after myocardial infarction in subsets of patients will be discussed further in Chapters 6 and 7 of this thesis.

In those eligible for predischarge exercise testing, the test will demonstrate whether the patient is indeed ready for discharge or that a few more days of rehabilitation in hospital are still indicated. In addition, a patient may develop angina pectoris at a low workload or will show other signs of serious myocardial ischemia necessitating early angiography and consideration for angioplasty or bypass surgery. Further, the test may enhance the patient's confidence and thus promote social and occupational rehabilitation in those with an uncomplicated course.

The data on one year prognosis that have been collected recently have shown that mortality after myocardial infarction relates a) to residual left ventricular function, reflected in exercise parameters like exercise tolerance, changes in heart rate and blood pressure and b) to signs of myocardial ischemia, such as angina, ST segment depression and c) to the development of ventricular arrhythmias. Table 5 summarizes data of studies on the prognostic value of exercise testing between 1 and 4 weeks after myocardial infarction (8,104-109). Only those studies which included

at least 20 deaths during one year follow up were selected. Endpoints like reinfarction, need for bypass surgery or recurrent angina were disregarded. A direct comparison of the data is hampered by the different exercise protocols as well as by the use of dissimilar electrocardiographic lead systems in the various reports. Nevertheless, when the data of these publications are combined, ST segment depression was observed in 531 out of 1679 postinfarction patients (32 percent); one year mortality associated with this criterion amounted to 52 patients (10 percent). This risk is 1.4 times greater than that of the 1148 patients without ST segment depression (78 deaths, 7 percent). The 95% confidence interval for the relative risk related to ST segment depression was between 1.0 and 2.0. A disproportionally high risk associated with exercise induced ST segment was reported by Theroux *et al.* (104). However, it should be noted that these authors later reported that four year mortality in their study population was no longer related to the presence of ST segment depression with exercise at discharge (110). Part of the differences between the studies has been caused by the medical care offered to patients with postinfarction angina or electrocardiographic signs of ischemia by selecting them subsequently for treatment with beta blockers or revascularization procedures. In his "meta-analysis" of postinfarction studies from 24 different institutions, Froelicher *et al.* found exercise induced ST segment depression to be suggestively predictive of increased risk in patients with inferior-posterior myocardial infarctions only (103).

Post infarction angina was a contraindication for the test in all studies presented in Table 5. Nevertheless, 19 percent of all exercised patients developed angina. The mortality in this group was 1.8 times higher than in the patients without this symptom. The increased risk associated with ventricular arrhythmias during exercise is difficult to evaluate since the criteria for these rhythm disturbances differ considerably between the studies. The combined subgroup of patients with so called "significant" ventricular arrhythmias had a relative risk of 2.8 (95% confidence interval 2.0-4.0).

The strongest predictors of outcome appear to be exercise tolerance and the blood pressure response during the stress test with combined relative risks of 6.3 and 4.6, respectively. Exercise parameters reflecting left ventricular function thus seem to correlate best with outcome after infarction. Information on this major prognostic variable can also be obtained by other means. In the study reported by the Multicenter Postinfarction Research Group, prospective risk stratification analysis was performed in 866 postinfarction patients using clinical variables, 24 hour Holter recordings and radionuclide determination of ejection fraction (110). Among the clinical variables, functional classification before entry and pulmonary rales early in the course of the infarction made a positive contribution to the model. Low ejection fraction and, to a lesser extent, frequent ventricular ectopic depolarizations also independently contributed to the survival model.

Left ventricular dysfunction and subsequent low workload during exercise will be observed more frequently in those with a history of a previous myocardial infarction or with a complicated course of the current event. It is evident that the additional

prognostic value of the exercise test will be more limited when other available data also are considered. Indeed, Madsen *et al.* observed no significant prognostic contribution of exercise variables when other clinical factors were taken into consideration by using multivariate analysis of clinical and exercise test data (112). Williams *et al.* also reported that prognosis after myocardial infarction was more accurately predicted by clinical than by exercise data (113). On the other hand, Fioretti and associates demonstrated that the extent of blood pressure rise during exercise slightly improved the predictive accuracy for survival beyond that of simple clinical characteristics (114). They, and others, concluded that, by the combined use of simple clinical characteristics and the predischarge exercise test, a large percentage of postinfarction patients at very low risk of mortality can be identified with easily obtainable and low cost techniques (109,115).

The symptom limited predischarge exercise test usually involves the most strenuous effort the patient has undergone since the acute event. Such testing is useful in shaping realistic expectations about the capacity of low risk patients to resume their customary activities. In general, well preserved functional capacity in these patients reflects the absence of severe myocardial ischemia and adequate left ventricular function. The ability of a patient to perform a high workload increases his or her confidence in the ability to engage in a number of physical activities, including rapid walking, cycling, yard work and normal sexual activity. A properly executed exercise test thus provides more insight into the measure of the heart's capacity to tolerate a wide variety of stimuli encountered during customary activities.

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CHAPTER 2

CHANGES IN THE ELECTROCARDIOGRAPHIC RESPONSE TO EXERCISE IN NORMAL FEMALES: COMPARISON WITH MALES

J.W. Deckers, R.V.H. Vinke, M.L. Simoons

ABSTRACT

Since the value of exercise electrocardiography in females is controversial, we quantitatively compared the changes in P wave, QRS complex, ST segment and T wave during and after maximal exercise in 116 healthy females (mean age 39 years) with those in 123 male volunteers (mean age 47 years). Exercise was performed on a bicycle ergometer, the orthogonal corrected Frank electrocardiogram was continuously recorded and computer processed. During exercise, maximal spatial P wave vectors shifted downward in both sexes. Q wave amplitude became more negative, R wave amplitude diminished in leads X and Y, and S wave amplitude decreased considerably, especially in males. QRS vectors shifted towards right and posterior with exercise, and shifted further in the recovery period in both sexes. In females, ST amplitudes at 60 msec after the J point were negative at higher heart rates (140 bpm) in leads X (-0.014 $\pm$ 0.031 mV, mean $\pm$ SD) and Y (-0.037 $\pm$ 0.077), but remained positive in the males (0.018 $\pm$ 0.048, and 0.030 $\pm$ 0.044). T wave amplitude decreased during exercise, and increased sharply in the recovery period. Although mean R wave amplitude in leads X and Y decreased with exercise, this response was unpredictable: the specificity of a decrease in R wave of 0.1 mV or greater in lead X amounted to only 34% in the female population. It is concluded that changes in P wave, QRS complex and T wave are similar between males and females. Changes in R wave amplitude should not be used for the diagnosis of coronary disease. ST segment depression is more pronounced in females, but the behaviour of the QRS vectors in the two sexes does not account for this difference.

INTRODUCTION

While exercise electrocardiography is an established method of predicting the presence of coronary disease in males, its value in females remains controversial (1). Some studies have described marked exercise induced ST segment depression in asymptomatic women (2-6), as well as in those without obstructions at coronary

angiography (7-10). Others claim that the value of the exercise test in females is similar to that in males (11-15), or that the high number of false positive tests in females can be solely attributed to the low prevalence of coronary disease in this gender (16,17). One recent study suggested that the diagnostic value of the test in females could be improved if exercise induced QRS changes were taken into account (18). Given these discrepancies, it is surprising that no prior study has quantitatively described the exercise induced electrocardiographic changes in females. For this reason, and in order to elucidate possible differences in the electrocardiographic response during exercise between females and males, we studied the electrocardiographic changes of the P wave, QRS complex, ST segment and T wave during and after exercise in 116 female volunteers presumed to be free of cardiac disease. These data were compared with the exercise induced electrocardiographic changes in 123 healthy males.

METHODS AND STUDY POPULATION

Exercise tests were performed in 116 females and 123 males. All subjects were healthy volunteers, without chest pain and without a history of cardiovascular disease. All had a normal electrocardiogram at rest, blood pressure below 165/95 mmHg, and fasting serum cholesterol below 6.7 mmol/l. Smoking history was not taken into account. The subjects did not use any medication. None had ausculatory findings suggestive of mitral valve prolapse or other forms of valvular disease. Details of the male subjects selected have been published previously (19). Mean age of the males was 47 years (SD 10 years). After a mean follow-up of 108 months (SD 9 months) 119 were alive and 4 had died. Mean age of the females was 39 years (SD 10 years). Seven female subjects were lost to follow-up: 2 because of emigration and 5 others who could not be located. The remaining 109 females were all alive at a mean follow-up of 53 months (SD 1 month). The electrocardiograms of the 4 deceased subjects and of the 7 females lost to follow-up were reviewed separately. Since these electrocardiograms fell within the 5th and 95th percentile of the other male and female subjects, they were retained in the study.

Exercise was performed in sitting position on a calibrated bicycle ergometer. Workload was increased in a stepwise manner by 10 Watts per minute. The test was terminated when the subjects neared exhaustion. Cycling was continued at a low load for 4 minutes after peak exercise.

The corrected orthogonal Frank lead electrocardiogram was recorded with the chest electrodes at the level of the fifth intercostal space. The F electrode was placed on the sacrum, the H electrode on the neck. Careful attention was paid to proper preparation of the skin and fixation of the electrodes and wires. The electrocardiograms were computer processed as described in detail elsewhere (20). In brief, the 3 orthogonal leads were sampled during 20 seconds at rest in sitting position, every minute during exercise and during six minutes in the recovery period. The

sampling frequency was 250 Hz. After QRS detection, complexes with deviant morphology or excessive baseline drift were rejected. From the remaining beats an average representative complex was calculated. Templates were used to define onset and termination of QRS complexes (21). The resting electrocardiogram of each subject was analyzed with a general template. After visual inspection and validation of the reference points, patient specific templates were calculated and recorded (20). Onset, peak, and end of the P and the T wave were also determined. For each lead, Q, R, and S waves were located. The baseline level was defined as the mean signal amplitude 5 to 3 samples (20 to 12 msec) before the QRS onset. All amplitudes were measured relative to this baseline.

RESULTS

The maximum workload achieved by the females was 156 ± 32 Watts (mean ± SD); the males reached 174 ± 42 Watts. Maximum heart rate was 170 ± 16 beats/min in females and 165 ± 18 beats/min in males. In both groups, maximal heart rate and workload decreased with age as illustrated in Table 1.

Table 1 Age distribution, mean values and ranges of maximal heart rate and workload during exercise in 116 healthy females and 123 healthy males

Age, years	FEMALES			MALES		
	n	Heart rate (range)	Workload (range)	n	Heart rate (range)	Workload (range)
< 20	2	187 (184-189)	160 (160)	1	180	210
20 - 29	24	178 (154-197)	171 (90-240)	12	172 (140-190)	221 (130-340)
30 - 39	34	173 (130-202)	169 (120-260)	13	165 (140-192)	166 (130-240)
40 - 49	41	164 (128-188)	143 (70-180)	41	171 (116-206)	178 (70-260)
50 - 59	12	154 (115-176)	136 (80-220)	48	161 (120-189)	163 (80-240)
> 60	3	145 (132-159)	127 (100-160)	8	151 (133-168)	159 (130-180)

Systolic blood pressure in the female population rose from a resting value of 137 ± 17 mmHg to maximum value of 195 ± 18 mmHg, and in males from 139 ± 15 mmHg to 204 ± 25 mmHg.

P wave

In both sexes, the interval between the maximal spatial magnitude of the P wave and the onset of QRS complex decreased during exercise, and lengthened again in the recovery period. Figure 1 depicts mean values of P amplitude in leads X, Y and Z at increasing heart rates during exercise, and at decreasing heart rates in the recovery period. With exercise, an increase in P wave amplitude was seen in all leads, especially in lead Y. These changes represent a gradual shift of the maximal P wave amplitude towards anterior, left and down in females as well as in males. P wave amplitude was higher in the recovery period then during exercise at corresponding heart rates.

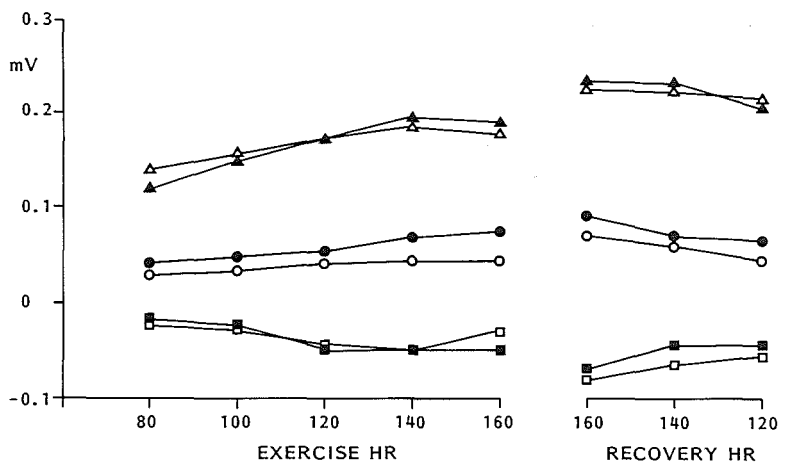

Figure 1 Changes in maximal P wave amplitude in females and males at heart rates of 80, 100, 120, 140 and 160 beats per minute during exercise, and at heart rates of 160, 140 and 120 beats per minute during recovery in Frank leads X, Y and Z.
Abbreviations: HR = heart rate
lead X, females: ○ *; lead X, males:* ●
lead Y, females: △ *; lead Y, males:* ▲
lead Z, females: □ *; lead Z, males:* ■

QRS complex

No significant change was observed in the QRS duration during exercise in either sex. The Q wave became slightly more negative in leads X and Y at the end of exercise, and less negative in lead Z (Figure 2). Q waves in lead Z were more deeper (more negative) in male than in female subjects at all heart rate levels. R waves in males in leads X and Z were higher (more positive) than in females at rest and at any level of exercise. On the other hand, R wave amplitude in lead Y in females was always higher than in males. In both sexes, the R wave decreased during exercise in leads X and Y (Figure 3), but became slightly more positive at the end of the test in lead Z.

The changes in R wave amplitude during exercise varied widely between individual subjects. In Figure 4, changes in R wave amplitude in lead X relative to control values in female volunteers are plotted against heart rate. A decrease in R wave amplitude greater than 0.1 mV was observed in 31 of 116 females, and in 64 of 123 males in lead X at peak exercise. More details of the R wave responses during exercise are presented for both sexes in Table 2.

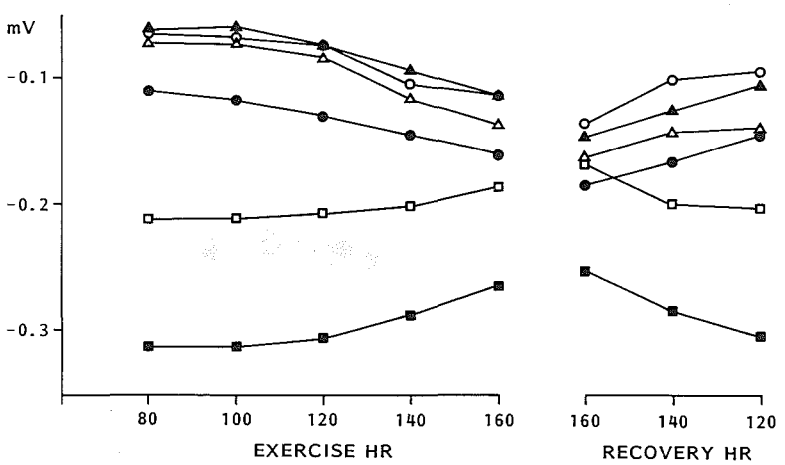

Figure 2 Changes in maximal Q wave amplitudes in females and males at different heart rates during exercise and recovery in Frank leads X, Y and Z. Abbreviations and symbols as in Figure 1.

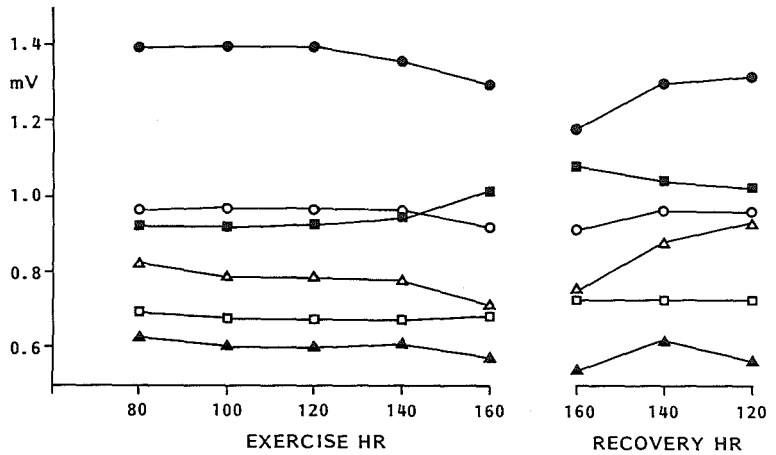

Figure 3 Changes in maximal R wave amplitudes in females and males at different heart rates during exercise and recovery in Frank leads X, Y and Z. Abbreviations and symbols as in Figure 1.

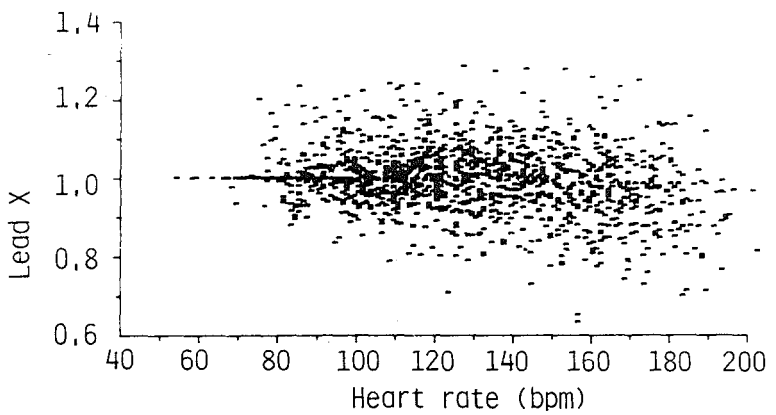

Figure 4 Individual changes in R wave amplitude during exercise in female volunteers in lead X: measurements have been made relative to control R wave values.

In concordance with the R wave response, the S wave amplitude became considerably more negative at the end of exercise in leads X and Y, but remained unchanged in lead Z (Figure 5).

Taken as a whole, the changes in the QRS complex in both sexes correspond to a gradual shift of QRS vectors during exercise towards right and posterior, with a further shift in the recovery period.

Table 2 Changes in R wave amplitude during exercise in Frank leads X and Y

	Lead X		Lead Y	
	Females n = 116	Males n = 123	Females n = 116	Males n = 123
Increase >0.1 mV (%)	7 (6)	10 (8)	6 (5)	9 (7)
No change (%)	70 (60)	14 (11)	7 (6)	40 (33)
Decrease >0.1 mV (%)	31 (27)	64 (52)	65 (56)	52 (42)
Decrease >0.2 mV (%)	8 (7)	35 (29)	38 (33)	22 (18)

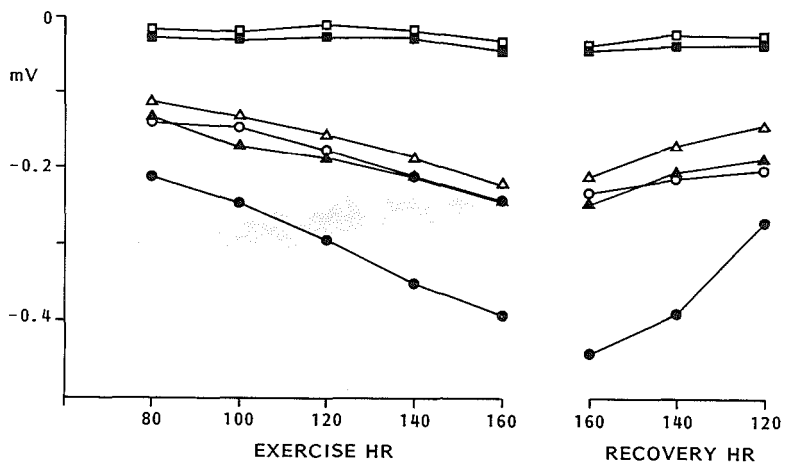

Figure 5 Changes in maximal S wave amplitudes in females and males at different heart rates during exercise and recovery in Frank leads X, Y and Z. Abbreviations and symbols as in Figure 1.

ST segment

A marked difference became apparent during exercise in ST segment amplitude changes between males and females. For example at a heart rate of 140 beats/min ST amplitude 60 msec after the J point in females was -.014 ± 0.031 mv (mean ± SD) and in males 0.018 ± 0.048 mV. This difference was even more pronounced in lead Y: at 140 beats/min ST 60 msec in females was -.037 ± 0.077 mV and in males 0.030 ± 0.44 mV. In Figure 6a + 6b, individual female ST segment amplitudes in leads X and Y are plotted against heart rate. The figures illustrate that a large number of these

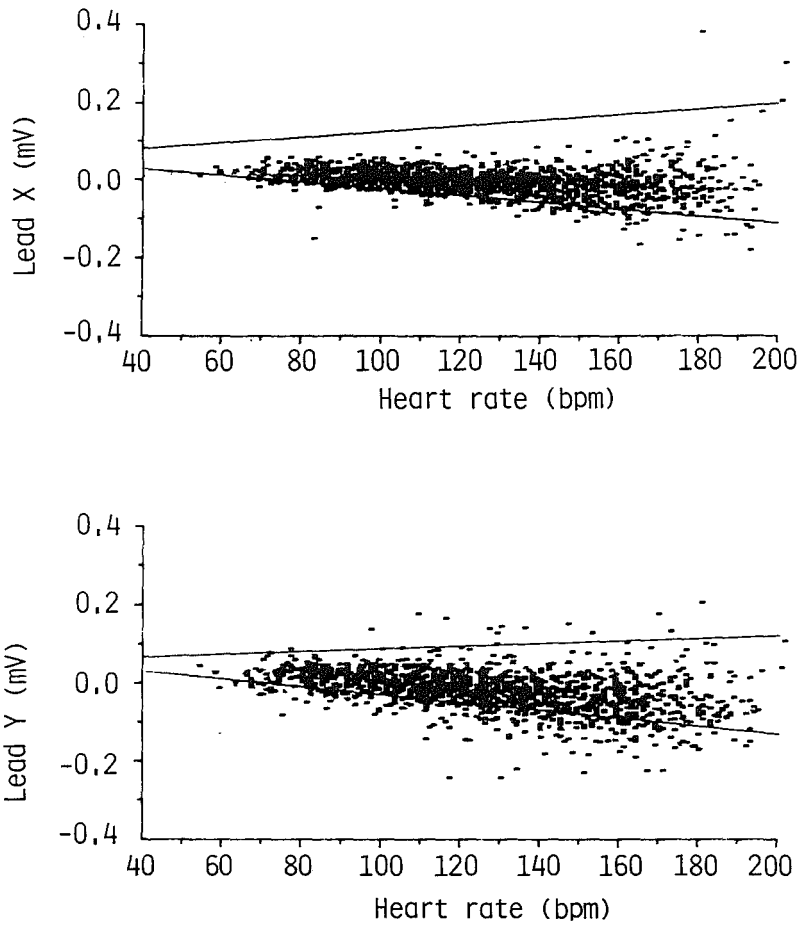

Figure 6a and 6b Individual changes in ST segment amplitude 60 msec after the J point in females in Frank lead X (Figure 6a) and Frank lead Y (Figure 6b) during exercise. The lines indicate the 5 and 95 percentile limits of the same measurement in the male population.

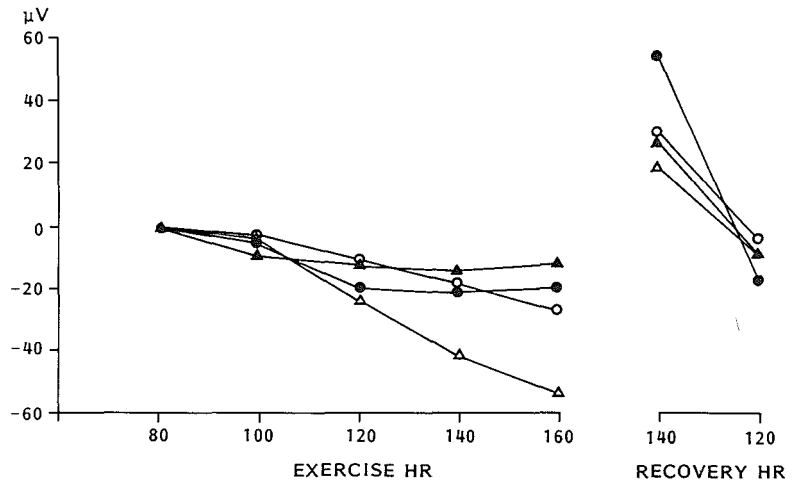

Figure 7 Changes in ST segment amplitude 60 msec after the J point at different heart rates during exercise and recovery in males and females in Frank leads X and Y: measurements have been made relative to control ST segment amplitudes. Abbreviations and symbols as in Figure 1.

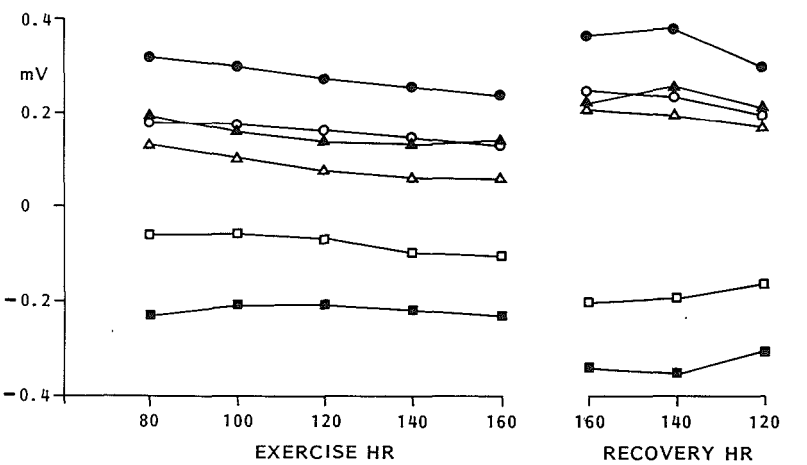

Figure 8 Changes in maximal T wave amplitudes in females and males at different heart rates during exercise and recovery in Frank leads X, Y and Z. Abbreviations as in Figure 1.

measurements fell in the lower range or even outside the 5 and 95 percentile limits of the males, especially at higher heart rates in lead Y. The different behaviour of the ST segment response in lead X and Y during exercise in females is also illustrated in Figure 7, in which ST segment changes during exercise are illustrated relative to resting ST segment amplitudes.

T wave

During exercise the Q - T interval shortened gradually in male and in female subjects. T wave amplitude decreased during early exercise, but increased sharply in all leads immediately after cessation of exertion (Figure 8). There was a shift of the T wave to right and superior, that was linear dependent on heart rate.

DISCUSSION

The continuing controversy regarding the clinical significance of electrocardiographic changes in females during exercise has limited the usefulness of the test in this gender (22). In males, reference values for the exercise induced electrocardiographic changes and variations in this response have been accurately established (19), and the observed electrocardiographic changes are in agreement with those reported by others (23,24,26-28). In females, however, such a description is lacking.

Therefore, we compared the electrocardiographic changes during exercise in females with those of male subjects in a study population without signs of or major risk factors for coronary disease. Follow-up revealed a low mortality in the males while no deaths occurred in the female population. The expected mortality for this population sample in The Netherlands at the time of follow-up was 12 for males and one for females. Since the observed mortality figures are lower, the study population can indeed be considered to represent a healthy group of middle aged men and women without significant coronary disease. Achieved workload, peak heart rate and systolic blood pressure in both populations correspond with earlier data and indicate near maximal levels of exercise (4,25,26,27).

The observed changes between males and females in resting electrocardiographic amplitudes are comparable to previous descriptions (29). The results of this study demonstrate that the exercise induced changes in P wave, QRS complex and T wave in females are largely similar to those observed in males. In both sexes, maximal P wave vectors shift predominantly downward, whereas maximal QRS vectors shift to the right and posterior during exertion. Significant sex differences exist in the ST segment response: with exercise, ST segment depression is more pronounced in the female population. This different response is present in Frank lead X as well as in lead Y. Since the data indicate that S wave amplitudes, which could be responsible for ST segment changes, were more negative in leads X and Y in males than in females, the difference in ST segment changes cannot be caused by different behaviour of QRS vectors in females.

Previous reports on exercise induced electrocardiographic changes in females have addressed only the ST segment response. In asymptomatic, healthy female volunteers, the incidence of 1 mm or greater ST segment depression has been reported as low as 2% (11), and as high as 50% in middle aged women (4,5). In follow-up studies, exercise induced ST segment depression proved a poor predictor of future coronary events in asymptomatic women and in females with atypical chest complaints (6,13,15). In a review by Val *et al.* (30), specificity of the exercise electrocardiogram in women with normal coronary arteries ranged from 63% to 92% (14,16). In all four studies in which ST segment changes in females were compared in those in males, the specificity in males was slightly higher (1,10,16,17). For example, in the large series reported by Weiner, the specificity of the electrocardiogram taken during exercise in the total population was 74% in men versus 64% in women (17). However, in a paired subgroup matched for age and the presence and extent of coronary artery disease, no statistically significant differences were found between men and women in the percentages of false positive and false negative responders.

In fact, these studies do not contradict our data, which indicate a higher incidence of ST segment depression at high heart rates in females. The lack of statistical significance between ST segment response in females and males in other studies is most likely due to the small number of subjects studied and to the limited accuracy of visual electrocardiographic interpretation in comparison to the presently available quantitative techniques (1,10,16). The most marked differences between females and males occurred in lead Y. This finding supports the observations by Sketch (1), who reported a higher incidence of ST segment depression in leads II, III, and aVF in 46 females without significant coronary disease. Val *et al.* also observed that the specificity of the exercise induced ST segment depression in females was dependent on the electrocardiographic lead chosen, with lowest specificity in leads II, III, aVF, V_5 and CM_5 (27).

Mechanisms which may contribute to the changes in P waves, QRS complexes and ST segment during exercise have been summarized earlier (19,24). Changes in the position of electrodes relative to the heart, in the ionic balance, in hematocrit levels and in alterations of intra cardiac volume have all been implicated contributing factors. There is no evidence that any one of these mechanisms acts differently in the two sexes. It seems thus unlikely that any of these factors can explain the different ST segment response to exercise in females. On the other hand, the observation that ST segment depression during exercise occurs more frequently in female volunteers that in healthy males cannot be explained by lower incidence of coronary disease in females (16). It is obvious that other studies are warranted to identify this "non-Bayesian factor" (10).

Some studies have suggested an increase in R wave amplitude during exercise to be diagnostic of coronary disease (31,32), but this view has met serious criticism (33-36). In fact, part of the reported difference between R wave changes in subjects with and without coronary disease may be due to differences in peak heart rate during the

test. For example, in the study by Ilsley *et al.*, women with coronary disease had lower peak heart rates compared to those without significant coronary obstructions (107 beats/min versus 130 beats/min)(18). In the present study, mean R wave amplitude decreased during peak exercise in leads X and Y, but individual R wave changes proved unpredictable. In a considerable number of tests, R wave amplitudes did not change, or actually increased either at the end of exercise or during lower levels of exercise (Figure 4). This phenomenon has also been observed by others (24). If a decrease in R wave amplitude greater than 0.1 mV in lead X during exercise was considered normal in females, this parameter would yield a specificity of only 34% in the present study. Specificity of lead Y for this response was higher at 77%, but the wide variability in R wave response during exercise certainly does not support the application of such changes for diagnosis of coronary disease in females or in males.

CONCLUSIONS

This study demonstrates that the exercise induced changes in P wave, QRS complex and T wave in females are comparable to those observed in males, particularly when adjustments are made for differences in resting electrocardiographic amplitudes. Changes in R wave amplitude are unpredictable, and cannot be used for the diagnosis of coronary disease in either sex. ST segment depression is more pronounced in females in leads X and Y, although changes in S wave amplitude are similar in both sexes. Thus, the differences in ST segment amplitudes cannot be explained by differences in QRS vectors between males and females.

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CHAPTER 3

COMPARISON OF EXERCISE ALGORITHMS FOR DIAGNOSIS OF CORONARY ARTERY DISEASE

J.W. Deckers, B.J. Rensing, J.G.P. Tijssen, R.V.H. Vinke, A.J. Azar, M.L. Simoons

ABSTRACT

In order to test their diagnostic accuracy, the following previously proposed exercise algorithms were evaluated: a) the cumulative area of ST segment depression during exercise normalized for workload and heart rate (exercise score), b) discriminant analysis of electrocardiographic exercise variables, workload and symptoms and c) heart rate adjusted ST segment amplitude changes during exercise. The study population comprised 345 males without a history of myocardial infarction and included 123 apparently healthy subjects. Prevalence of coronary artery disease was 51%. All had a normal ECG at rest. Frank lead ECG was computer processed during symptom limited bicycle ergometry. The exercise score yielded low accuracy (sensitivity 67%, specificity 90%). Discriminant analysis and heart rate adjusted ST segment amplitude changes proved to have excellent diagnostic characteristics (sensitivity 80%, specificity 90%), which were hardly affected by concomitant use of beta blockers. Both methods seem well suited for diagnostic application in clinical practice.

INTRODUCTION

In 1977, a system for computer assisted interpretation of the exercise electrocardiograms was introduced in our institution. This system employed heart rate adjusted ST segment amplitudes and ST segment slopes, and yielded a higher diagnostic accuracy than visual interpretation of the exercise electrocardiogram (1). Since then, a variety of other sophisticated diagnostic algorithms has been described which not only include electrocardiographic variables, but other exercise parameters as well (2-5). Hollenberg *et al.* proposed a treadmill exercise score which quantifies the cumulative area of ST segment depression during exercise normalized for workload (2,3). In 116 male subjects with a high prior probability of coronary disease, this score yielded a sensitivity of 85% and a specificity of 91%. Among 45 males with low likelihood of coronary disease but with a positive test according to conventional interpretation, the score identified the one subject who had coronary

artery disease and produced no false positive responses (3). Detry *et al.* developed a discriminant function which correctly classified 83% of a study population of 370 males without previous myocardial infarction (4). 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 yielded the highest diagnostic accuracy (5). Respective claims that these techniques enhance the diagnostic accuracy of exercise electrocardiography have however not yet been confirmed in independent series of patients. This study was undertaken in order to compare the merits of these approaches in a study population of 345 subjects without previous myocardial infarction.

METHODS

Study population

The study population consisted of 345 males. None of them had a prior myocardial infarction or used digitalis. All had a normal ECG at rest. The study group included 222 symptomatic male patients 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 CASS register criteria (6). Left ventriculography and coronary angiography were performed within three months after the exercise test. The presence of a diameter stenosis of at least 50% in one or more major coronary arteries was considered evidence for coronary disease. Angiograms were interpreted by two experienced cardiologists without knowledge of the exercise test results. Beta blocking drugs were continued at the time of the exercise test in 95 patients with coronary disease and in 21 patients with normal angiograms.

The other 123 subjects were studied in the framework of the Kaunas-Rotterdam Intervention Study. In this WHO project, a representative sample of the Rotterdam male population 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 used cardiac medication.

Exercise test

A symptom limited exercise test was performed in sitting position on a bicycle ergometer. Workload was increased in a stepwise manner with 10 or 20 Watts/min until moderate symptoms appeared or until exhaustion occurred. Cycling was then continued at a low load for 4 minutes after peak exercise.

The corrected orthogonal Frank lead ECG was recorded with the chest electrodes attached at the level of the fifth intercostal space. The ECG was computer processed as published earlier (8). In short, the ECG was sampled during 20 seconds

at rest in sitting position, every minute during exercise and during a six minute recovery period. Sampling frequency was 250 Hz. After rejection of complexes with deviant morphology or excessive baseline drift, an average representative complex was calculated (9). The baseline level was defined as the mean signal amplitude 5 to 3 samples (20 - 12 msec) 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 at 20 msec intervals between J and 100 msec after J in leads X and Y. ST_{20} denotes the ST amplitude 20 msec after J.

The following diagnostic algorithms, outlined in Table 1, were evaluated:

1) Instantaneous heart rate adjusted ST segment measurements (1). The diagnostic accuracy of the combination of ST_{20} and ST_{80} in Frank lead X, corrected for heart rate, was re-evaluated.
2) A modification of the treadmill exercise score as described by Hollenberg *et al.* This score quantifies the electrocardiographic response to exercise by the cumulative area of ST segment amplitude during exercise and recovery in leads V_5 and aVF, which is then normalized for QRS amplitude and for workload-- this is achieved by dividing the ST segment sum by the product of the duration of exercise (in minutes) and the fraction of the maximal predicted heart rate (MPHR) achieved (2,3,10). The following modifications of the original method were made in this analysis: Frank leads X and Y were employed instead of ECG leads V_5 and aVF; electrocardiographic measurements in the recovery period were limited to six minutes after peak exercise instead of 10 minutes. ST segment slope was calculated from ST segment amplitudes at 20 and 60 msec, since this proved to be the most informative slope in our study population. The slope measurements in the original publication were not specified. Maximal predicted heart rate was calculated as MPHR = 220 - age. Mean R wave amplitude values obtained in the present study population were entered as $\overline{R}$ in the algorithm. We therefore evaluated the following formula:

$$\text{exercise score} = \frac{\begin{array}{c}\text{area (J point + ST slope) lead X} * \overline{R} / \text{R lead X} \\ + \\ \text{area (J point + ST slope) lead Y} * \overline{R} / \text{R lead Y}\end{array}}{\text{exercise duration} * \text{fraction of MPHR}}$$

3) Discriminant analysis as described by Detry *et al.* (4). The discriminant function (D) is the sum of the exercise variables presented in Table 2.
4) The ECG method as proposed by Detrano *et al.* (5). Adjustments of ST amplitude changes for heart rate were made in Frank lead X only:

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

Table 1 Electrocardiographic and exercise parameters of the various diagnostic exercise algorithms

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

HR = heart rate; ex = peak exercise
ST_{20} denotes ST segment amplitude at 20 msec after J
X and Y: Frank leads X and Y

Table 2 Results of discriminant analysis of exercise variables in 345 male patients without previous myocardial infarction with coefficients derived by Detry (4) and with those obtained in the present study

	Detry			This study		
	Weight	Discriminant score*		Weight	Discriminant score*	
Exercise variables		CAD	Normals		CAD	Normals
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, Watts	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 item at issue*

** *calculated as the sum of the item-specific scores; this score can be interpreted as the discriminant score of the average patient*

Univariate analysis with unpaired Student's t test for continuous variables, and with Fisher's exact test for discrete variables was utilized. Stepwise discriminant analysis was performed with the BMDP 7A statistical package. Receiver operator characteristic curves were used to present sensitivity and specificity of the various electrocardiographic variables and of the different diagnostic algorithms and their subelements.

RESULTS

Details of the study population are presented in Table 3. Among 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 symptomatic males had normal coronary arteries or non-significant lesions at angiography. No angiography was performed in the 123 asymptomatic men. However, their absence of significant heart disease was confirmed by 9 years (SD 9 months) follow-up. At that time, only six of them had died while the expected mortality for a random sample of Dutch males of similar age would have been 12 subjects (11).

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

Sensitivity for the prediction of coronary disease of ST_{60} and ST_{80} in lead X amounted to around 70% at a specificity of 90%. $ST_{20\text{-}60}$ slope in that lead had similar diagnostic value (Figure 1). ST_{20} yielded a lower diagnostic accuracy, while intermediate values were obtained for ST segment measurements at 40 and 100 msec in that lead (not illustrated). Other electrocardiographic variables used in the various algorithms, such as J point amplitudes in leads X and Y, and $ST_{20\text{-}60}$ slope in lead Y were rather inaccurate indicators for the presence or absence of coronary disease (Figure 1).

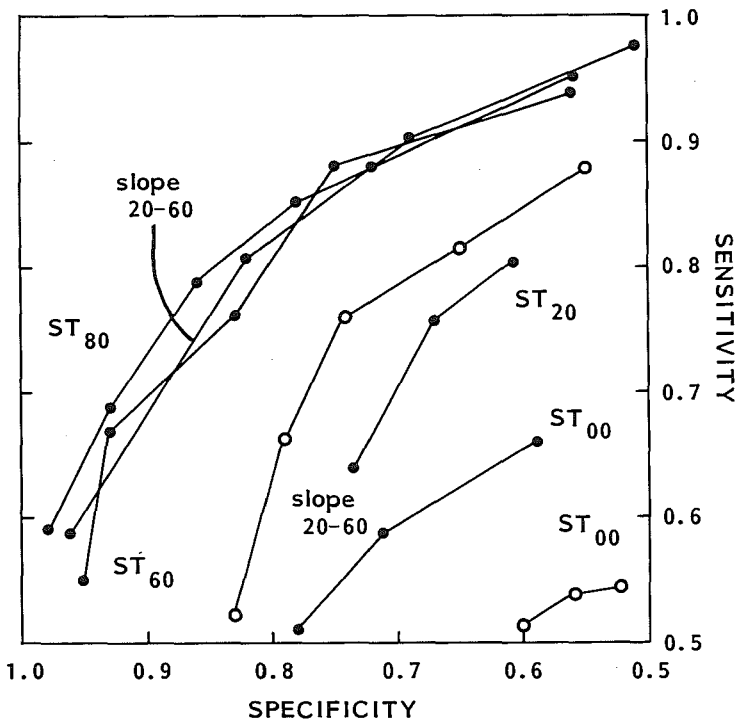


Figure 1 Sensitivity and specificity for the prediction of coronary disease of ST_{00} in Frank leads X and Y, ST_{20}, ST_{60} and ST_{80} in lead X, and $ST_{20\text{-}60}$ slope in leads X and Y in 345 male subjects without previous myocardial infarction.

Table 3 Clinical and angiographic data of 345 male subjects without previous myocardial infarction

History	N	age, years mean	range	CAD N	%
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

The diagnostic yield of instantaneous heart rate adjusted ST segment measurements was good with a sensitivity of 74% at a specificity level of 90% in the study population as a whole (Figure 2, Table 5). However, these measurements were less reliable in the 116 subjects with beta blockers (95 subjects with coronary disease and 21 males with normal angiograms) (Table 5).

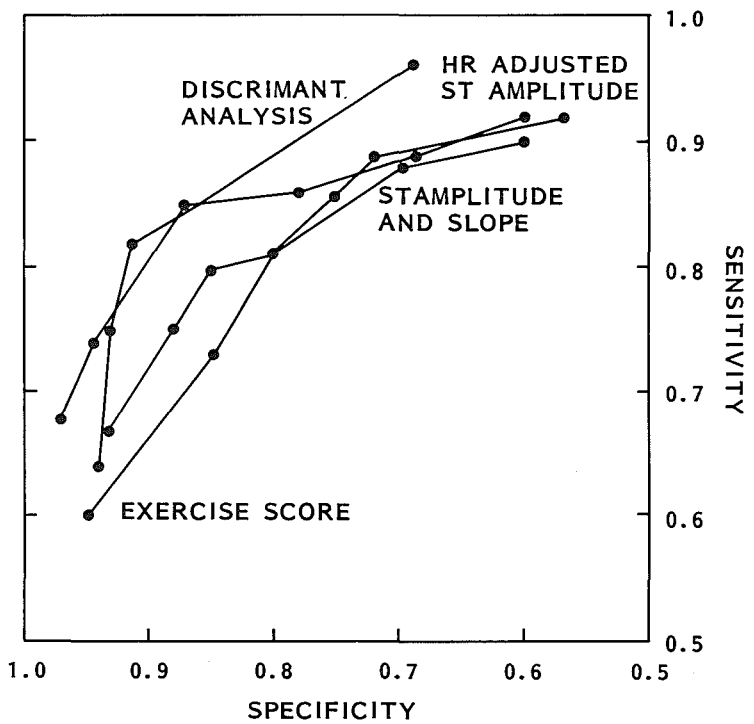


Figure 2 Sensitivity and specificity for the prediction of coronary disease of ST segment changes adjusted for instantaneous heart rate, exercise score, discriminant function according to Detry et al. and heart rate adjusted ST amplitude changes as proposed by Detrano in 345 male subjects.

Table 4 Exercise test data in 170 patients with coronary disease (CAD), in 52 patients with normal coronary angiograms (NoCAD) and in 123 asymptomatic male subjects. Measurements are given at peak exercise, unless otherwise indicated. All data, with the exception of angina, are represented as mean ± SD.

	CAD n = 170		All normals n = 175	NoCAD n = 52		Healthy men n = 123
Max workload, Watts	115 ± 33	**	168 ± 43	156 ± 46	*	173 ± 41
Angina (%)	103 (61%)	**	7 (4%)	7 (13%)		--
Max heart rate, bpm	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/sec	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} slope lead Y, μV	-46 ± 63	**	10 ± 66	-16 ± 55	*	21 ± 67
ST_{80} slope lead Y, μV	-31 ± 76	**	51 ± 92	2 ± 69	*	70 ± 92
ST_{20-60} slope lead Y, μV/sec	0.43 ± 0.62	**	1.28 ± 0.84	0.97 ± 0.70		1.40 ± 0.87

** *p = < 0.001 CAD vs all normals*

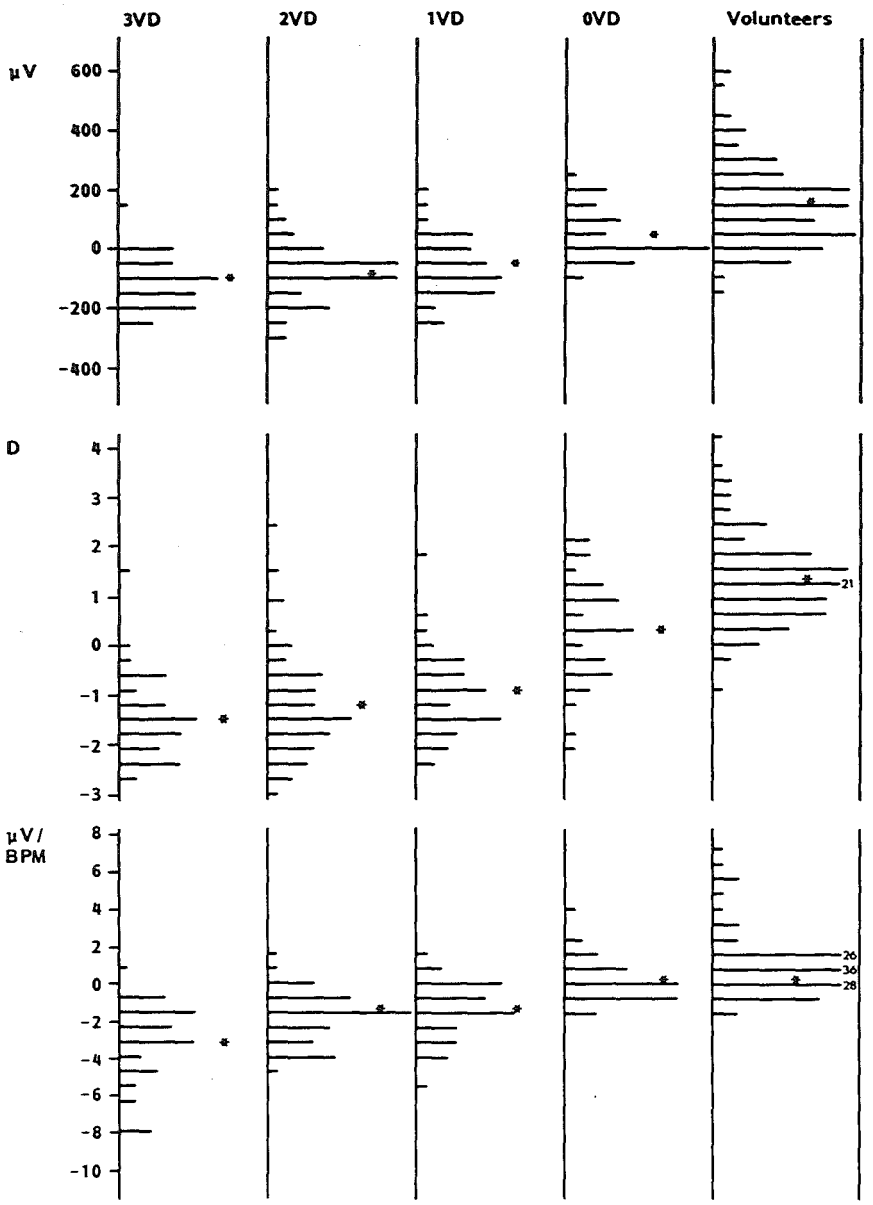
* *p = < 0.02 NoCAD vs healthy men*

Table 5 Sensitivities (%) at fixed specificity for various diagnostic exercise algorithms and their components

	SPECIFICITY (%)			
	80	85	90	95
HR adjusted ST amplitudes and slope (1)				
All patients	82	79	74	58
Patients with beta-blockers	73	64	63	43
Patients without beta-blockers	84	81	76	68
Exercise score (2,3)				
All patients	82	73	67	60
Patients with beta blockers	74	68	66	58
Patients without beta-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 (4)				
All patients	88	86	84	50
Patients with beta-blockers	89	82	71	66
Patients without beta-blockers	91	89	84	54
Present analysis	95	92	91	78
HR adjusted ST segment changes (5)				
All patients	84	82	78	73
Patients with beta-blockers	81	81	80	77
Patients without beta-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

The diagnostic accuracy of the exercise score was low, even in patients without beta blockers (Figure 2, Table 5). Conventional ST segment measurements in lead X were more powerful predictors. In order to determine the strong and weak components of the exercise score, the various elements of the original algorithm were analyzed. 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 in the denominator of the equation decreased the diagnostic value of the test (Table 5).


3VD
2VD
1VD
0VD
Volunteers
µV
600
400
200
0
-200
-400
D
4
3
2
1
0
-1
-2
-3
21
µV/
BPM
8
6
4
2
0
-2
-4
-6
-8
-10
26
36
28

Relatively high levels of sensitivity and specificity were obtained with discriminant analysis (Figure 2). The method also proved to be accurate in patients with beta blockers, although sensitivity was higher at corresponding levels of specificity in patients without these drugs (Table 5). In order to determine the coefficients of the discriminant function in this independent series of patients, stepwise discriminant analysis was performed in this study population with the same variables. The derived coefficients are presented in Table 2; sensitivity and specificity of this analysis are provided in Table 5. ST segment amplitude carried more weight in this "optimised" equation, and the differences between the coefficients of the two discriminant functions related to ST_{60} indeed reached statistical significance.

The adjustment of the ST segment changes for heart rate yielded a high sensitivity for the presence of coronary disease at all levels of specificity (Figure 2, Table 5). The results of the analysis were not affected by the use of beta blocking agents during exercise. The test yielded only mediocre levels of sensitivity and specificity when the unadjusted difference between ST segment measurements at peak exercise and at rest was 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).

Figure 3 Exercise variables ST_{80} in lead X, values obtained with discriminant function according to Detry and heart rate adjusted ST segment amplitudes in 345 male subjects with different severity of disease: three vessel disease (VD), two vessel disease, single vessel disease, patients with normal findings at angiography (NoCAD) and volunteers.

top panel : distribution of ST_{80}
middle panel : discriminant analysis
bottom panel : HR adjusted ST segment amplitudes
One whole column represents 20 subjects
The asterix indicates the mean in that group
Note:
- *overlap between the various groups, in particular between one VD and two VD*
- *three VD most abnormal, volunteers most normal*

DISCUSSION

Promising new diagnostic techniques often generate limited success after subsequent application in other populations (12). Methodological defects in the selection of patients and biased evaluation of test and disease status are the main source for this phenomenon (13). The role of different stress test protocols or electrocardiographic techniques between the various studies seems less crucial (14). The present study population can indeed be considered to represent a broad range of male patients, although the subjects without disease were a mixture of asymptomatic, apparently very healthy, and symptomatic male subjects without significant coronary disease. This latter group obviously shared many characteristics of the patients with disease, as demonstrated by their mean hemodynamic and electrocardiographic exercise parameters. This continuous spectrum of the population at study is reflected in Figure 3, in which the subjects are classified in relation to the severity of disease and the results of the exercise test.

Discriminant function analysis of exercise variables and heart rate adjusted ST segment amplitude changes appeared to be the best methods to predict the absence or presence of obstructive coronary disease. Both analyses yielded a sensitivity between 70% and 80% at a specificity level of 90%. The highest diagnostic accuracy was obtained with discriminant analysis according to Detry. Repeat computation of the discriminant function in this population yielded rather similar coefficients as the original values of Detry, although the weight of ST segment changes in our equation was higher. The relative significance of the various exercise variables in the discriminant analyses can be appreciated when the mean exercise variables of the two patient groups are entered in the two equations (Table 2). Heart rate at peak exercise, ST_{60} in lead X and the appearance of angina during exercise are the most important variables in these functions, corroborating data from other studies (15-17). Although exercise tolerance is a major indicator of prognosis in patients with known coronary disease (18), workload was not an important adjunct for the diagnosis of coronary disease in either function in these patients without previous myocardial infarction. The use of the parameter anginal symptoms during exercise in the discriminant function deserves some comment: since Bayesian probability analysis is only appropriate in case of mutual independence of variables, the presence of this variable in the function could limit its Bayesian application in case the variable angina had already been used to calculate the pre-test risk of coronary disease (19).

The adjustment of ST segment amplitude for heart rate in the manner proposed by Detrano *et al.* yielded similar diagnostic results: a sensitivity of 78% at a specificity level of 90%. This is even more remarkable because we evaluated ST segment changes in Frank lead X only. The processing of the electrocardiographic variables by computer, as well as the exclusion of data from females in this study are probably responsible for this excellent achievement (20,21).

Surprisingly, the exercise score yielded the lowest diagnostic accuracy among all methods reviewed. Yet, some features of this score are appealing from a theoretical

point of view. Its use of the total amount of J point and ST segment slope changes during the full test period seems attractive, since this will reduce errors inherent to single measurements at peak exercise. On the other hand, the test score is negatively affected in case of low exercise capacity not caused by cardiac factors, such as poor general physical shape, or the presence of other disorders precluding normal exercise capacity. Such conditions are frequently met in symptomatic patients of middle age and could to some extent explain the relatively poor performance of the exercise score in this study. In addition, exercise capacity was a relatively unimportant variable in the discriminant analyses, while it is included in the exercise score. Also, the J point amplitude in the numerator of the equation was not the most accurate among the various electrocardiographic variables studied. The differences between the exercise score in this study and its original description by Hollenberg *et al.* should be emphasized. The use of a bicycle complicates a direct comparison between the two methods. Nevertheless, exercise tests in both studies were symptom limited, and a stepwise increase in workload was used in both. The different duration of exercise measured in minutes would have affected the outcome of the score in a predictable manner. Since only relative differences between the patient groups were evaluated, it is doubtful that this disparity significantly influenced our results.

Earlier, we reported a sensitivity of 84% and a specificity of 88% using a combination of ST measurements at 20 and 80 msec and instantaneous heart rate levels in Frank lead X. In the current population, the diagnostic accuracy of the method was lower (sensitivity 74% at specificity 90%): in addition, the diagnostic merit of the method was strongly influenced by the use of beta blockers during exercise, which makes it less reliable than the other methods tested.

The comparison of various diagnostic exercise algorithms against each other in male subjects with a normal ECG at rest indicated that the most complicated technique considered, the discriminant function as described by Detry, yielded the highest diagnostic accuracy. The simplest analysis, adjustment of the ST segment amplitude changes for heart rate, came second. Both methods were not affected by the use of beta blockers with exercise. Since the exercise variable workload contributed relatively little to the strength of the discriminant analysis, both techniques employ essentially the same hemodynamic and electrocardiographic variables: heart rate and ST segment depression. The presence of angina in the discriminant function could be responsible for its superior performance. Thus, discriminant analysis as well as heart rate adjusted ST segment changes are both excellent diagnostic methods to diagnose or exclude coronary disease in males. For physicians without access to computer processing of exercise electrocardiograms, heart rate adjusted ST amplitude measurements seem the most logic choice. When computer facilities are available, there is a choice between discriminant analysis and heart rate adjusted ST segment measurements.

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CHAPTER 4

DIAGNOSTIC MERITS OF EXERCISE TESTING IN FEMALES

J.W. Deckers, B.J. Rensing, M.L. Simoons

ABSTRACT

The diagnostic accuracy of conventional exercise electrocardiography was compared with exercise algorithms specifically aimed at application in females, with R wave and heart rate adjusted ST segment changes, and with discriminant analysis. A symptom limited bicycle exercise test was performed by 189 females without previous infarction with a normal ECG at rest. Frank lead ECG was computer processed. ST segment amplitudes in lead X were superior to measurements in lead Y, but their sensitivity amounted only to 50% at specificity of 90%. Correction for R wave amplitude marginally increased sensitivity. It was confirmed that leads with inferiorly directed vectors like standard leads II, III, aVF or Frank lead Y should not be used for diagnostic purposes in females. Exercise induced increases in R wave amplitude of at least 0.1 mV occurred in only 8% of females with coronary disease. Previously described discriminant function using attained heart rate, ST segment depression and a sex-dependent ST segment correction factor yielded a sensitivity of 60% at a specificity of 90%. Sensitivities of heart rate adjusted ST segment changes and of a discriminant function were greater than 70% at a specificity of 90%. It is concluded that, just as in males, ST segment depression in females with low probability of disease must be interpreted with caution.

INTRODUCTION

As a consequence of the low prevalence of obstructive coronary artery disease in females, the development of new and more accurate diagnostic exercise electrocardiographic methods has remained confined to predominantly or exclusively male subjects, with inherent problems of subsequent application of these criteria to a female group of patients (1-4). This is even more significant since pertinent differences in exercise induced ST segment changes between the two sexes have been described (5,6). In an attempt to counterbalance the high incidence of ST segment depression with stress in females, Barolsky *et al.* developed a discriminant function with a sex-dependent ST segment correction factor (7). Ilsley *et al.* suggested the

combined use of ST segment depression and an abnormal R wave response in order to overcome the low diagnostic accuracy of conventional ST segment measurements in women (8). The present study was conducted in order to compare the diagnostic accuracy of these methods with conventional ST segment measurements and with newer and more sophisticated diagnostic analyses that were not specifically aimed at application in female patients (3,9-11). The latter included R wave and heart rate adjusted ST segment changes and discriminant analysis of electrocardiographic exercise variables, symptoms and achieved workload.

METHODS

Study population

The study group comprised 189 females with a normal electrocardiogram at rest. None had a previous infarction nor used digitalis. The population included 73 symptomatic female patients who were consecutively referred for evaluation of chest discomfort between January 1979 and May 1984. In these 73 patients, the presence or absence of obstructive coronary disease was confirmed by coronary angiography within three months after the exercise test. A diameter stenosis of at least 50% in a major coronary artery was considered evidence for coronary disease. The angiograms were interpreted by two experienced cardiologists blinded to the exercise test results. The remaining 116 females were ostensibly healthy asymptomatic subjects who volunteered for an exercise test in the second half of 1978. Most of them were spouses of cardiac patients; some were employees of our institution. None had auscultatory findings suggestive of mitral valve prolapse or other forms of valvular disease: none used any cardiac medication. Their absence of significant coronary artery disease was confirmed through follow-up of 53 months (SD 1 month). A that time, 109 females were alive, while 7 were lost to follow-up.

Exercise test and ECG analysis

A symptom limited exercise test was performed in sitting position on a bicycle ergometer. Workload was increased in a stepwise manner with 10 or 20 Watts/min. Cycling was continued at a low load for 4 minutes after peak exercise. The corrected orthogonal Frank lead ECG was recorded with the chest electrodes at the level of the fifth intercostal space and computer processed (12). The ECG was sampled during 20 seconds at rest in sitting position, every minute during exercise and during a six minute recovery period. Sampling frequency was 250 Hz. After rejection of complexes with deviant morphology or excessive baseline drift, average representative complexes were calculated (13). All amplitudes were measured relative to a baseline defined as the mean signal amplitude 5 to 3 samples (20 - 12 msec) preceding the QRS complex. The electrocardiographic parameters included heart rate, R wave and J point amplitude, and ST segment amplitude at 20 msec intervals

after the J point in Frank leads X and Y. ST_{20} denotes ST segment amplitude at 20 msec after the J point.

Previously, we developed a diagnostic algorithm that employed a combination of ST_{20} and ST_{80} in lead X, corrected for instantaneous heart rate (14). This analysis, which also takes into account the slope of the ST segment, originally yielded a sensitivity of 84% and a specificity of 88% in males with a normal ECG at rest and was re-evaluated in these female subjects.

R wave measurements

According to some reports, diagnostic accuracy is enhanced when ST segment amplitudes are normalized for height of R wave amplitude: a high R wave amplitude may be correlated with a greater amount of ST segment depression: comparable ST segment changes may be an expression for coronary disease in the presence of a low R wave amplitude (10,11). ST segment amplitude was adjusted for the R wave amplitude in that lead as follows: individual R wave amplitude at rest was normalized by dividing it by the mean R wave amplitudes derived from the tracings at rest for the same lead of the 189 subjects. The R wave adjusted ST segment amplitude was subsequently calculated by dividing the ST segment measurement by the normalized R wave amplitude.

The diagnostic use of R wave amplitude changes during exercise has been advocated by Ilsley *et al.* (8). In their study including 76 women without previous infarction, sensitivity and specificity of ST segment and R wave changes alone were similar at about 67%. Combination of both measurements was helpful and increased the diagnostic characteristics of the test significantly. Therefore, the diagnostic value of R wave amplitude changes during exercise was examined in the present study.

Heart rate correction.

The presumption that ST segment depression at a low heart rate is more indicative of coronary disease than the same amount of ST segment change at higher heart rates has led to numerous attempts to improve the diagnostic accuracy of exercise electrocardiography (15,16). In this study, ST segment amplitude changes were adjusted for heart rate according to recent proposals by Detrano *et al.*: the difference between ST segment amplitude at peak exercise and at rest was divided by the exercise induced increase in heart rate (3).

Discriminant analysis

Two different discriminant functions were evaluated (7,9). The discriminant function published by Barolsky *et al.* was obtained in a mixed study population with similar prevalence of coronary disease in males and in females, using ST segment response, attained heart rate and a sex-dependent ST segment function (7). The diagnostic model described by Detry *et al.* derived its variables from a stepwise discriminant multivariate analysis of 18 exercise parameters in male patients,

including ST segment measurements, blood pressure, heart rate, workload and symptoms during exercise (9). Details of both equations are outlined in Table 1.

Table 1 Coefficients of exercise variables in various discriminant functions

Detry (9)			
0.021	x	heart rate	(beats/min)
3.776	x	ST_{60} lead X	(mV)
0.781	x	(angina yes: 1, no : 2)	
0.004	x	workload	(Watts)
0.156	x	ST_{20-60} slope lead X	(mV/s -1)
intercept -5.213.			
Barolsky (7)			
1.745		if ST segment depression > 0.1 mV	
-0.026	x	heart rate	(bpm)
-0.832		if female with ST segment depression > 0.1 mV	
intercept 3.443			
Present analysis			
-0.018	x	ST_{80} lead X	(μV)
7.66	x	(angina yes: 1, no: 0)	
-0.061	x	workload	(Watts)
intercept 2.50			

Statistical analysis

Univariate analysis was applied with Student's t test for continuous variables and with Fisher's exact test for discrete variables. Stepwise discriminant analysis of exercise parameters was performed with the BMDP 7A statistical package. Receiver operator characteristic curves were used to present sensitivities and specificities of the various electrocardiographic variables and the algorithms.

RESULTS

Among the 73 females who underwent coronary angiography, coronary artery disease was diagnosed in 37 patients. Left main disease was present in one subject, seven females had three vessel disease, 10 two vessel disease and 19 one vessel disease. The mean ejection fraction of the patients with coronary disease was 64% (range 48 - 81). The other 36 symptomatic females had normal coronary arteries or non-significant obstructive lesions at coronary angiography. Age, symptoms and disease classification of the study population are presented in Table 2.

Table 2 Clinical and angiographic data of 189 female subjects without prior myocardial infarction

History	N	age, years mean	range	CAD N	%
Typical angina	27	58	41-69	23	85
Atypical angina	26	54	30-68	12	46
Non-anginal pain	20	51	35-72	2	10
Volunteers	116	39	19-64	-	-

CAD = coronary artery disease

Beta blockers were used at the time of the exercise test by 28 (76%) of patients with coronary artery disease and by 24 (67%) patients with normal angiograms. Exercise variables are presented in Table 3. Patients with coronary disease attained a lower workload and lower peak heart rate than subjects without disease. Mean exercise variables of subjects with normal findings at angiography fell between the mean values of the diseased and the healthy group. Mean values of ST_{60} at peak exercise in lead Y and in lead X were negative in all three groups at peak exercise; mean ST_{80} in lead X was only negative in patients with coronary disease and in patients with normal findings at angiography.

Conventional ST segment analysis

Sensitivities for the prediction of coronary disease at fixed specificity of 90% of ST segment amplitude at 20 msec intervals between J point and 100 msec after J at peak exercise in Frank leads X and Y are presented in Figure 1. Sensitivity of ST segment amplitude in lead Y was very low and did not exceed 20%. Sensitivity in lead X was highest at 60 and 80 msec after J, but remained below 55% at a specificity level of 90%. Sensitivity for the prediction of coronary disease of ST_{60} and ST_{80} in leads X and Y at various levels of specificity are presented in Table 4. At all levels of specificity, sensitivity of ST segment amplitude in lead X was higher than in lead Y. ST_{80} in lead X was a better predictor of coronary disease than ST_{60} in that lead. The combination of ST_{20} and ST_{80}, corrected for instantaneous heart rate, was not superior to these conventional ST segment measurements (Table 4).

R wave amplitude adjustment

The correction of ST_{80} in lead X for R wave amplitude at rest slightly increased the accuracy for the prediction of coronary disease at higher levels of specificity (Table 4).

Table 3 Exercise test data in 37 females with coronary artery disease (CAD), in 36 females with normal coronary angiograms (NoCAD) and in 116 asymptomatic females. Measurements at peak exercise, unless otherwise indicated. All data, with the exception of angina, are represented as mean ± SD.

	CAD n = 37		All normals n = 152	NoCAD n = 36		Volunteers n = 116
Max workload	93 ± 23	**	145 ± 35	129 ± 24	*	155 ± 33
Angina (%)	15 (41)	**	9 (3)	4 (11)		--
Max heart rate, bpm	118 ± 22	**	153 ± 27	111 ± 19	*	161 ± 23
R wave lead X at rest, μV	1083 ± 289		959 ± 299	956 ± 324		960 ± 293
ST_{60} lead X, μV	-83 ± 57	**	-19 ± 60	-42 ± 52	*	-12 ± 60
ST_{80} lead X, μV	-76 ± 61	**	36 ± 84	-24 ± 62	*	54 ± 82
$ST_{20\text{-}60}$ slope X, μV/s	0.34 ± 0.48	**	1.24 ± 0.70	0.57 ± 52	*	1.45 ± 0.98
R wave lead Y at rest, μV	606 ± 288	**	805 ± 370	680 ± 356		843 ± 368
ST_{60} lead Y, μV	-60 ± 54		-34 ± 64	-42 ± 62		-31 ± 65
ST_{80} lead X, μV	-54 ± 54	**	-11 ± 79	-30 ± 67		-5 ± 81

** $p < 0.001$ *CAD vs all normals*
* $p < 0.01$ *NoCAD vs volunteers*

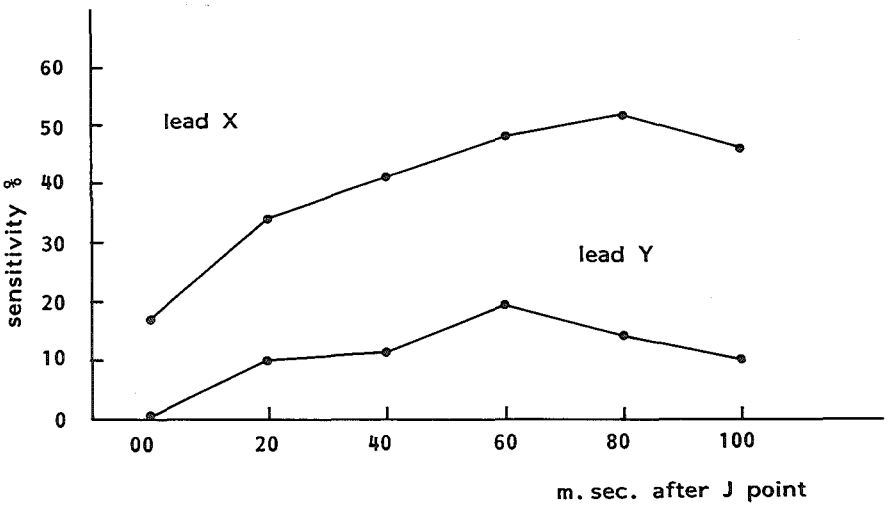

Figure 1 Sensitivity for the prediction of coronary disease in 189 females of ST segment amplitude at 20 msec intervals between J point and 100 msec after J in Frank leads X and Y at fixed specificity of 90%.

R wave amplitude changes

Exercise induced changes in R wave amplitude in lead X are presented in Table 5. An increase in R wave amplitude of at least 0.1 mV was observed in ten subjects without significant disease, and in three females with coronary disease. None of these, however, exhibited ST segment depression of 0.1 mV or more in that lead. Increases in R wave amplitude were thus not helpful in the diagnosis of coronary artery disease.

Heart rate correction

Sensitivity and specificity for the prediction of coronary disease of the difference between ST_{80} at peak exercise and at rest in lead X were slightly lower than ST_{80} measured at peak exercise in that lead (Table 4). However, the subsequent adjustment for heart rate markedly increased the diagnostic accuracy of the method. The ratio of peak exercise and resting ST segment amplitude and increase in heart rate yielded a sensitivity of 77% at specificity of 90% (Figure 2).

Table 4 Sensitivities at fixed specificity for various electrocardiographic variables and diagnostic exercise algorithms

	SPECIFICITY (%)			
	80	85	90	95
Conventional analysis				
ST_{60} lead X	60	56	48	38
ST_{80} lead X	77	66	51	41
ST_{60} lead Y	30	23	20	15
ST_{80} lead Y	29	22	14	10
ST_{80} lead X R wave adj	74	69	62	43
HR adj ST ampl and slope (15)	62	60	49	30
HR adj ST measurements (3)				
HR adj ST ampl	83	81	77	54
ST_{80} max - ST_{80} rest	73	67	41	33
Discriminant functions				
Barolsky's algorithm (7)	76	73	60	54
Detry's algorithm (9)	89	80	70	60
present analysis	90	80	73	65

HR = heart rate; adj = adjusted; ampl = amplitude; max = peak exercise

Table 5 Changes in R wave amplitude at peak exercise relative to resting value in lead X in 37 females with coronary disease (CAD), in 36 females without coronary disease (NoCAD) and in 116 female volunteers. Numbers in parentheses denote percentages.

	CAD n = 37	normals n = 152	NoCAD n = 36	volunteers n = 116
≥ 0.2 mV	3 (8)	2 (1)	1 (3)	1 (1)
0.10 - 0.19 mV	--	8 (5)	2 (6)	6 (5)
-0.09 - 0.09 mV	25 (68)	91 (60)	20 (56)	71 (61)
-0.1 - -0.19 mV	5 (14)	36 (24)	6 (17)	30 (26)
≤ -0.2 mV	4 (11)	15 (10)	7 (19)	8 (7)

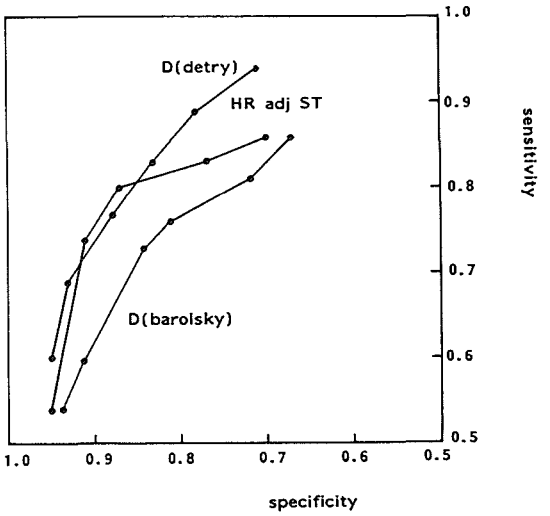

Figure 2 Sensitivity and specificity for the prediction of coronary disease of heart rate corrected ST segment amplitude changes and of discriminant functions according to Detry and Barolsky in 189 females without previous infarction.

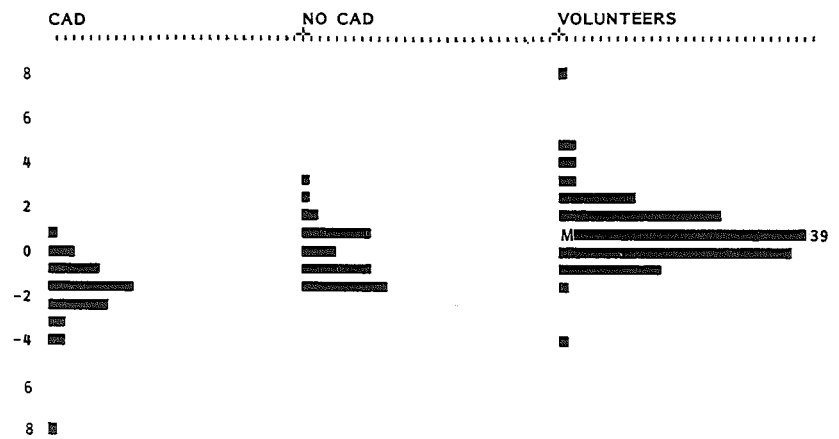

Figure 3 Distribution of exercise variable heart rate adjusted ST segment amplitude in 37 females with significant coronary disease (CAD), in 36 females with normal angiographic findings (NoCAD) and in 116 female volunteers. One whole column represents 30 subjects.

Discriminant analysis

The diagnostic accuracy of the discriminant function described by Barolsky is presented in Figure 2 and in Table 4. Sensitivity was 60% at a specificity of 90%. Since ST_{80} was more predictive for coronary disease than ST_{60} in this population, ST measurements at 80 msec in lead X were entered in the discriminant function of Detry. Sensitivity and specificity of this analysis are presented in Figure 2 and in Table 4. Relatively high levels of accuracy were obtained: sensitivity amounted to 70% at specificity level of 90%.

In order to determine the coefficients of discriminant analysis in this series of female individuals, stepwise discriminant analysis was performed using peak exercise variables heart rate, workload, ST_{80} in lead X, $ST_{20\text{-}60}$ slope in lead X and angina during exercise. The obtained equation is illustrated in Table 3. The diagnostic characteristics of this analysis are presented in Table 4. The method yielded a sensitivity of 73% at a specificity of 90%, more or less comparable to the diagnostic characteristics of heart rate adjusted ST segment measurements and the algorithm proposed by Detry.

DISCUSSION

The results of this analysis confirm that unadjusted measurements of ST segment amplitude are relatively poor predictors for the presence or absence of coronary disease in females. This proved especially true for ST segment changes in lead Y and our results indicate that measurements in this lead, or, for that matter, in the conventional 12 lead ECG leads II, III or aVF, should not be used for diagnostic purposes in this gender. These observations are in agreement with those by Sketch *et al.* and Guiteras Val *et al.*, who also observed that the specificity of ST segment depression during exercise in females was dependent on the ECG lead chosen (6,17). In their reports, the lowest specificity of exercise induced electrocardiographic changes was achieved in leads with inferiorly orientated vectors (6,17). Furthermore, the present findings also enhance our previous observations that exercise induced ST segment depression in asymptomatic females is more marked than in asymptomatic males, particularly at higher heart rates (18).

The highest diagnostic accuracy of conventional ST segment amplitudes was obtained with measurements taken at 80 msec in lead X. Nevertheless, the sensitivity of these amplitudes only amounted to about 50% at a specificity level of 90%. In males, ST segment changes at that interval have a higher diagnostic yield: studies with sufficient observations in which the exercise induced electrocardiographic changes were compared between both sexes always found the specificity of ST segment changes in males to be higher than in their female counterparts (2,6,7,19). This was also demonstrated in this study: application of our in males developed ECG analysis criteria yielded disappointingly low diagnostic merits in these female subjects.

Attempts to increase the diagnostic yield of exercise electrocardiography have focussed on the influence of the R wave amplitude on ST segment changes, on changes in R wave amplitude with exercise, and on influences of heart rate on ST segment changes. The effect of R wave amplitude on ST segment depression during exercise has only recently been investigated: tall R waves have been associated with increased magnitude of ST segment depression during exercise, while a low R wave amplitude may be a determinant of failure to develop ST depression during exercise (10,11). However, correction of ST segment change for R wave amplitude only marginally increased the diagnostic yield of the ST segment measurements.

R wave amplitude changes during exercise have been extensively studied in males; some reports advocated their diagnostic use, while results obtained by others were less promising (20,21). The behaviour of R wave amplitudes in normal males does not support their diagnostic employment (22). Nonetheless, in female subjects, Ilsley *et al.* reported that the combined use of ST segment and R wave amplitude changes significantly increased the predictive accuracy of the exercise test (8). Results of the present study, however, were less encouraging and R wave amplitude change was found to be highly variable. Exercise induced increase in R wave amplitude in lead X only occurred infrequently, even in females with coronary disease.

ST segment depression during exercise is a better indicator of coronary artery disease when it occurs at lower heart rates. Detrano *et al.* measured the ratio between the difference of ST amplitude at peak exercise and at rest and the increase in heart rate during exercise. In a carefully designed study of 303 consecutive male and female patients without previous myocardial infarction, this so called heart rate adjusted ST segment amplitude proved superior to other electrocardiographic methods and approached the diagnostic accuracy obtained with planar thallium image (3). In the current female population, this method also proved its worth with a sensitivity of 77% at a specificity of 90%.

Discriminant analysis is an other approach to evaluate the diagnostic yield of exercise variables. Barolsky *et al.* reported lower predictive values for a positive exercise test in females than in males with similar prevalence of disease. These investigators thus developed a discriminant function which accounted for the different behaviour of the ST segment to exercise in the females (7). The present prospective evaluation of this function demonstrated its superiority over conventional ST measurements, but the discriminant analysis according to Detry, although derived in an exclusively male population, yielded better diagnostic results (9). The presently performed discriminant analysis was only marginally better. Surprisingly, heart rate at peak exercise was not an important diagnostic adjunct in the present analysis: the high number of subjects with beta blockers may have underestimated the diagnostic importance of this variable.

The diagnostic value of stress testing in females remains to be controversial. Hung *et al.* compared the diagnostic value of exercise electrocardiography, cardiac fluoroscopy and thallium perfusion scintigraphy in 92 symptomatic women without

previous infarction (23). Prevalence of disease was 30%. In their multivariate analysis, none of the exercise variables was predictive of coronary disease: additional independent information of ST segment depression and angina during exercise was only obtained for the prediction of multivessel disease. They concluded that exercise testing was of limited value in women with low prior probability of disease. These conclusions were not shared by Melin *et al.* (24), who prospectively examined the usefulness of post-exercise test probability analysis in a similar group of females. These authors demonstrated that the physicians' knowledge of these estimates reduced the number of unnecessary angiographic procedures and that additional thallium scintigrams could have been avoided without loss of accuracy in one third of the cases.

Because of the different ST segment response to exercise, the diagnostic merits of exercise testing in females will be lower than in males. Nevertheless, the results of the present study indicate that employment of more sophisticated electrocardiographic variables can markedly improve the diagnostic value of the test. In particular, reliable results can be achieved with discriminant analysis or heart rate adjustment of ST segment amplitude changes even in this sex. However, measurements of ST segment amplitudes in ECG leads with inferiorly directed vectors like standard leads II, III, aVF, or Frank Lead Y should not be used for diagnostic purposes nor should such parameters be included as components in diagnostic algorithms. Exercise induced changes in R wave amplitude do not provide further help in the diagnosis of obstructive coronary disease in women. Good clinical judgment should prevail in the interpretation of exercise test results and, just as in their male counterparts, ST segment changes in females with low prior probability of disease must be interpreted with caution.

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CHAPTER 5

STRATEGIES FOR THE DIAGNOSIS OF CORONARY ARTERY DISEASE BASED ON LOGISTIC AND BAYESIAN ANALYSIS OF CLINICAL AND EXERCISE VARIABLES

J.W. Deckers, J.G.P. Tijssen, B.J. Rensing, A.J. Azar, M.L. Simoons

ABSTRACT

In order to study the relationship between clinical and exercise variables with regard to their diagnostic properties, logistic regression analysis of clinical and exercise variables was performed in 295 patients without a previous myocardial infarction. Prevalence of coronary disease was 77% in males and 51% in females. Obtained probabilities were compared with estimates provided by the Bayesian oriented CADENZA algorithm. The analysis revealed the mutual dependance of various clinical and exercise parameters. The final diagnostic model included severe angina, cigarette smoking, high cholesterol, heart rate adjusted ST segment amplitude changes and angina during exercise in males. Probabilities obtained with logistic regression analysis were slightly better than those based on CADENZA. Correct diagnostic classification was substantially improved by exercise testing in males, but not in females.

INTRODUCTION

Exercise electrocardiography has gradually become a standardized technique, with well known diagnostic characteristics and well recognized limitations. For most physicians, the exercise test is the initial noninvasive investigation in the evaluation of patients suspected of coronary artery disease (1). In order to estimate the post-test probability of disease in a given patient, the test should be interpreted with regard to the pre-test likelihood of disease, which is related to multiple clinical variables like sex, age, risk profile and symptom classification (2,3). The use of Bayes' theorem of conditional probability can assist in this interpretation and can also provide a meaningful estimate of the probability of disease in the individual patient (4,5). Application of Bayes' theorem to multiple clinical and test variables presupposes mutual statistical independence of these variables in patients with and without disease, as well as stability of the test properties in patients with varying

degrees of severity of disease (6). There is, however, suggestive and cumulating evidence that sensitivity and specificity of exercise test variables are not constant and can vary according to clinical characteristics, disease severity and details of test performance (7,8). This has at least in theory implications and restrictions for the application of Bayesian probability analysis. Logistic regression analysis, which accounts for this mutual dependance of variables, may be more suited to estimate the probability of coronary disease. In the current study, logistic regression analysis was performed on clinical and exercise variables of male and female patients without a history of previous myocardial infarction in order to: a) study the relationship between clinical and exercise variables with regard to their diagnostic properties, b) determine the additional diagnostic merits of exercise variables to clinical variables, and c) construct a model to determine the probability of coronary disease based on clinical and exercise variables. The thus obtained probabilities were compared with pre- and post-test probabilities provided by the Bayesian oriented CADENZA algorithm (9).

METHODS

The study population comprised 222 male and 73 female subjects who were consecutively referred to our institution for evaluation of chest pain between January 1978 and May 1984. All performed a symptom limited exercise test and underwent coronary angiography. None had a previous myocardial infarction or used digitalis. All had a normal ECG at rest. Patients were considered to have "typical angina" if their complaints met the following three criteria: a) substernal discomfort that was b) precipitated by exercise, emotion or cold and c) relieved within 10 minutes after rest or sublingual nitroglycerine. "Atypical angina" was diagnosed if only two of these characteristics were present and chest pain was considered to be "non-anginal" if only one of these criteria was met. The severity of "typical angina" was stratified according to the Canadian Cardiovascular Society Classification: Canadian Class III and IV were considered severe angina and Class I and II moderate angina (10). Symptoms were classified without knowledge of exercise or angiographic results. Other clinical variables included age, systolic blood pressure, cigarette smoking, total serum cholesterol and diabetes. Left ventriculography and coronary angiography were performed within three months after the exercise test. Significant coronary artery disease was considered present if a luminal diameter stenosis of at least 50% in one or more major coronary arteries was observed at angiography. Angiograms were evaluated by two experienced cardiologists blinded to the patients history and to other test results.

A symptom limited exercise test was performed in sitting position on a bicycle ergometer. Workload was increased in a stepwise manner with 20 Watts per minute until moderate symptoms appeared or until exhaustion occurred. Cycling was continued at a low load for 4 minutes after peak exercise. The corrected orthogonal

Frank lead ECG was recorded with the chest electrodes attached at the level of the fifth intercostal space. The ECG was sampled during 20 seconds at rest in sitting position, every minute during exercise and during a six minute recovery period. Sampling frequency was 250 Hz (11). After rejection of complexes with deviant morphology or excessive baseline drift, an average representative complex was calculated (12). Electrocardiographic amplitudes were measured relative to a baseline defined as the mean signal amplitude 5 to 3 samples (20-12 msec) before the QRS complex. Electrocardiographic variables included heart rate and ST segment amplitudes at 20, 60 and 80 msec in Frank lead X. Heart rate adjusted ST segment amplitude was defined as the ratio of the difference in ST segment amplitude in lead X at 80 msec after J point at peak exercise and at rest and the increase in heart rate with exercise (13). Other exercise parameters included age predicted maximum workload and the presence of angina during exercise.

In the multivariate analysis, we employed the linear logistic model which relates a probability (P) for the outcome to the value of a baseline characteristic (X) using the linear logistic function:

$$P = \frac{1}{1 + e^{-(a+bX)}}$$

Alternatively, the equation can be written as:

$$\ln (P/(1-P)) = a + bX$$

Use of the model assumes that, although every patient may have his own values of X in the equation, the parameters a and b are characteristic for the population the patients belongs to. The above equation is referred to as a regression equation, which indicates that the variate X (the independent variate) is used to predict P (the dependent variate). Additional independent variates (X_1, X_2, etc. with corresponding coefficients b_1, b_2) can be accommodated in the model. The form of the logistic regression model then becomes:

$$\ln (P/(1-P)) = a + b_1 X_1 + b_2 X_2 + ... + b_n X_n.$$

where a represents a constant, X_1 ..., X_n the chosen variables, and b_1 ..., b_n the relative weight assigned to the chosen variables. From a set of observations on the variables X_1, X_2, ..., X_n in a group and the actual presence of coronary artery disease, the parameters a, b_1, b_2, ..., b_n, which are characteristic for the patient group as a whole, can be estimated using the method developed by Walker and Duncan (14).

The logistic model for the prediction of the probability of coronary artery disease was constructed in a stepwise manner for males and females. All variables with significant incremental correlations with the presence of coronary disease that improved the overall accuracy of the model were included, provided that their addition to the model was medically plausible. The model was first constructed using

Table 1 Clinical variables in relation to the presence of coronary artery disease in patients with different types of chest pain

	TYPE OF CHEST PAIN*			
	nonspecific	atypical	moderate	severe
Males (n=222)	**n=35**	**n=63**	**n=61**	**n=63**
Age				
< 45 years	33% (5/15)	44% (8/18)	79% (11/14)	100% (7/7)
45-55 years	45% (5/11)	78% (18/23)	81% (25/31)	96% (27/28)
> 55 years	67% (6/9)	77% (17/22)	81% (13/16)	100% (28/28)
Diabetes				
no	45%(15/33)	66% (38/58)	80% (43/54)	100% (49/49)
yes	50% (1/2)	100% (5/5)	86% (6/7)	93% (13/14)
Smoking				
no	42% (5/12)	72% (18/25)	67% (22/33)	96% (22/23)
yes	48%(11/23)	66% (25/38)	96% (27/28)	100% (40/40)
Systolic BP				
< 155 mmHg	39%(11/28)	53% (19/36)	82% (32/39)	100% (39/39)
≥ 155 mmHg	71% (5/7)	89% (24/27)	77% (17/22)	96% (23/24)
Serum cholesterol				
≤ 8 mmol/l	42%(14/33)	64% (34/53)	76% (37/49)	100% (49/49)
> 8 mmol/l	100% (2/2)	90% (9/10)	100% (12/12)	93% (13/14)
Females (n=73)	**n=20**	**n=26**	**n=19**	**n=8**
Age				
< 45 years	0% (0/6)	0% (0/5)	67% (2/3)	100% (1/1)
45-55 years	17% (1/6)	57% (4/7)	83% (5/6)	100% (1/1)
> 55 years	13% (1/8)	57% (8/14)	80% (8/10)	100% (6/6)
Diabetes				
no	11% (2/19)	45% (10/22)	76%(13/17)	100% (7/7)
yes	0% (0/1)	50% (2/4)	100% (2/2)	100% (1/1)
Smoking				
no	0% (0/1)	33% (5/15)	83%(10/12)	100% (7/7)
yes	11% (2/19)	64% (7/11)	71% (5/7)	100% (1/1)
Systolic BP				
< 155 mmHg	0% (0/14)	40% (8/20)	82% (9/11)	100% (6/6)
≥ 155 mmHg	33% (2/6)	67% (4/6)	75% (6/8)	100% (2/2)
Serum cholesterol				
≤ 8 mmol/l	11% (2/18)	38% (8/21)	75% (9/12)	100% (6/6)
> 8 mmol/l	0% (0/2)	80% (4/5)	86% (6/7)	100% (2/2)

BP = blood pressure
Percentages are observed rates of patients with angiographically proven coronary artery disease
** For definitions, see text*

the clinical variables outlined above. Subsequently, a model was constructed for exercise variables only. Finally, a model was constructed which included the previously selected clinical and exercise variables in unity. At each step of the procedure, the variable most significantly associated with the presence of coronary disease was selected, conditioning on all variables previously chosen.

The diagnostic algorithm CADENZA, developed by Diamond and Forrester, calculates the pre-test probability that a patient has significant coronary disease given the clinical variables age, sex, type of chest pain and risk factors, including cigarette smoking, total serum cholesterol, diabetes and systolic blood pressure (8). The results of various tests can subsequently be added to this pre-test probability and, under the assumption of independence of these observations, Bayes' theorem is then utilized to calculate the posterior probability of disease, $P(D|O)$, given the test observation (O) and the pre-test probability p:

$$P(D|O) = \frac{1}{1 + \frac{1-p}{p} * \frac{P(O|\bar{D})}{P(O|D)}}$$

The program is based on data from the literature of more than 60,000 patients. In the current study, pre-test probability was calculated by entering the above clinical variables in the CADENZA program. Exercise test results were subsequently added so as to obtain the post-test probability of disease. In order to obtain ST segment amplitude at 80 msec and ST segment slope at 20-60 msec after J in lead V_5, ST segment amplitudes of Frank leads X, Y and Z were converted to 12 lead ECG V_5 amplitudes according to Dower (15). The mean value of ST segment amplitude in lead V_5 of was -100 μV (SD 109) in males with coronary artery disease, and 46 μV (SD 98) in males without coronary disease. Respective values for the females were -84 μV (SD 68), and -27 μV (SD 68). Although CADENZA allows the use of exercise induced R wave changes, these were not considered in the present study since their diagnostic value is disputed (16,17).

RESULTS

Significant coronary disease was present in 170 male and in 37 female subjects. Prevalence of disease thus amounted to 77% in males and to 51% in females. Only two subjects had left main disease, 60 patients had three vessel disease, 74 two vessel disease and 81 single vessel disease. Clinical characteristics of the study groups are presented in Table 1. Severe angina was almost invariably associated with the presence of significant coronary disease: only one (male) patient with these symptoms had normal findings at coronary angiography. The presence of non-specific chest pain implied a disease prevalence of 10% in females, but these symptoms were associated with significant coronary disease in 46% of the males.

Table 2 Distribution and weight of clinical and exercise variables in the diagnostic logistic regression analysis in males

	NoCAD	CAD	Weight (C,E)	Weight (C + E)
Number of patients	52 (100%)	170 (100%)		
Clinical variables				
Age, years			0.084	0.065
mean ± SD	45 ± 11	52 ± 8		
Nonspecific chest pain	37%	9%	-	
Atypical angina	38%	25%	0.85	-
Moderate angina	23%	29%	1.56	-
Severe angina	2%	36%	4.12	3.08
Cigarette smoking	46%	58%	1.33	1.45
Cholesterol				
> 8 mmol/l	4%	21%	1.92	1.33
Constant			-5.16	
Exercise variables				
HR adj ST ampl, μV/s			-0.92	-0.87
mean ± SD	0.0 ± 1.3	-2.7 ± 2.2		
range	-3.0 - 1.7	-11.0 - 1.7		
Relative workload < 80%	33%	68%	0.91	-
AP during exercise	14%	61%	1.64	-
AP during exercise*				1.59
Constant			-0.78	-4.71

CAD = coronary artery disease; adj = adjusted; ampl = amplitude; AP = angina pectoris

C,E = coefficients obtained with logistic regression analysis of clinical variables (C), and obtained with logistic regression analysis of exercise variables (E)

C + E = coefficients obtained with logistic regression analysis of clinical and exercise variables in unity.

* *only in patients with non-specific, atypical or moderate angina*

Among the various electrocardiographic variables, heart rate adjusted ST segment amplitudes were selected for the logistic model since they proved to be the strongest predictors of coronary disease in a broad range of measurements in univariate analysis.

Clinical and exercise variables retained in the logistic models and obtained coefficients are provided in Table 2 for males and in Table 3 for females. The clinical variable age and the exercise variable heart rate adjusted ST segment changes were entered as continuous variables. Surprisingly, among the exercise variables consider-

Table 3 Distribution and weight of clinical and exercise variables in the diagnostic logistic regression analysis in females

	NoCAD	CAD	Weight (C,E)	Weight (C + E)
Number of patients	36 (100%)	37 (100%)		
Clinical variables				
Age, years			0.11	0.13
mean ± SD	51 ± 10	57 ± 7		
Nonspecific chest pain	50%	5%	-	
Atypical angina	39%	32%	1.78	-
Moderate angina	11%	41%	3.43	1.28
Severe angina	-	22%	17.93	17.05
Cigarette smoking	19%	41%	1.48	1.93
Cholesterol				
> 8 mmol/l	11%	32%	1.88	-
6-8 mmol/l	50%	41%	1.43	-
Constant			-9.49	
Exercise variables				
HR adj ST ampl, μV/s			-1.12	-1.03
mean ± SD	-0.5 ± 0.8	-2.1 ± 2.9		
range	-0.3 - 2.0	-16.7 - 0.2		
Relative workload < 80%	11%	30%	1.16	1.50
AP during exercise	11%	41%	-	-
Constant			-1.33	-9.74

CAD = *coronary artery disease; adj = adjusted; ampl = amplitude; AP = angina pectoris*

C,E = *coefficients obtained with logistic regression analysis of clinical variables (C), and obtained with logistic regression analysis of exercise variables (E)*

C + E = *coefficients obtained with logistic regression analysis of clinical and exercise variables in unity.*

ed, angina during exercise was not selected in the females. Logistic regression analysis in males indicated that angina during exercise did not significantly contribute to the diagnosis of coronary disease in patients with severe angina. As this finding accords with clinical experience, angina during exercise was only included in the model in males with non-specific, atypical or moderate angina. Low workload was not associated with the presence of coronary artery disease in males, but this variable proved to be significant in females.

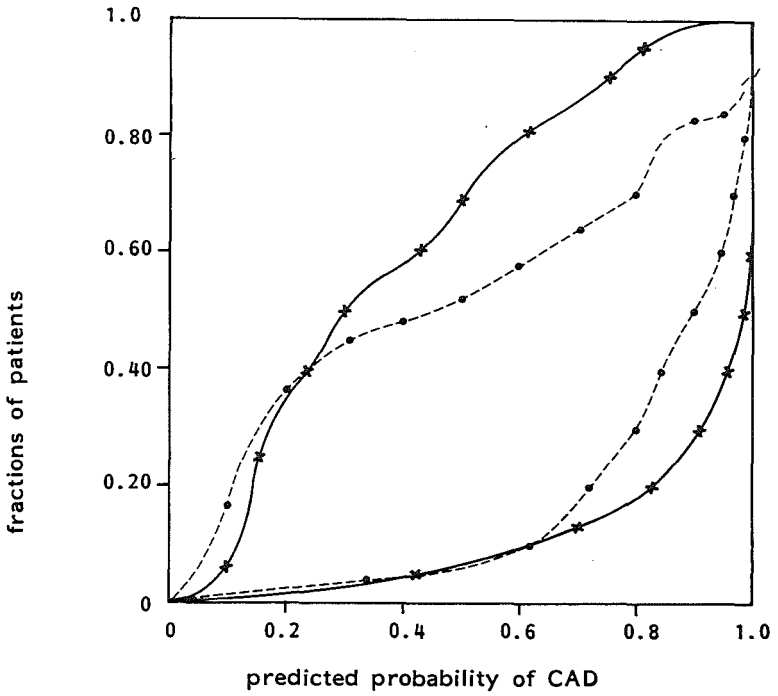

Figure 1 Logistic regression analysis in males
The dotted lower line represents the cumulative distribution of the predicted probability of coronary artery disease (CAD) according to logistic regression analysis of clinical variables in 170 males with *disease -- that is, it represents for each percentage (horizontal) the fraction of patients with a predicted probability of CAD of at least that percentage. Similarly, the upper dotted line represents the cumulative distribution of predicted probability of CAD according to logistic regression analysis of clinical variables in 52 males* without *disease. The solid lines indicate, in the same fashion, probability distributions according to logistic regression analysis of clinical and exercise variables in males with and without CAD, respectively.*

CADENZA somewhat underestimated the probability of coronary disease when the results of the exercise test were added to the pre-test estimate of disease: post-test probability of disease amounted to 70% in the males and to 48% in the females according to this algorithm.

Estimates of the probability of coronary artery disease derived from logistic regression analysis of clinical variables and estimates based on logistic regression analysis of clinical and exercise variables in males with and without coronary disease

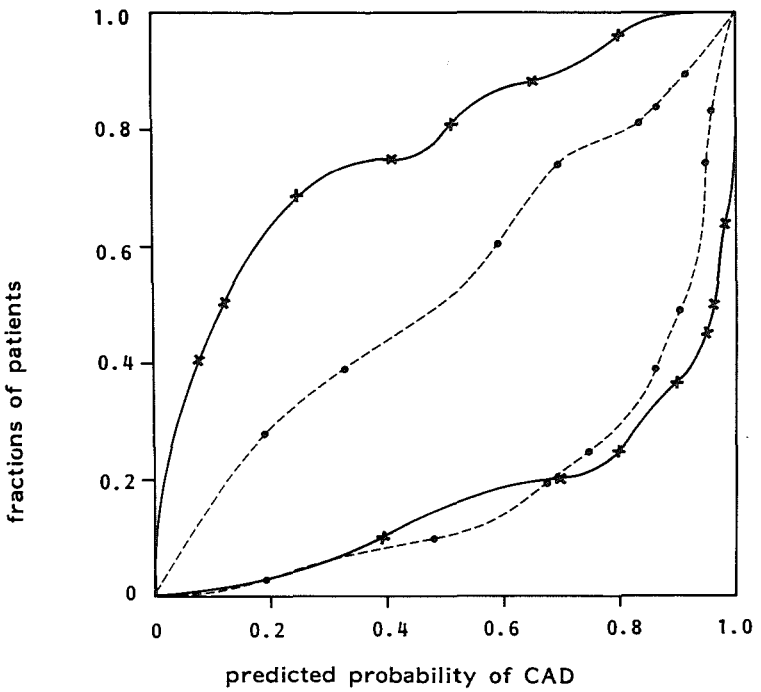

Figure 2 The dotted lower line represents the cumulative distribution of the pre-test probability of CAD according to CADENZA in 170 males with *disease. The upper dotted line represents the cumulative distribution of pre-test probability of CAD according to CADENZA in 52 males* without *disease. Similarly, the solid lines indicate distributions of post-test probability of CAD according to CADENZA in males with and without CAD, respectively.*

are outlined in Figure 1. The improvement in diagnostic classification obtained by the addition of exercise data into the model can be appreciated by the increased distance between the curves representing the (two) models. In a similar fashion, pre- and post-test probability of disease are illustrated in Figure 2 for CADENZA. The logistic regression model proved to be slightly better than the estimates obtained with CADENZA. Data for women with and without coronary disease are presented in Figures 3 and 4 in a comparable way. In females, the curves of the model based on only clinical variables and the model containing clinical and exercise variables hardly diverged: the diagnostic yield of the exercise test in females was thus much lower than in males.

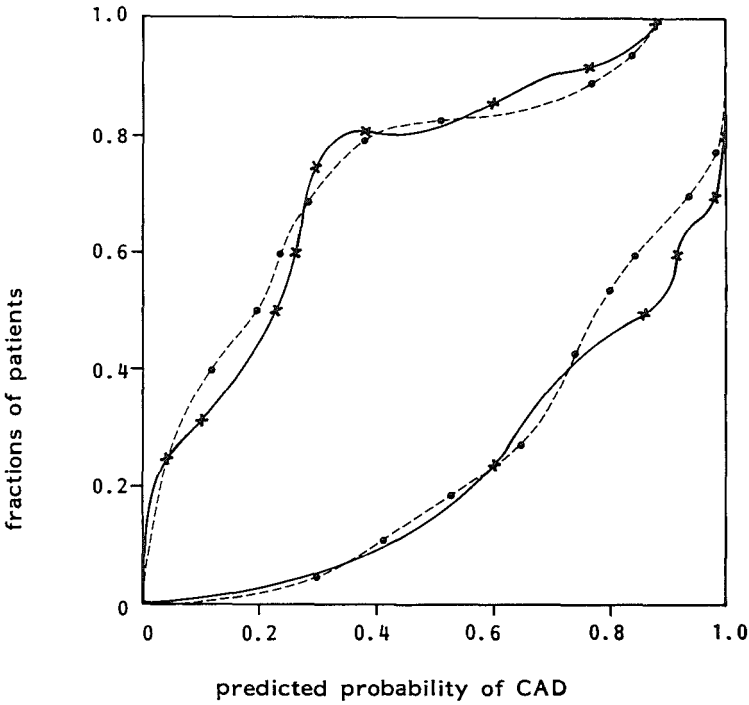

Figure 3 Logistic regression analysis in females
Cumulative distribution of the predicted probability of CAD according to logistic regression analysis of clinical variables (dotted lines) and according to logistic regression analysis of clinical and exercise variables (solid lines) in 37 females with and in 36 females without CAD. For details : see Figure 1.

DISCUSSION

In the current paper, logistic regression analysis was used to predict the presence of coronary artery disease from clinical and exercise variables. The logistic model provides an unrestricted way of assessing the simultaneous diagnostic capacity of these variables. Use of the Bayesian model, on the other hand, presupposes that the influence of clinical variables is independent of the influence of the exercise test variables. This presumption is, generally speaking, untenable. For instance, the occurrence of angina during the exercise test cannot be isolated from the presence of typical angina at effort in the patient's history. Thus, many clinical and exercise variables are in reality interrelated. The mutual dependance of some of these parameters was indeed revealed in the present analysis. Furthermore, the results indicate that exercise variables are of considerable value in the assessment of the diagnosis of coronary artery disease in male subjects, but much less so in females.

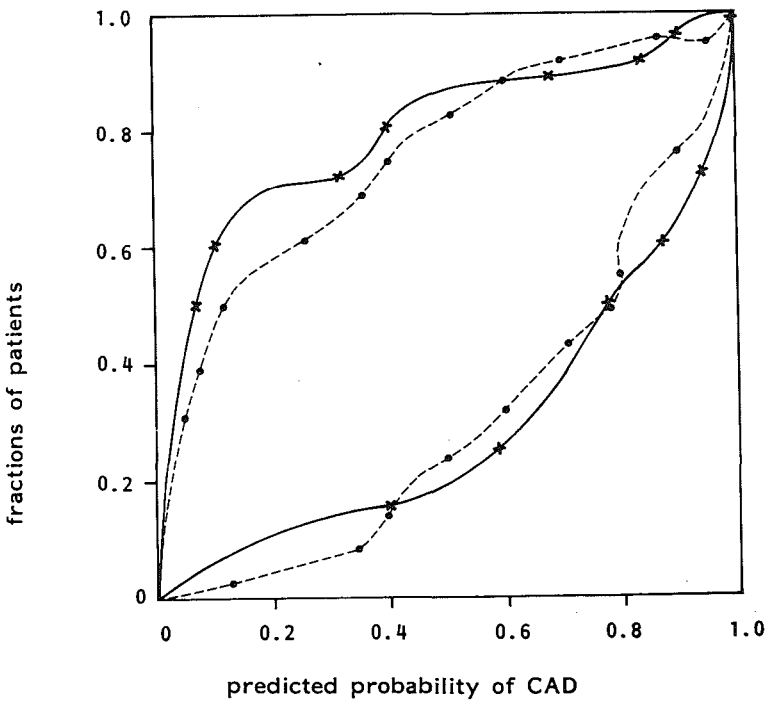

Figure 4 The dotted lower line represents the cumulative distribution of the pre-test probability of CAD according to CADENZA in 37 females with *disease. The upper dotted line represents the distribution of pre-test probability of CAD according to CADENZA in 36 females* without *disease. Similarly, the solid lines indicate distributions of post-test probability of disease according to CADENZA in females with and without CAD, respectively.*

Not surprisingly, these observations confirm and emphasize the diagnostic importance of simple clinical characteristics like age and type of symptoms. The relevance of these parameters has amply been described previously. The CASS registry in particular has provided data for prevalence and severity of coronary artery disease in males and females with different symptoms without a history of myocardial infarction (18). In the present study, patients with severe angina were found to have significant disease in all but one case: clearly, exercise testing does not serve any useful diagnostic purpose in such patients, although the test can be of help in the assessment of the functional impairment and in the evaluation of anti-anginal therapy in these patients.

In agreement with other observations, logistic regression analysis of clinical variables identified age, the different types of chest pain and the risk factors smoking

and high cholesterol levels to be associated with coronary disease (2,3,19). Logistic regression analysis of exercise parameters in males selected heart rate corrected ST segment amplitude changes, workload and the appearance of angina during exercise. The latter variable proved to be unrelated to the presence of coronary artery disease in patients with severe angina. When angina during exercise was only considered for males with non-specific, atypical or moderate angina, the clinical type of chest pain proved to be no longer relevant in these patients when exercise variables thus defined were added to the clinical variables.

In females, however, symptoms during exercise were not of diagnostic value. Explanation of this phenomenon is uncertain. Correct interpretation of exercise induced symptoms in females with or without coronary disease is apparently complex, and one should perhaps consider the possibility that thoracic symptoms in many females are not related to cardiac disorders. On the other hand, the relatively small number of females in the present study may have been responsible for this unexpected finding. The exercise parameters low performed workload proved to be of diagnostic value in females, but not in males. Again, it may be speculated that the appropriate classification of the clinical symptoms in the latter may have overruled this variable in the males.

One of the most influential parameters in the final logistic model in both sexes proved to be heart rate corrected ST segment amplitude changes. Heart rate adjusted ST segment amplitudes were recently described by Detrano *et al.* in a carefully designed study encompassing 303 patients without previous infarction (12). These measurements yielded a diagnostic accuracy similar to that obtained with planar thallium imaging in their original report. In fact, the weight of this adjusted ST segment measurement in the model was such that the value of this parameter decisively determined the outcome of the function in a large number of patients. These observations indicate that the diagnostic yield of exercise testing in male patients is higher than previously reported. In females, however, exercise test results were not very helpful and the addition of exercise test variables to clinical data did not improve their diagnostic classification.

The risk factor profile was not very important when exercise parameters were taken into account. Among the classic risk factors, only cigarette smoking and elevated cholesterol levels were associated with the presence of coronary disease when all other variables were considered. This is not surprising when it is realized that all patients were symptomatic. While it is generally agreed that risk factor profile is an important predictor of future coronary events in asymptomatic subjects (20), correlation of risk factors with disease prevalence is less evident. Risk factors were also of only limited value in predicting the anatomical presence of coronary disease in CASS registry (21). Similar negative findings were reported by Goldman *et al.* (22). Furthermore, total serum cholesterol level reportedly looses some of its predictive strength as a risk determinant in men older than 55 years of age (20).

Multivariate analyses of clinical and exercise data have been performed in a number of publications (2,19,22-24). Although a direct comparison of the results of

the various studies is hampered by the inclusion of patients with a previous myocardial infarction in several, the clinical and stress variables most strongly associated with significant coronary disease include age, type or severity of chest pain and ST segment depression with exercise (Table 4). Logistic regression analysis of clinical and exercise test variables in patients without a history of myocardial infarction has been performed in a limited number of these studies. Hung *et al.* employed this technique in 171 symptomatic men in order to assess the relative diagnostic yield of clinical data and multiple non-invasive tests, including exercise electrocardiography (24). Using ST segment depression of at least 0.1 mV as a positive criterion, exercise variables were of limited diagnostic use, even though patients who did not reach 85% of age predicted maximum heart rate were excluded. The same authors, utilizing linear discriminant analysis of clinical and exercise data, also found exercise parameters of little additional diagnostic value in 92 symptomatic women without previous infarction (25). Results from discriminant analysis of clinical and exercise test results in 1351 men in the CASS registry indicated that the greatest diagnostic yield of exercise testing was obtained in patients with probable angina (2). The results of the current study indicate that exercise testing in males may have a greater diagnostic value when a more powerful electrocardiographic indicator of exercise induced ischemia is used.

Table 4 Clinical and exercise variables associated with the presence of coronary artery disease with multivariate techniques in different studies

Variables	Pruvost(23) n=558	Hung(24) n=171	Goldman(22) n=321	Fisher(2) n=1351	Currie(19) n=105
Angina (history)	v	v	v	v	v
Age	v		v	v	
Smoking			v	v	
Cholesterol					v
ST segment depression		v	v	v	v
Heart rate	v	v		v	
Angina during exercise	v			v	
Workload	v				v

While logistic regression analysis confirmed that many clinical and exercise variables are in fact interrelated, it is only fair to mention that the Bayesian oriented CADENZA algorithm also proved its diagnostic worth in the present study population. The practical usefulness of the program has been the subject of a few other reports (6,26). Since the present analysis was performed in retrospective, the results of this study are by definition in favour for the presently constructed logistic model. Nevertheless, the currently obtained results may not be applicable to patients evaluated in different circumstances; future evaluations of the model in other

patient populations will be needed to verify its prospective trustworthiness. Although the reliable performance of the CADENZA program was thus confirmed, the results of the present study provide a few hints that could allow a further refinement of the algorithm: heart rate adjusted ST segment amplitude changes will offer a significant improvement over "conventional" ST segment measurements. Also, without affecting the presumed independence of various parameters in the Bayesian approach too much, the appearance of anginal symptoms during exercise in male subjects with non-specific or atypical complaints could be used to "upgrade" their pre-test chest syndrome classification to true anginal symptoms.

In conclusion, the present findings indicate that many clinical and exercise variables are mutually dependent. Logistic regression analysis of these variables is thus more suitable for diagnostic applications than the Bayesian approach. The correct diagnostic classification in males, in particular in those with non-specific or atypical complaints, is substantially improved by exercise testing. The additional diagnostic value of the exercise test in females, however, remains indeed questionable.

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CHAPTER 6

INELIGIBILITY FOR PREDISCHARGE EXERCISE TESTING AFTER MYOCARDIAL INFARCTION IN THE ELDERLY: IMPLICATIONS FOR PROGNOSIS

J.W. Deckers, P. Fioretti, R.W. Brower, M.L. Simoons, T. Baardman, P.G. Hugenholtz

ABSTRACT

This study describes the clinical profile and prognosis of elderly patients not eligible for predischarge exercise testing. The database consisted of 133 patients 55-64 years of age, and 111 patients older than 64 years of age who survived an acute myocardial infarction. Follow-up was one year. In the younger age group, 24 (18%) patients were unable to perform the test, in contrast to 63 (57%) of the elderly subjects. In these two groups, one-year mortality rates were 13% and 37%, compared with 6% and 4% for the respective patients eligible for stress testing. Clinical profile and radionuclide ejection fraction between ineligible patients in both age groups were similar. Ejection fraction measurement was the best predictor of late mortality in those patients who did not have an exercise test. It is concluded that ineligibility for predischarge exercise test identifies a high-risk group, especially in patients older than 64 years of age.

INTRODUCTION

The prognostic value of a symptom-limited predischarge exercise test in patients who survive the acute phase of their myocardial infarction has been well documented. Exercise-induced ST-segment changes, major ventricular arrhythmias, low workload and inadequate rise in blood pressure identify patients at high risk for subsequent cardiac death (1-5). However, little or no attention has been paid to the prognosis of patients who are unable to perform the test (1-4); furthermore, elderly patients have been excluded in a considerable number of studies (1,3,4). Therefore, the present study was undertaken in an attempt to assess the one-year mortality in subgroups of elderly patients not eligible for exercise testing, and to evaluate whether clinical data or non-invasive measurements could predict the mortality in this group in the year following acute myocardial infarction.

PATIENTS AND METHODS

Between March 1981 and December 1982, 336 consecutive patients older than 54 years of age were admitted at the coronary care unit of our institute with a documented myocardial infarction. Diagnosis of a definite infarction was made by the usual clinical features, typical ECG changes and elevated serum creatine kinase levels.

During the initial hospitalization 58 patients died, whilst 34 underwent coronary artery bypass grafting or percutaneous transluminal coronary angioplasty. The remaining 244 patients form the basis of this report, and were divided in two age groups: a group of 133 patients between 55 and 64 years of age, and an older group of 111 patients older than 64 years of age.

The following variables were analysed: age, history of prior myocardial infarction, location of infarction, MIRU classification, late heart failure, angina pectoris and maximum creatine kinase levels.

Every attempt was made to ensure that as many hospital survivors as possible performed the predischarge exercise test. Nevertheless, 87 patients were considered ineligible for the test. Contraindications and reasons for ineligibility are summarized for both age groups in Table 1.

Table 1 Reasons for ineligibility for predischarge exercise test

	No. of patients	
	55-64 yrs	>64 yrs
Cardiac contraindications:		
congestive heart failure	12	10
severe angina pectoris	1	2
other	-	2
Non-cardiac contraindications:		
peripheral vascular disease	2	6
cerebral vascular disease	1	3
other disease	5	10
poor general condition	-	29
other reason	3	1
Total	24	63

Before discharge, radionuclide ventriculography was performed in the 45° LAO view after an in vitro labelling of the blood cells with 15 mCi of Tc99m.

Acquisition time was 6 min. An automated contour detector was used with correction for background activity.

Following hospital discharge, all patients were seen at regular intervals in the outpatient clinic: one-year follow-up for all subjects was complete.

Statistical analysis

Univariate analysis with unpaired Student's t-test for continuous variables and chi-square or Fisher's exact test, when appropriate, was applied for the discrete variables. Receiver-operator characteristic (ROC) curves were used to compare the predictive value of the continuous variables.

RESULTS

Clinical variables of the four groups are presented in Table 2.

Table 2 Clinical profile of hospital survivors

	Patients in 55-64 year age group		Patients in >64 year age group	
	XT	No XT	XT	No XT
No. of patients	109	24	48	63
Age	60 ± 3	61 ± 3	68 ± 3	73 ± 5*
Previous MI (%)	23	37	33	39
Location MI (%)				
anterior	35	50	18	30
inferior	43	29	54	37
Non transmural MIRU	22	21	27	33
I or II (%)	98	62*	98	86*
III or IV (%)	2	38	2	14
Max CPK (IU/l^{-1})	574 ± 456	863 ± 576*	383 ± 276	376 ± 273
Late heart failure (%)	13	37*	10	28*
Angina (%)	17	25	10	25*
Ejection fraction (%)	47 ± 15	38 ± 19*	49 ± 15	42 ± 16*

** P <0.05 vs stress test (XT) performed*
MI = myocardial infarction

One-year mortality in the younger age group was 10% (rate of reinfarction 7%), in the elderly patients 21% (rate of reinfarction 8%). Of 133 patients in the younger age group, 24 (18%) could not perform the exercise test, mainly because of cardiac limitations (Table 1). One-year mortality in this subgroup was twice as high as in the patients who did undergo exercise testing. However, as the total number of deaths was only three, no attempt was made to relate mortality with available clinical data. In all three subjects death was sudden.

In the older age group (n=111), 63 patients (57%) were judged not eligible for exercise testing, non-cardiac reasons being responsible in the majority of subjects (Table 1). This ineligibility implied a nearly ten-folded increase in one-year mortality, which was of cardiac origin in all subjects but one (thirteen sudden, four fatal reinfarctions, five congestive heart failure, one carcinoma). Mean age of survivors and non-survivors was not different (74 *vs* 72 yrs, NS).

Congestive heart failure and angina pectoris during hospitalization were associated with a higher one-year mortality; no relation was found between a history of previous infarction and one-year mortality.

In 38 of 63 elderly patients without exercise test, ejection fraction measurements were obtained. One-year mortality in this subgroup of patients was 34%. Ejection fraction in these 38 patients was superior to age and MIRU classification in predicting late mortality (Figure 1).

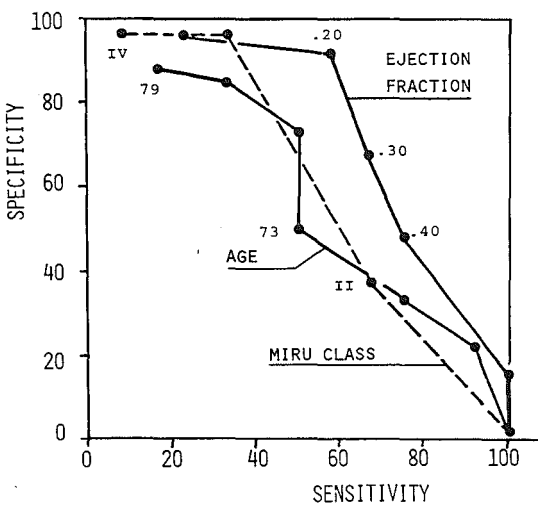

Figure 1 Specificity vs sensitivity (ROC curve) for late mortality for age, MIRU classification and ejection fraction in 38 patients >65 years ineligible for predischarge stress test.

A surprising similarity was noted between clinical profile and ejection fraction in patients in both age groups not eligible for the exercise test; nevertheless, despite smaller infarction size estimated by peak creatine kinase levels in the elderly, their one-year mortality was much higher.

DISCUSSION

Only a limited number of studies have addressed the prognosis of patients ineligible for predischarge exercise testing (5-7). DeBusk *et al.* evaluated 702 patients who survived an acute myocardial infarction (6); the rate of cardiac events within 6 months and within five years was significantly higher in the 265 patients (38%) who did not perform the exercise test. Madsen and Gilpin recently compared the prognostic significance of variables from a symptom limited bicycle exercise test shortly after myocardial infarction with clinical variables (7). Clinical exclusion criteria, applied in 49% of their study population of 886 patients, defined a high-risk group of 430 patients not eligible for exercise testing with a more than four-fold increased mortality (28.4% *vs* 6.6%). Fioretti et al analyzed the relative merits of resting ejection fraction measurement and predischarge exercise testing in 214 hospital survivors of myocardial infarction (5). The inability to perform the exercise test in 18% was the best predictor of mortality (23% *vs* 5%). However, in these studies, patients older than 69 years old were excluded (6), and stratification of patients in different age groups as in the present study, was not performed.

Exclusion criteria for exercise testing as used in this study are similar to other studies (2-7). The percentage of ineligible patients was 37% (18% in the younger, 57% in the older group): in view of the age distribution of our patients, this number seems even lower than the figures of the studies cited earlier (6-7).

The value of the resting ejection-fraction measurement as a predictor of late mortality is in agreement with other reports (5,8). However, the value of this test in very old patients seems limited, as life expectancy in these patients appears short.

In conclusion, for elderly hospital survivors (1) eligibility for stress testing in patients older than 55 years of age defines a subgroup with a relatively low risk for late mortality, (2) ineligibility for stress testing identifies a high-risk group, especially in patients older than 65 years, (3) clinical variables such as angina pectoris and congestive heart failure during hospitalization, as well as resting radionuclide ejection fraction can be used to predict late mortality in patients unable to perform the exercise test.

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CHAPTER 7

PREDICTION OF 1-YEAR OUTCOME AFTER COMPLICATED AND UNCOMPLICATED MYOCARDIAL INFARCTION: BAYESIAN ANALYSIS OF PREDISCHARGE EXERCISE TEST RESULTS IN 300 PATIENTS

J.W. Deckers, P. Fioretti, R.W. Brower, T. Baardman, A. Beelen, M.L. Simoons

ABSTRACT

After myocardial infarction (MI), the additive prognostic value of exercise variables to clinical variables has been questioned. The merits of a symptom-limited predischarge exercise test were therefore evaluated in clinically defined subgroups of patients. Exercise tests were consecutively performed by 208 survivors of uncomplicated MI (no heart failure, postinfarction angina, recurrent infarction, or late arrhythmias) and by 92 survivors of complicated MI. After uncomplicated MI (1-year mortality rate 4%), an achieved workload >70% of age-predicted maximum identified 145 patients at very low risk (predictive value for survival 98%). After complicated MI (1-year mortality rate 13%), an exaggerated heart rate response was the best predictor of outcome, but had low (92%) predictive value of survival at 155 bpm. It is concluded that stress testing has only limited value after complicated MI. After uncomplicated MI, exercise variables are extremely helpful in identifying patients at very low risk in whom further investigations are not warranted.

INTRODUCTION

During the past few years, the predischarge exercise test has become generally accepted as a useful step in the management of patients who have survived a myocardial infarction. In previous studies, exercise parameters reflecting ischemia and left ventricular function have stratified postinfarction patients into different prognostic groups (1-8). Two recent reports, however, cast some doubt on the additive prognostic value of the predischarge stress test. First, it was demonstrated that the addition of exercise test variables to clinical data did not improve the ability to predict subsequent death in unselected patients with a myocardial infarction (9). Results from the second study discourage even the use of a predischarge treadmill test, since the test was a less reliable predictor of future events than other variables, such as ST segment depression on resting ECG and peak creatine kinase levels (10).

In our series (11), stepwise discriminant analysis of clinical and stress variables showed the magnitude of systolic blood pressure increase to be an independent predictor of death in unselected survivors of myocardial infarction. These results seem to indicate that the merits of the predischarge exercise test may be less that initially expected. Therefore, we thought it appropriate to determine the prognostic value of this test in clinically defined subgroups of patients. The present study evaluates the clinical significance of the predischarge exercise test in 208 hospital survivors of an uncomplicated infarction and in 92 survivors of a complicated infarction during a 1-year follow-up period.

METHODS

Study population

Between March 1, 1981, and December 31, 1982, a total of 529 consecutive patients were admitted to the coronary care unit of our institution with a myocardial infarction. The diagnosis of myocardial infarction was based on the presence of the following criteria: (1) typical ischemic chest pain of at least 45 minutes' duration; (2) dynamic ECG changes defined as evolving QR complexes or Q waves of width 0.04 seconds with ST and T wave changes or, in the case of non-Q wave infarction, as T wave inversion or ST segment depression persisting for at least 24 hours without loss of R wave voltage or new Q wave development; and (3) a typical rise and fall in total creatine kinase levels with a peak concentration of more that twice the upper limit of normal for our laboratory. A diagnosis of previous infarction was determined from past clinical details or from diagnostic Q wave abnormalities on the ECG at admission. As part of an ongoing trial, 50 of these patients were treated with intracoronary streptokinase (12). Metoprolol, 50 or 100 mg twice daily, was used for the treatment of angina or hypertension and was given as a general secondary preventive agent after the first week in the absence of contraindications in 215 patients.

During the initial hospital stay 72 patients died. They and 52 patients who underwent coronary artery bypass graft surgery or percutaneous transluminal coronary angioplasty before discharge because of medically refractory angina pectoris were excluded. The remaining 405 patients were divided by clinical criteria into two groups: one group having sustained a complicated infarction and the other group having sustained an uncomplicated infarction. Complicated infarction was defined in the presence of clinical signs of left ventricular failure (Killip class III and IV), recurrent infarction, angina pectoris at rest or during normal ward activities, or late sustained ventricular or supraventricular arrhythmias.

The symptom-limited exercise test was performed in the upright position with stepwise increments in load of 10 Watts/minute on a bicycle ergometer 1 day before planned discharge. During exercise and for 6 minutes following peak exercise, the corrected orthogonal Frank lead ECG was recorded (13). Cuff blood pressure was

measured at 2-minute intervals during exercise and in the recovery period. All prescribed medication was continued on the day of exercise testing. In the absence of symptoms, the test was terminated by the attending physician if a drop in systolic blood pressure >10 mmHg occurred or when ventricular tachycardia or sustained supraventricular arrhythmia was observed. After hospital discharge, patients returned to the outpatient clinic at regular intervals. One-year follow-up was completed in all.

Statistical analysis

Univariate analysis with unpaired Student's t test for continuous variables and Fisher's exact test, when appropriate, were applied to discrete variables. Levels of $p<0.05$ were considered significant. For continuous exercise variables associated with death, receiver-operator characteristics curves were constructed to select the most advantageous cutoff points (14).

RESULTS

Complicated infarction existed in 157 patients, mostly because of heart failure (n=74) or angina pectoris (n=65). Recurrent myocardial infarction during hospitalization occurred in four patients. Among the 157 patients who survived a complicated infarction, 92 were able to perform the exercise test (group A). Cardiac contraindications for the test were present in most of the 65 patients who could not exercise (persistence of heart failure in 33, severe angina in eight). The 1-year mortality rate in this subgroup was 37% (n=24). The remaining 248 patients had an uncomplicated course. Of these, 208 were able to performed the exercise test (group B); the 40 patients who did not exercise had contraindications of a noncardiac origin, such as general disability or serious pulmonary or cerebrovascular disease precluding exercise. Their 1-year mortality rate was 10% (n=4).

Clinical characteristics of the 300 patients who were able to exercise are profiled in Table 1. A higher incidence of complications occurred with anterior infarction, with high peak creatine kinase levels, and with a discharge radiographic cardiothoracic ratio >50%. At 1-year follow-up, 12 patients in group A and eight patients in group B had died. The mortality rate after complicated infarction was significantly higher than that after an uncomplicated event (13% *vs* 4%, $p<0.001$). In group A, sudden death occurred in eight (group B = 6) and fatal reinfarction in two (group B = 2) patients. Also, one patient died because of heart failure and one preoperatively. Among the various clinical variables, a previous myocardial infarction was associated with a higher mortality rate after complicated infarction, and a cardiothoracic ratio >50% was positively related to late death after uncomplicated infarction.

Table 1 Clinical variables of postinfarction patients who performed an exercise test

Clinical variables	Total (n=208)	Uncomplicated MI Survivors (n=200)		Nonsurvivors (n=8)	Total (n=92)	Complicated MI Survivors (n=80)		Nonsurvivors (n=12)
Age (yr)(range)	54 (22-74)	54 (22-74)		52 (32-68)	55 (28-74)	55 (28-74)		53 (37-69)
Previous MI (%)	51 (25)	47 (24)		4 (50)	31 (34)	20 (25)	*	11 (92)
Previous angina(%)	59 (28)	58 (29)		1 (13)	36 (39)	31 (39)		5 (42)
Anterior MI (%)	63 (30)	60 (30)		3 (38)	46 (50)**	40 (50)		6 (50)
CTR >50% (%)	28 (13)	24 (12)	*	4 (50)	26 (28)**	21 (26)		5 (42)
Maximum CPK (IU/L)	527±436	519±425		690±664	739±599**	766±624		533±311
Digitalis (%)	19 (9)	16 (8)		3 (38)	32 (35)**	25 (31)		7 (58)
Beta blockers (%)	114 (55)	110 (55)		4 (50)	40 (43)	37 (46)		3 (25)

MI = myocardial infarction; CTR = cardiothoracic ratio; CPK = creatine phosphokinase

* $p < 0.02$; *survivors vs nonsurvivors*

** $p < 0.005$; *complicated vs uncomplicated*

Exercise test results and late death

In Table 2 the exercise test results are detailed. Only exercise parameters reflecting left ventricular function proved to be related to late death. Among the various exercise variables, the most sensitive predictors of death after uncomplicated infarction were an inadequate rise in systolic blood pressure and the inability to reach age-predicted maximum workload. An achieved workload of less than 70% of predicted maximum correctly identified five of the eight nonsurvivors (sensitivity 63%) and correctly predicted survival in 145 of 200 patients (specificity 72%) (Figure 1).

Table 2 Exercise test variables of postinfarction patients

Variables	Uncomplicated MI		Complicated MI	
	Nonsurvivors (n=8)	Survivors (n=200)	Nonsurvivors (n=12)	Survivors (n=80)
Maximum workload (watts)	100 ± 21	118 ± 33	98 ± 28	109 ± 35
% Maximum work capacity	63 ± 15	81 ± 17	67 ± 17	75 ± 19
Heart rate (bpm)				
At rest	92 ± 25	83 ± 16	93 ± 17	84 ± 18
Maximum	130 ± 31	132 ± 24	150 ± 21*	132 ± 23
Systolic blood pressure (mmHg)				
At rest	124 ± 26	123 ± 16	122 ± 21	119 ± 16
Maximum	145 ± 28*	68 ± 28	144 ± 23*	155 ± 29
Rise	21 ± 14*	45 ± 23	22 ± 16*	36 ± 27
No. (%) of patients with				
Angina	1 (13)	34 (17)	2 (17)	24 (30)
ST depression >0.1 mV	3 (38)	88 (44)	5 (42)	35 (44)
ST elevation >0.1 mV	5 (63)	75 (38)	7 (58)	39 (49)
Couplets	0 (0)	10 (5)	3 (25)	9 (11)
VT	0 (0)	0 (0)	1 (8)	2 (3)

** $p < 0.05$; survivors vs nonsurvivors*

The 1-year survival rate was 98% for the 148 patients who were able to reach at least 70% of predicted workload. This subgroup at low risk constituted 71% of all patients discharged after uncomplicated infarction. The 1-year mortality rate was 8% for the 60 patients (constituting 29% of the study population) who were unable to reach the 70% level. Table 3 details predictive values and risk ratios for various exercise parameters at different cutoff points. After complicated infarction, a low achieved workload was not associated with an increased mortality rate, but inadequate rise in systolic blood pressure and excessive rise in heart rate were related to subsequent death. The ability of these variables to correctly predict survival or death was, however, lower than that after uncomplicated infarction. For example,

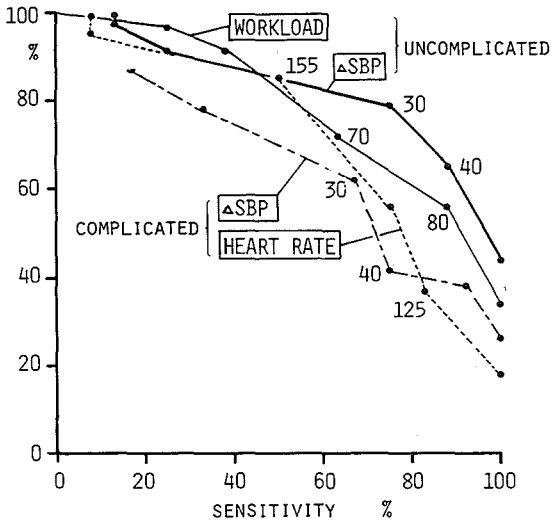

Figure 1 Sensitivity vs specificity of exercise variables in predicting late death after uncomplicated and complicated myocardial infarction.

Table 3 Predictive values for survival and risk ratios for various exercise parameters related to survival

Criteria		Survivors	Nonsurvivors	PV survival (%)	Risk ratio
Uncomplicated infarction (1-year mortality rate 4%)					
% Maximum workload	> 70%	145	3	98	4.1
	< 70%	55	5	92	
Blood pressure rise	> 30 mmHg	158	2	99	10
	< 30 mmHg	42	6	87	
Complicated infarction (1-year mortality rate 13%)					
% Maximum workload	> 70%	47	4	92	2.6
	< 70%	31	8	79	
Blood pressure rise	> 30 mmHg	48	4	92	2.7
	< 30 mmHg	30	8	79	
Heart rate	< 155 bpm	66	6	92	4
	> 155 bpm	12	6	67	

PV = predictive value

the specificity of an exercise-induced rise in systolic blood pressure of more than 30 mmHg was significantly lower after complicated infarction than the specificity of this parameter after uncomplicated infarction (60% *vs* 79%, $p<0.002$); this was also true at cutoff point 40 mmHg (42% *vs* 65%, $p<0.006$). Also, as can be appreciated from Figure 1, the curves representing exercise variables related to outcome after complicated infarction lie clearly below those related to outcome after uncomplicated infarction, indication a lower sensitivity for any value of specificity or, vice versa, a lower specificity for any value of sensitivity. Furthermore, after an uncomplicated event, exercise parameters were highly predictive of survival in a substantial number of patients. After complicated infarction, however, the ability of any exercise parameter at realistic cutoff points to reliably predict survival was very limited.

DISCUSSION

The independent prognostic merits of the predischarge test have only recently been questioned. Birk Madsen and Gilpin (9), as well as Williams *et al.* (10), have demonstrated that the addition of exercise variables to historic and clinical data did not improve the ability to predict 1-year mortality rates in survivors of a myocardial infarction (9,10). As their results actually discourage the use of the exercise test in unselected postinfarction patients, the present study was designed to determine the value of the test in clinically defined subgroups of patients.

The results of our study reaffirm the value of clinical variables in predicting 1 year outcome after myocardial infarction. Recent studies have also established that the inability to exercise, particularly in the presence of cardiac limitations, carries a poor prognosis (9,11,15,16). The 1-year mortality rate amounted to 38% in that subgroup of our patients who sustained a complicated infarction. Although the diagnosis of complicated infarction was based on a heterogeneous group of symptoms, patients in this category obviously had many characteristics which have previously been associated with an adverse outcome (9,15-18). Even when the exercise test could be completed, a prior complicated course carried a 1-year mortality rate of 13%, three times that of an uncomplicated course.

In patients who could perform the exercise test, exercise variables related to left ventricular function were the best predictors of outcome. Exercise-induced ST segment depression, associated with an increased mortality rate in several previous studies (1-3), proved unrelated to the mortality rate in this study. Other authors have also questioned the value of this parameter (4,8,10,16,19). We were unable to confirm the prognostic significance of ST segment elevation, as reported by others (8).

Our study illustrates that the exercise test results can only be interpreted when the clinical status of the patient is taken into account. For instance, after complicated infarction, the best exercise predictors of outcome --an exaggerated

heart rate response and a low increase in systolic blood pressure-- had both relatively low specificity and sensitivity. Specificity only reached clinically useful levels at very high heart rates (Figure 1). Also, the interpretation of the value of this exercise parameter is hampered by its dependence on the level of exercise achieved and on the use of beta-blocking agents. Given these limitations, after complicated infarction with its high ensuing mortality rate, exercise variables were not reliable predictors of survival.

Rather, exercise testing identified two subgroups of patients, and the number in each was dependent on chosen cutoff points; one group with a very high (17% to 33%) and another with a much lower, but still relatively high (6% to 8%), 1-year mortality rate. Most clinicians would agree that additional testing would be indicated in both groups, and our results indicate that the value of the predischarge exercise test in these patients may be limited. Although the use of the test after complicated myocardial infarction has been discouraged on safety grounds (15), no complications were observed in our series. Other studies have also assessed the value of exercise testing after complicated infarction. Saunamaki and Andersen (20) separately reported exercise test results in a subgroup of 32 patients with clinical heart failure and/or previous myocardial infarction. In their small study group, a high increase in the pressure-rate product and the absence of major arrhythmias during exercise indicated that one third of these patients actually had good left ventricular function and an excellent long-term prognosis. In earlier reports by Hunt *et al.* (21) who studied 56 postinfarction patients with a 1-year mortality rate of 14%, and by Srinivasan *et al.* (22), who investigated 154 patients with a 1-year mortality rate of 8%, a relation was found between angina as well as ST segment depression during exercise and subsequent matching. Hemodynamic exercise variables, however, were not taken into account by these authors.

In survivors of uncomplicated myocardial infarction, exercise variables were able to identify a large proportion of patients at very low risk of dying in the year following infarction. Achievement of 70% of age-predicted maximal workload or a 30 mmHg increase in systolic blood pressure during exercise had a predictive value for survival of 98% and 99% in, respectively, 71% and 77% of the 208 patients who survived an uncomplicated event. Of the relatively small number of patients who were unable to satisfy these criteria, the 1-year mortality rate was between 8% and 13%, and this subgroup would probably benefit most from further evaluation and more intensive management.

In accordance with our analysis, Weld *et al.* (5) previously reported a 1-year mortality rate of only 1% in 115 postinfarction survivors, constituting 47% of their study population, who were able to exercise longer than 6 minutes during a 9-minute exercise protocol (5). Our study illustrates that when clinical and exercise variables are combined, a much larger fraction of patients at very low risk can be delineated. Results of a recent multicenter study are in agreement with these findings. Krone *et al.* (16) demonstrated that in 665 patients undergoing exercise testing, a subgroup of 454 (69%) patients could be identified with a 1-year mortality rate of 1%. This group

was characterized by the absence of pulmonary congestion on chest x-ray examination and by a blood pressure higher that 110 mmHg during exercise. Patients at such low risk do not require further testing and, in the absence of symptoms, they will not benefit from coronary bypass surgery (23).

CONCLUSIONS

The usefulness of a predischarge exercise test can be greatly enhanced when interpreted in combination with clinical data, After a complicated infarction with clinical signs suggestive of a poor prognosis, exercise test results have only limited value in identifying patients at low risk; additional tests will have to be performed to further stratify these patients. After an uncomplicated infarction without the clinical features to suggest a poor outcome, exercise parameters reflecting left ventricular function can identify a large number of patients at very low risk. Additional testing or intensive therapy in this group seems unnecessary, and it is unlikely that cardiac surgery will improve the prognosis of these patients. These results indicate that the predischarge exercise test can be of most use in predicting survival in patients recovering from an uncomplicated myocardial infarction.

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CHAPTER 8

EPICRISIS

Exercise testing can be used for different purposes in various groups of subjects. In most circumstances, the procedure can be applied as described in Chapter 1 and in the recent report of the Joint College of Cardiology / American Heart Association Task Force on Assessment of Cardiovascular Procedures, Subcommittee on Exercise Testing (1). The interpretation of the exercise test results depends on the history and clinical situation of the subject tested, as discussed in the previous chapters. On the basis of these observations and data available from the literature, guidelines for the interpretation of exercise tests are provided in this chapter.

The exercise test procedure

Either a treadmill or a bicycle ergometer should be used with stepwise or continuous increases in workload. Heart rate, blood pressure and the electrocardiographic response to exercise should carefully be monitored and recorded during each stage of exercise. Time of onset of ST segment depression, rhythm and conduction disturbances, chest pain or other symptoms must be recorded. Symptom limited testing is preferable to so-called submaximal testing for reasons outlined in Chapter 1. Irrespective of the patients' symptoms, indications for terminating exercise include signs of inadequate cardiac output such as a decrease in systolic blood pressure or heart rate at increasing workloads. In a clinical exercise laboratory with adequate equipment and a physician present, electrocardiographic changes are rarely reason to terminate exercise unless these coincide with other symptoms. Ventricular and supraventricular rhythm disturbances in particular are no argument to terminate the test if these arrhythmias are well tolerated. However, the appearance of ST segment elevation in leads without Q waves must be regarded as a sign of severe transmural ischemia and the test should be terminated if this (rare) finding occurs, even in the absence of symptoms (2). In other conditions, for instance in laboratories outside a clinical environment or in occupational health services, more restricted guidelines may be applied, provided that when exercise is terminated for electrocardiographic changes, the test is repeated in a clinical exercise laboratory.

The merits of exercise testing can be enhanced by computer assistance (3,4). The use of a computer will facilitate the technical execution of the test for instance by regulating workload and recording of the electrocardiogram at appropriate times. This will provide the physician with more and better opportunity to examine the patient during the test. In this way, the appearance and the course of symptoms during the test as well as adverse reactions to exertion can be observed in more

detail. Furthermore, computer processing of the exercise electrocardiogram facilitates its interpretation. Several systems developed in the seventies were based on three electrocardiographic leads, such as the corrected orthogonal Frank lead system (3). This approach was chosen because on-line processing of more than three leads was not available at that time. Nowadays, computers are more powerful and, since most physicians are more familiar with the standard 12 leads, it is now recommended to record 12 lead electrocardiograms during exercise. Although more elaborate systems such as body surface mapping can provide some additional information, their use should be restricted for special studies only.

Table 1 Weight of coefficients related to six year coronary heart disease incidence according to the Framingham Study (7)

Coefficient	Men	Women
Intercept	-22.227532	-19.066572
Age, years	0.460575	0.311558
Age x age	-0.002882	-0.001724
Cholesterol, mg/dl	0.028590	0.016802
Systolic blood pressure, mmHg	0.012444	0.015278
Cigarette use, yes/no	0.447815	0.049966
Left ventricular hypertrophy, yes/no	0.743158	0.441707
Glucose intolerance, yes/no	0.265016	0.416906
Cholesterol x age	-0.000416	-0.000190
HDL intercept	-2.825595	3.665357
HDL, mg/dl	-0.046643	-0.038380

Six year coronary heart disease incidence probability tables can be estimated using the weight of the above coefficients and the probability function:

$$P = \frac{1}{1 + e^{-(a + b_1x + b_2x + \ldots)}}$$

Example: In a 50 year old male subject with the following characteristics: systolic blood pressure 180 mmHg, cholesterol level of 310 mg/dl, cigarette smoking, presence of left ventricular hypertrophy and glucose intolerance, estimated probability for six years coronary heart disease incidence amounts to 42.7%.

Interpretation of exercise tests in asymptomatic subjects

Information on the prevalence of coronary disease in asymptomatic subjects is scarce since only few angiographic studies have been performed in such individuals. Some autopsy studies in persons not known to have coronary artery disease before death, such as those dying of trauma or other unrelated conditions, are available (5). When these data are combined, the prevalence of disease in symptomatic subjects appears to be less than five percent. Differences in disease prevalence occur when subjects are classified according to age and sex: the prevalence of significant coronary disease ranges from less than one percent for women 30 to 39 years of age to 12 percent for men 60 to 69 years of age. Thus, given its imperfect diagnostic characteristics and ensuing low predictive value under these circumstances, exercise testing is not recommended in asymptomatic subjects to detect the presence of coronary artery disease. The outcome of the test will only in very rare cases establish the presence of coronary disease with reasonable accuracy and "false positive" findings will be the rule rather than the exception (6). Attempts to detect coronary disease in asymptomatic subjects are also futile since no therapeutic consequences can be derived from the findings.

Prognostic information in asymptomatic subjects has become available from the Framingham Heart Study in which middle aged men and women were examined for cardiovascular risk factors (7). The history, physical examination and laboratory tests performed included smoking habits, blood pressure, total serum cholesterol, HDL cholesterol, glucose level and a 12 lead electrocardiogram. Participants free of coronary disease at entry were followed for 16 years for the appearance of new heart disease or death attributable to coronary disease. This 16 year experience has been converted to a six year rate in order to provide a meaningful short term estimate of cardiovascular risk. Using logistic regression analysis, a model was constructed that allowed calculation of coronary artery risk for men 45 to 65 years old and women 45 to 65 years old, given available information of these risk factors (Table 1). Modelled incidence rates range from less than one percent to greater than 80 percent; typically, they are less than ten percent, and rarely exceed 45 percent in men and 25 percent in women. However, despite this information on available risk factors, the model accounts for no more than about 50 percent of the variance in coronary incidence. Other factors relevant for future coronary disease like apolipoprotein levels, diet, physical activity, genetic markers and disease susceptibility in particular are not included in the model. Nevertheless, the Framingham data are probably the best available, and they were found to be a reliable predictor of future coronary disease for similar U.S. populations (8).

Exercise testing in asymptomatic persons has been used for prognostic reasons. Indeed, the occurrence of ST segment depression of at least 0.1 mV during exercise has been associated with an increased risk of future cardiovascular events in nearly all studies (9,10). It would therefore seem logical to combine the use of the Framingham coronary risk profile and exercise test results to estimate the future cardiovascular risk of a given subject in a more reliable manner. Such estimates are

Table 2

Exercise testing in asymptomatic subjects

Clinical variables	Exercise variables
Detection of coronary artery disease	
None	Not advised
Assessment of prognosis	
Age Sex Risk factors Electrocardiogram	ST segment (workload)

sometimes required for certain insurance policies and for the evaluation of those engaged in occupations where the presence of coronary disease might create undue risk for others; i.e., airline pilots. Some precautions are however necessary. Available information on risk factors should be complete and the electrocardiographic interpretation should be strict and comply with criteria applied in previous studies (9,10). Thus, only ST segment depression of at least 0.1 mV in lead V_5 should be considered abnormal (Table 2). Although low workload has also been associated with future coronary events, the specificity of this exercise parameter is too low for reliable use in these circumstances. Since it may be assumed that the occurrence of ST segment depression with exercise is independent of the risk profile (9,10), the appearance of ST segment depression with exercise can be considered an additional risk indicator for the development of manifest coronary disease within the next six years. In fact, it might be better to interpret this exercise induced ST segment depression as an early sign of latent coronary disease (11,12). According to previous publications, the augmentation in risk in the ensuing six years associated with ST segment depression six years can be considered to be two to three fold in men (9,13). In women, data are more scarce and the increase in risk in this sex should be estimated to be lower, for instance 1.5 to two fold (14,15). The product of these values and the Framingham risk estimate yields the probability of coronary events in the next six years. However, very high estimates should be interpreted with caution, and, in order to be realistic, a predicted estimate should not exceed the 50 percent limit.

In our opinion there is little need to execute exercise tests in asymptomatic individuals. If such tests are nevertheless performed, their purposes and indications should be well defined and the consequences of an "abnormal" test should be seriously considered before the test. Cases where severe iatrogenic damage was inflicted on the basis of an "abnormal" electrocardiographic response to exercise are not infrequent and should be avoided (12).

Interpretation of exercise tests in subjects suspected of coronary artery disease

Much research has been devoted to the use of the exercise test in the diagnosis of coronary artery disease; that is, in symptomatic patients without a previous myocardial infarction and with a normal resting electrocardiogram. It was demonstrated in Chapters 3 and 4 that heart rate corrected ST segment amplitude changes correlate best with the presence or absence of coronary artery disease. Other electrocardiographic measurements such as changes in R wave amplitude, the influence of the height of the R wave on the magnitude of ST segment depression and the slope of the ST segment are only of limited diagnostic value. The concept to relate the amount of exercise induced ST segment amplitude changes to heart rate is not new. A similar approach, described by Simoons and Hugenholtz in 1977, is currently in use at the Thoraxcenter (16). Heart rate corrected ST segment amplitude measurements are simple. They are hardly affected by the concomitant use of beta blockers during exercise, and repolarization abnormalities in the resting electrocardiogram are accounted for by the comparison of the ST segment amplitude at peak exercise and at rest.

Results of exercise tests must be interpreted in light of clinical findings. However, many clinical and exercise variables are mutually dependent and interrelated. For instance, patients with severe symptoms will often have more extensive disease than patients with mild symptoms. As a consequence, exercise performance will be lower in the former patients, they will more often experience angina during exercise and will generally exhibit a greater amount of ST segment depression with stress than patients with lesser disease. Because of these associations, illustrated in Chapter 5, logistic regression analysis may be preferable to the Bayesian approach. In clinical practice, however, the latter method proved to be reliable, provided that the number of variables used is limited (17). A diagnostic model based on logistic regression analysis of clinical and exercise variables was developed in Chapter 5 which emphasizes the importance of simple clinical characteristics (Table 3). Interestingly but not surprisingly, the classic Framingham risk factors (Table 1) appear to be relatively unimportant diagnostic adjuncts in patients in whom the presence of disease is suggested by symptoms (18,19). Finally, it should be stressed that the diagnostic contribution of exercise testing in females and males is different when all clinical and exercise parameters are considered: the additional diagnostic role of the exercise test is limited in women, while its diagnostic contribution in males is greater. A reasonably reliable diagnostic probability statement can be made

Table 3

Exercise testing in symptomatic subjects suspected of coronary artery disease with a normal electrocardiogram at rest

Clinical variables	Exercise variables
Diagnosis of coronary artery disease	
Age	ST segment
Sex	Heart rate
Type and severity of symptoms	Angina
Cigarette smoking	Workload
Serum cholesterol	
Assessment of prognosis	
Age	Workload
Severity of symptoms	ST segment
	Heart rate

in most patients after the test; knowledge of these estimates will be of help in the clinical management of many.

Assessment of prognosis in symptomatic patients suspected of having coronary disease is not of primary interest. Evaluation of diagnosis has priority and prognosis will depend on the actual diagnosis. In subjects with low probability of disease or in those without coronary disease prognosis is excellent (20,21). Estimates of coronary risk incidence can be obtained as described above and in Table 2. In patients who appear to suffer from coronary artery disease, prognosis depends on left ventricular function, the extent of coronary disease and the severity of ischemia (22,23). A normal resting electrocardiogram, the absence of significant cardiac events in the past will generally indicate that left ventricular function is normal or only mildly impaired. Course and severity of symptoms are thus of primary importance (21). Exercise variables which can assist in the assessment of the symptoms and prognosis of these patients include performed workload, maximal heart rate as well as severity of ST segment depression (Table 3)(21,24,25).

Exercise testing in patients with known coronary artery disease

In patients in whom a diagnosis of coronary artery disease has been made, exercise testing can be used to detect left ventricular ischemia, provided that the ST segment at rest is normal. Thus, the electrocardiographic response to exercise can be interpreted in patients with a normal electrocardiogram at rest and in patients with a right bundle branch block or an inferior wall infarction. In these circumstances, the "diagnostic" procedure outlined in Table 3 can be followed, and exercise induced ST segment depression can be interpreted as a sign of ischemia. Exercise induced ST segment elevation in leads with a pathological Q wave can be related to left ventricular wall motion abnormalities as well as extensive ischemia (26). When ST segment at rest is abnormal, for instance in the presence of a left bundle branch block, large anterior or lateral wall infarction, exercise Thallium scintigraphy is preferred to assess the presence of ischemia.

In patients with known coronary disease, substantial prognostic information is available with simple investigations: a careful history and physical examination as well as the resting electrocardiogram will supply details of current symptoms and of cardiac events in the past. This knowledge alone provides a sound basis for prognostic assessment. The importance of these variables has recently been underscored by investigators from Duke University (27). The combination of a simple "angina score" and an electrocardiogram at rest proved to be a powerful predictor of prognosis, which added independent prognostic information to the patient's age, sex, coronary anatomy and left ventricular function.

Prognosis in patients with coronary artery disease is related to age, residual left ventricular function and the extent of coronary disease (20,22,28). Clinical determinants of these variables include a history of previous myocardial infarction, cardiac enlargement and use of digitalis and/or diuretics and angina (22,28). Simple investigations like a chest X ray and echocardiogram can provide an additional estimate of left ventricular function.

The general role of testing in patients with known coronary artery disease is concerned with prognosis and with identification of those patients who could benefit from therapeutic interventions. Normal achieved workload and absence of ST segment depression with exercise have been associated with favorable outcome in all studies (20-25,28). Also, in patients with three vessel disease and impaired left ventricular function, survival was not different between medically and surgically treated patients when exercise capacity was normal, while mortality was higher in patients with similar findings at angiography and low exercise tolerance (29). Thus, even in patients with defined coronary anatomy, exercise variables primarily related to the functional state of the left ventricle are helpful in assessing prognosis.

The role of exercise testing in patients recovering from a recent myocardial infarction has emerged during the last decade. The test can be used to promote the patient's confidence, as a guide to rehabilitation programs, to detect ischemia and as a prognostic tool. Patients at high risk for future coronary events are usually excluded: older patients, patients with postinfarction angina or with clinical signs of

Table 4

Exercise testing in subjects with coronary artery disease

Clinical variables	Exercise variables
Detection of myocardial ischemia	
Symptoms	ST segment Angina during exercise Workload Blood pressure response Thallium
Assessment of prognosis	
Age LV function - previous infarction - heart failure - digitalis, diuretics - CT ratio Severity of symptoms	Workload Blood pressure response ST segment Heart rate Angina during exercise

left ventricular failure (30). In those eligible for a predischarge exercise test, one year mortality rate will generally be between five and ten percent. Exercise variables reflecting left ventricular function are of primary importance, while ST segment deviation and ventricular arrhythmias have limited prognostic significance (Chapter 1). In patients considered to be at low risk on a clinical basis, normal or near normal achieved workload, rise in systolic blood pressure of at least 30 mm Hg and the absence of ST segment depression indicate an excellent short term prognosis. Additional investigations are unnecessary in this large group of postinfarction patients.

The guidelines described in the previous paragraphs can be implemented in computer systems for analysis and interpretation of exercise test data. In each patient the clinical question to be answered by the test should be indicated, and its

interpretation should be based on a combination of the patient's history, his clinical status prior to the test and the test result. Properly conducted exercise tests provide useful diagnostic and prognostic information in patients with suspected or known coronary artery disease. This information can be obtained at moderate financial cost and without excessive risk or discomfort to the patient.

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SAMENVATTING

In dit proefschrift wordt een beschrijving gegeven van de diagnostische en prognostische waarde van inspanningsonderzoek bij patiënten met klachten wijzend op hartlijden en bij patiënten die recent een hartinfarct hebben doorgemaakt.

In de introductie wordt ingegaan op bestaande gegevens uit de literatuur. Benadrukt wordt dat de test meer gegevens oplevert dan alleen elektrocardiografische bevindingen. Het verloop van de bloeddruk en hartfrequentie tijdens inspanning, de behaalde belasting en het optreden van klachten tijdens het onderzoek hebben eveneens belangrijke betekenis. Een korte beschrijving van diverse inspanningsprotocollen voor de fietsergometer en loop band wordt gegeven. Richtlijnen voor de uitvoering van de test worden verstrekt en de voordelen van het gebruik van een computer voor de praktische uitvoering van de test en de beoordeling van het elektrocardiogram worden besproken. Gewezen wordt op de betekenis van de selectie van de test personen voor de interpretatie van de uitslag, met name bij patiënten bij wie de test om diagnostische redenen wordt uitgevoerd. Wederzijds beïnvloeding van de definitieve diagnose en de test uitslag kan leiden tot een afname van de oorspronkelijk gemeten betrouwbaarheid van de test bij prospectieve toepassingen in andere patiënten groepen. Diverse elektrocardiografische diagnostische criteria worden vergeleken en een overzicht van de diagnostische waarde van het onderzoek bij symptomatische patiënten zonder doorgemaakt hartinfarct wordt gegeven. Een goede beoordeling van de diverse inspanningsparameters, met name de door inspanning geluxeerde daling van het ST segment, is alleen mogelijk indien rekening wordt gehouden met andere klinische variabelen die de kans op aanwezigheid van ziekte beïnvloeden, zoals leeftijd, geslacht en klachten patroon. Het theorema van Bayes, inhoudende dat de kans op ziekte niet alleen afhangt van de uitslag van de test maar ook van het voorkomen van de ziekte in de populatie, kan behulpzaam zijn bij deze interpretatie. Ook kwamen studies aan de orde die multivariate statistische technieken toepasten op klinische en ergometrische variabelen.

De prognostische waarde van de inspanningstest wordt beschreven bij asymptomatische personen, bij patiënten met bekend hartlijden en bij patiënten die kort tevoren een hartinfarct doormaakten. Bij personen zonder klachten kan het optreden van ST segment daling van ten minste 0.1 mV beschouwd worden als een aparte risico-indicator, die de kans op overlijden in de volgende zeven a acht jaar verdrievoudigt. Bij patiënten met bekend hartlijden is de inspanningstest van waarde voor het onderscheiden van groepen patiënten met een hoge en lage sterfte, zelfs ook indien andere gegevens, zoals bijvoorbeeld een coronair angiogram, ter beschikking staan. Bij patiënten die herstellend zijn van een doorgemaakt hartinfarct geeft de test uitslag informatie over de prognose in het jaar volgend op het infarct. In deze categorie patiënten zijn inspanningsvariabelen gerelateerd aan de functie van de linker hartkamer, zoals bloeddruk verloop en inspanningstolerantie, van groter belang dan uitsluitend elektrocardiografische afwijkingen tijdens het onderzoek.

De diagnostische waarde van de inspanningstest bij vrouwen is omstreden vanwege het frequent optreden van inspanningsgebonden ST segment daling, ook zonder de aanwezigheid van hartafwijkingen. In hoofdstuk 2 worden om deze reden bij mannen en vrouwen de veranderingen beschreven van de P top, het QRS complex en het ST segment die optreden tijdens inspanning. De wijzigingen van P top en QRS complex zijn in beide groepen vergelijkbaar: de amplitude van P vectoren nemen toe en verplaatsen zich in caudale richting terwijl de QRS vectoren zich tijdens en vooral direct na inspanning naar rechts en naar achteren richten. Het verloop van de R amplitude blijkt zeer variabel. Duidelijke verschillen tussen beide sexen werden gesignaleerd voor wat betreft het ST segment: met name in de onderwandsafleidingen bij hoge hartfrequentie is de ST segment daling bij vrouwen meer uitgesproken dan bij mannen. Het blijkt dat deze verschillen niet samenhangen met een verschillende respons van de S golf van het QRS complex.

In hoofdstuk 3 wordt de diagnostische waarde van eerder gepubliceerde algoritmes die gebruik maken van inspanningsgegevens beschreven bij 345 mannen met een normaal elektrocardiogram in rust. Beoordeeld worden het huidige in het Thoraxcentrum gebruikte systeem, dat gebruikt maakt van voor hartfrequentie gecorrigeerde amplitude en helling van het ST segment, een elektrocardiografische inspanningsscore die de cumulatieve som van de ST segment amplitude relateert aan behaalde belasting en hartfrequentie, discriminant analyse van diverse elektrocardiografische variabelen en klachten tijdens de test en behaalde belasting, alsook ST segment metingen gecorrigeerd voor hartfrequentie. Beide laatste methoden, die in essentie dezelfde elektrocardiografische metingen hanteren, blijken de meest betrouwbare diagnostische resultaten op te leveren: een sensitiviteit van ongeveer 80% wordt gemeten bij een specificiteit van 90%.

Een vergelijkbaar onderzoek, maar dan bij 189 vrouwen zonder doorgemaakt hartinfarct, wordt beschreven in hoofdstuk 4. Daarnaast wordt in deze studie de waarde onderzocht van ongecorrigeerde ST segment metingen in de orthogonale afleidingen X en Y, de invloed van de amplitude van de R top op de daling van het ST segment, door inspanning veroorzaakte wijzigingen in de amplitude van de R top en de diagnostische waarde van enige specifiek voor vrouwen ontwikkelde diagnostische algoritmes. De conclusies van deze studie luiden eveneens dat discriminant analyse en voor hartfrequentie gecorrigeerde ST segment metingen de meest betrouwbare diagnostische informatie opleveren bij vrouwen. Elektrocardiografische metingen in de onderwandsafleidingen zijn echter onbetrouwbaar en toename van de R top tijdens inspanning heeft geen diagnostische betekenis bij vrouwen.

In hoofdstuk 5 wordt de additionele diagnostische waarde van de inspanningstest bepaald, indien rekening wordt gehouden met reeds beschikbare klinische gegevens, zoals leeftijd, aard van de klachten en risicofactoren. De wederzijdse afhankelijkheid van deze gegevens wordt bij 295 gecatheteriseerde mannen en vrouwen bestudeerd en aangetoond door middel van logistische regressie analyse van klinische en inspanningsgegevens. Tevens wordt deze analyse gebruikt ter ontwikkeling van een diagnostisch model, waarvan de uitkomsten werden vergeleken met de Bayesiaanse

benadering. In het uiteindelijke diagnostische model blijken risico factoren slechts een geringe rol te spelen. Ernstige hartklachten gaan vrijwel altijd gepaard met hartafwijkingen. Van de inspanningsvariabelen blijken de voor hartfrequentie gecorrigeerde ST metingen bij zowel mannen als vrouwen van belang te zijn. Angineuze klachten zijn alleen bij mannen van betekenis, terwijl behaalde belasting een diagnostische rol speelt bij vrouwen. Bij mannen levert zowel de logistische regressie analyse als de Bayesiaanse methode additionele en nuttige diagnostische informatie op; bij vrouwen blijkt de aanvullende diagnostische informatie van de inspanningstest echter beperkt te zijn.

In de hoofdstukken 6 en 7 wordt de relatieve prognostische waarde van eenvoudige klinische variabelen en inspanningsparameters beoordeeld. Het belang van de klinische variabelen wordt in hoofdstuk 6 geïllustreerd door de cardiale uitsluitingscriteria voor het doen verrichten van de fietstest voor ontslag uit het ziekenhuis bij 111 patiënten ouder dan 65 jaar die een hartinfarct doormaakten. De door toepassing van deze criteria geïdentificeerde groep patiënten had een eenjaars sterfte die bijna tien maal hoger was dan die van patiënten die wel in staat werden geacht de fietstest te verrichten.

Het belang van eenvoudige klinische gegevens voor de interpretatie van inspanningsgegevens wordt in hoofdstuk 7 beschreven. Bij 92 patiënten met een hartinfarct bij wie het beloop in het ziekenhuis gecompliceerd werd door het optreden van angina pectoris, hartfalen of late ritmestoornissen bedroeg de eenjaars sterfte 13%. Resultaten van de voor ontslag verrichte inspanningstest blijken in deze groep slechts van geringe waarde om patiënten met een gunstiger eenjaars afloop te identificeren. Bij 208 patiënten bij wie het hartinfarct ongecompliceerd verliep bedroeg de sterfte na een jaar 4%. Inspanningsgegevens gerelateerd aan de linker kamer functie zoals behaalde belasting en toename van de systolische bloeddruk blijken van aanzienlijke waarde om een groep van 145 patiënten te onderscheiden met een zeer laag risico voor overlijden in het jaar volgend op het hartinfarct.

In hoofdstuk 8, tenslotte, worden specifieke richtlijnen gegeven voor de uitvoering van de inspanningstest en voor de interpretatie van inspanningsgegevens bij asymptomatische personen, bij symptomatische patiënten bij wie hartafwijkingen worden vermoed, bij patiënten bij wie zekerheid bestaat over het bestaan van hartlijden en bij patiënten met een recent hartinfarct bij wie de inspanningstest wordt verricht voor het verlaten van het ziekenhuis.

WOORDEN VAN DANK

Dit proefschrift had alleen tot stand kunnen komen in het Thoraxcentrum en aan alle medewerkers van dit zo bijzondere instituut ben ik veel dank verschuldigd. Mijn gevoelens van grootste erkentelijkheid gaan uit naar Prof. P.G. Hugenholtz, Dr. M.L. Simoons en Prof. Dr. J.Lubsen. Waarde Paul, welk een genoegen is het om te werken in dit centrum, en met veel genoegen denk ik nog terug aan mijn eerste schreden binnen dit gebouw. Je hebt mij altijd alle gelegenheid gegeven en mogelijkheden geschapen mij te ontplooien: hiervoor is de grootste dankbaarheid op zijn plaats. De genegenheid en vriendschap ondervonden van jou en je familie hebben een bijzondere stempel gedrukt op de afgelopen tien jaren. Maarten, zonder jouw hulp zou dit proefschrift nooit het licht hebben gezien. Jij was de initiator en de stuwende kracht achter het onderzoek. Altijd kon ik een beroep op je doen, en altijd bleken je adviezen uiterst waardevol. Het is een voorrecht geweest met je samengewerkt te hebben en onder je begeleiding te hebben kunnen promoveren. Koos, jij hebt getracht mij de nuances van het medisch denken en handelen te brengen. Je kennis en inzichten zijn voor mij een voortdurende bron van verrijking geweest. Ik ben je dankbaar voor alle energie en tijd aan mij besteed gedurende de afgelopen jaren. Grote dank ben ik eveneens verschuldigd aan de overige leden van de Prommotie Comissie, en vooral aan Prof. Dr. J-M.R. Detry, voor waardevolle adviezen. Gevoelens van erkentelijkheid zijn ook op zijn plaats voor het huidige hoofd van het Thoraxcentrum, Prof. Dr. J.R.T.C. Roelandt.

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CURRICULUM VITAE

De auteur van dit proefschrift werd op 15 oktober 1951 te Heerlen geboren. In 1971 behaalde hij het eindexamen Gymnasium B aan het Grotius College in deze plaats. Tijdens de studie geneeskunde aan de Erasmus Universiteit te Rotterdam was hij werkzaam bij het Institut de Cancerologie et d'Immunogenetique te Villejuif in Frankrijk en op de afdeling Experimentele Cardiologie van het Thoraxcentrum onder toezicht van Dr. P.D. Verdouw. Het artsexamen werd behaald in 1979. Na het volgen van de stage Inwendige Geneeskunde bij Dr. M. de Jong in het Sint Franciscus Gasthuis te Rotterdam werd de opleiding tot cardioloog vanaf juli 1981 gevolgd in het Thoraxcentrum van het Academisch Ziekenhuis Rotterdam "Dijkzigt" onder leiding van Professor P.G. Hugenholtz. Vanaf 1985 is hij als cardioloog werkzaam in het Van Dam-Bethesda ziekenhuis te Rotterdam; daarnaast is hij als wetenschappelijk medewerker verbonden aan de afdeling Klinische Epidemiologie van het Thoraxcentrum.