# Exercise Electrocardiographic Stress Testing

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**Summary**

- EECG provides essential information for diagnosis, prognosis, and management of patients with cardiovascular disease by a safe, relatively inexpensive method that does not use ionizing radiation.
- EECG can provide objective evidence of myocardial ischemia and thereby of CAD, the leading cause of mortality in our society.
- Large studies correlating exercise-induced ST-segment deviation with angiographically diagnosed CAD indicate that sensitivity for CAD is 60–70% and specificity is closer to 80%.
- Comparisons of the diagnostic utility of EECG to noninvasive imaging tests have been based exclusively on the ST-segment response to exercise, thereby excluding vital prognostic information gained from exercise testing.

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- The traditional formula for peak HR (target HR = 220 minus age) is based on convention rather than scientifically derived. Therefore, this HR should not be an indication to terminate an exercise test if the patient has no abnormal signs of symptoms.
- Exercise-induced ischemic ST depression does not localize the area of myocardial ischemia or the diseased coronary artery. If this information is desired, a cardiac stress imaging test should be performed.
- Transient exercise-induced ST-segment elevation during EECG in leads without a pathologic Q wave is usually related to severe spasm of a "normal" or atherosclerotic coronary artery. It reflects transmural myocardial ischemia and localizes the area of ischemia and involved artery.
- In low-intermediate-risk women and men evaluated for chest pain, EECG is usually considered the first cardiac test for symptom evaluation. The sensitivity and specificity for detection of CAD are comparable in men and women ≥10 years post-menopause.
- The most important predictors of prognosis from EECG are non-ECG variables such as functional capacity (METs) and heart rate recovery.
- It may be reasonable to consider EECG in selected asymptomatic individuals with a high coronary risk profile and a family history of premature CAD or in sedentary middle-aged or elderly persons prior to engaging in an exercise program.

## 1 Introduction

After its introduction almost a century ago, formal exercise testing has evolved into one of the most widely employed noninvasive methods for assessment of the clinical and physiologic status of the heart and circulatory system. This evolution has been documented by a number of excellent reviews during the past several decades [1–4]. The extensive and vital information obtained during standard exercise electrocardiography (EECG) includes symptoms, functional capacity (FC) and the responses of heart rate (HR), blood pressure (BP), and electrocardiogram (ECG), as well as unique non-ECG features (functional capacity [FC], heart rate recovery [HRR]) of significance for diagnosis, prognosis, and management of cardiovascular disease (CVD).

Master and Oppenheimer introduced clinical exercise testing in 1929 to assess "circulatory efficiency" [5]; an ECG was not included in the procedure, and the treadmill was not yet applied. In 1942, Master and colleagues published their first paper on EECG [6]. These seminal studies presaged what were to become major contemporary goals of exercise testing: (1) exercise-induced ECG evidence of myocardial ischemia and thereby coronary artery disease (CAD) and (2) recognition of the clinical importance of functional capacity (FC) and other non-ECG exercise variables. The twentieth century epidemic of ischemic heart disease aroused concern for

early detection of CAD, which EECG offered by noninvasive provocation of ischemic ECG alterations. Subsequently, the non-ECG information afforded by EECG has assumed increasing attention for its unique diagnostic and prognostic utility [2, 4, 7–10]. Exercise tests with imaging are now the most frequently performed of all noninvasive cardiac stress modalities in patients younger than 65 years, but EECG has maintained a steady rate as reflected by a recent report of over 2 million referrals for all noninvasive cardiac stress tests during a 4-year period [11]. Single-photon emission computed tomography (SPECT) was the most frequent test and EECG was second. Recent publications have suggested that EECG is underused in patients with a high exercise capacity, in many of whom it can obviate the need for costlier stress imaging tests, some of which use ionizing radiation [7–10].

The goal of this chapter is to consolidate current knowledge and extend it with a focus on further advances in exercise electrocardiographic testing (EECG).

## 2 Exercise Physiology and the Cardiac Response

EECG is based on increased intensity of dynamic exercise which requires an increased supply of oxygen and substrate to the working muscles, i.e., the lower extremity muscle groups during treadmill or other methods of dynamic lower extremity exertion, e.g., cycle ergometry. Increased work is accomplished by a rise in HR and cardiac output, and regional dilation of resistance vessels augments oxygen supply and its extraction from perfusing blood. The increase in cardiac function is reflected by elevation of major determinants of myocardial oxygen consumption (HR, BP, myocardial contractility) [12] (Table 1). HR and systolic BP are readily measured during EECG, and their double product (HR X systolic BP) closely correlates with relative myocardial oxygen demand [12] (Table 2). Thus, increase in the exercise double product yields an approximation of the relative increase in myocardial oxygen consumption and thereby of coronary blood flow. In individuals with normally patent coronary arteries, coronary blood flow can increase fivefold or more to support augmentation of total body and cardiac work. The former can be directly measured as total body oxygen consumption ($VO_2$) as performed during cardiopulmonary exercise testing [16]. The latter is not usually measured during standard EECG, but nomograms have been developed to estimate $VO_2$ in terms of METs (Table 2) based on the external work performed during a standard exercise test [13]. Figure 1 is a nomogram of the relationship between exercise capacity and

**Table 1** Determinants of myocardial oxygen demand

| Major | Minor |
|---|---|
| Heart rate | External work (load x shortening) |
| Left ventricular systolic pressure (afterload) | Activation energy |
| Left ventricular volume (preload) | Basal energy |
| Myocardial contractility | |

**Table 2** Terms used to describe performance and interpretation of exercise test and performance

| | |
|---|---|
| These equations (and nomograms, Fig. 1) provide standards for comparing individuals' exercise performance with reference data for age and sex | |
| Maximum age-predicted heart rate | Men: 208 – (0.70 × Age)<br>Women:<br>206 – (0.88 × Age) |
| METs: Exercise capacity is frequently expressed in terms of METs which provide an estimate of total body work in terms of total oxygen consumption ($VO_2$). One MET = basal oxygen consumption (3.5 cc/kg/min); five METs reflect a light workload; ten METs indicate high exercise capacity | |
| Average peak METs based on age and sex | Predicted METs = 16.2 – 0.11 (age) |
| Predicted METs for age and sex | Men: 18.0 – (0.15 × Age)<br>Women:<br>14.7 – (0.13 × Age) |
| *Term* | *Definition* |
| True positive (TP) | Abnormal result associated with disease |
| False positive (FP) | Abnormal result associated with no disease |
| True negative (TN) | Normal result associated with no disease |
| False negative (FN) | Normal result associated with disease |
| Sensitivity | Percent of TP/number of subjects with disease × 100 |
| Specificity | Percent of TN/number of subjects without disease × 100 |
| Positive predictive value (PPV) | TP/TP + FP × 100 |
| Negative predictive value (NPV) | TN/TN + FN × 100 |
| Total predictive accuracy of a test | TP + TN divided by total number of tests |
| Double product (DP) | HR x systolic blood pressure |
| This parameter is closely related to myocardial oxygen demand and coronary blood flow, and symptoms of myocardial ischemia (e.g., angina) are precipitated at the same DP in a given individual under the same ambient conditions | |
| Duke treadmill score (Bruce protocol): Min of exercise *minus* 5 × mm ST-segment depression *minus* 4 × degree of chest pain (0 = no chest pain, 1 = mild, 2 = strong enough to stop exercise) | |

Based on data from Refs. [1, 4, 14, 15]

age in sedentary and physically active males. Similar nomograms have been published for women [17].

In the presence of obstructive CAD, coronary blood flow reserve is limited, which may preclude an adequate increase in regional myocardial perfusion at augmented

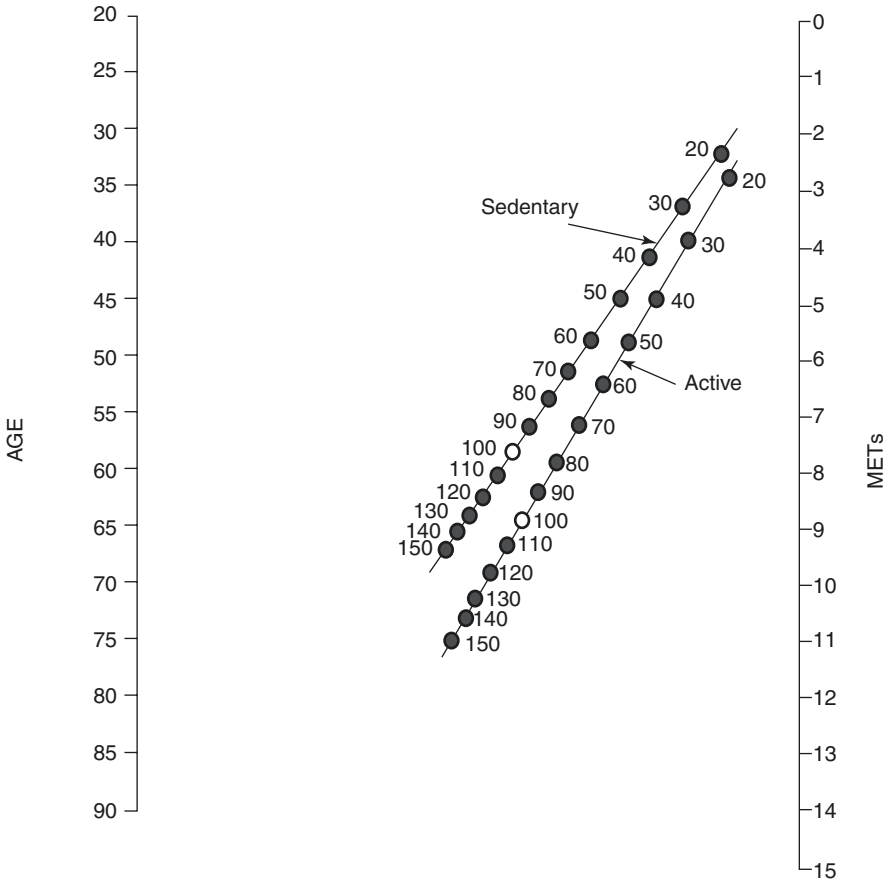


**Fig. 1** Nomogram of percent predicted functional capacity (METs) for age in sedentary and active men referred for exercise testing. (Reprinted from Morris et al. [13]. With permission from Elsevier)

cardiac work, thereby resulting in a disparity between myocardial oxygen demand and supply, which can produce myocardial ischemia. This disparity generally occurs when coronary lumen diameter is reduced by ≥70%; the more severe the coronary stenosis, the greater the limitation of coronary flow reserve [18] (Fig. 2). These relationships are the basis for unmasking of myocardial ischemia, detected by characteristic ECG alterations, in the controlled setting of the exercise testing laboratory. Ischemia and myocardial dysfunction may be detected by characteristic symptoms, specific ECG alterations, and abnormalities of non-ECG variables.

A frequently used testing method is the Bruce protocol (Fig. 3), in which the increased exercise intensity of successive stages may be excessive for patients with limited capacity. In these instances, a protocol with less intensive stress, such as the modified Bruce test, is commonly used (Fig. 3). Age-predicted maximum HR

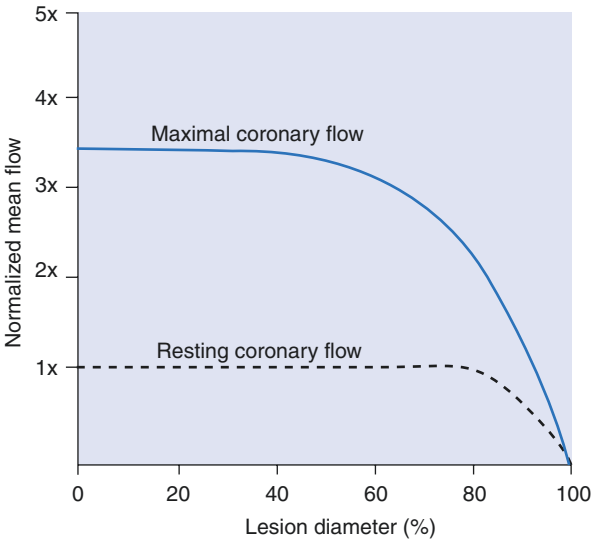


**Fig. 2** These curves from an experimental study depict the response of coronary blood flow reserve (upper curve) and resting coronary blood flow to graded coronary artery narrowing. Resting flow does not decline until coronary lumen diameter is reduced by approximately 80%, whereas coronary flow reserve starts to decrease with approximately 50% narrowing of coronary lumen diameter. (Reprinted from Gould [18]. With permission from Elsevier)

is the rationale for selecting target HR which presumably provides an adequate level of intensity to determine if ischemia can be induced. Age-predicted maximum HR is generally estimated by the following equation: 220 - age = maximum HR. It has been widely accepted that an HR at least 85% of age-predicted maximum is required to consider a stress test adequate for detection of ECG evidence of myocardial ischemia. If this exercise intensity is reached, the EECG can be interpreted as sufficient for unmasking ischemic ECG abnormalities (positive test) or documenting absence of ischemic ECG alterations (negative test). If the ECG remains normal but peak HR during the test is <85% of age-predicted maximum, the test is considered nondiagnostic because of failure to reach "target" HR.

This approach to age-predicted maximum HR is based on convention rather than scientific study and persists in the current era. It is reasonable for estimating average age-predicted maximum HR in populations, but the spread around the mean is wide (10–25 beats/min), yielding either an excessive or inadequate target HR for many individuals. More rigorous methods based on large studies report more accurate relationships for age-predicted maximum HR and total work during exercise testing [4, 14, 15, 19–21] (Table 2). However, in a small study performed in our laboratory ($n$ = 164), the positive predictive value of EECG increased at HRs between 65 and 80% and plateaued above 80% [22]. This concept requires further study. In addition, instead of reporting EECG as dichotomously positive or negative, it is more useful to interpret an abnormal exercise test in terms of the risk conveyed or degree of abnormality based on the composite of data from the test, including ECG findings and other information such as functional capacity [1–4]. Terms commonly used in describing the results of exercise testing and performance are described in Table 2.

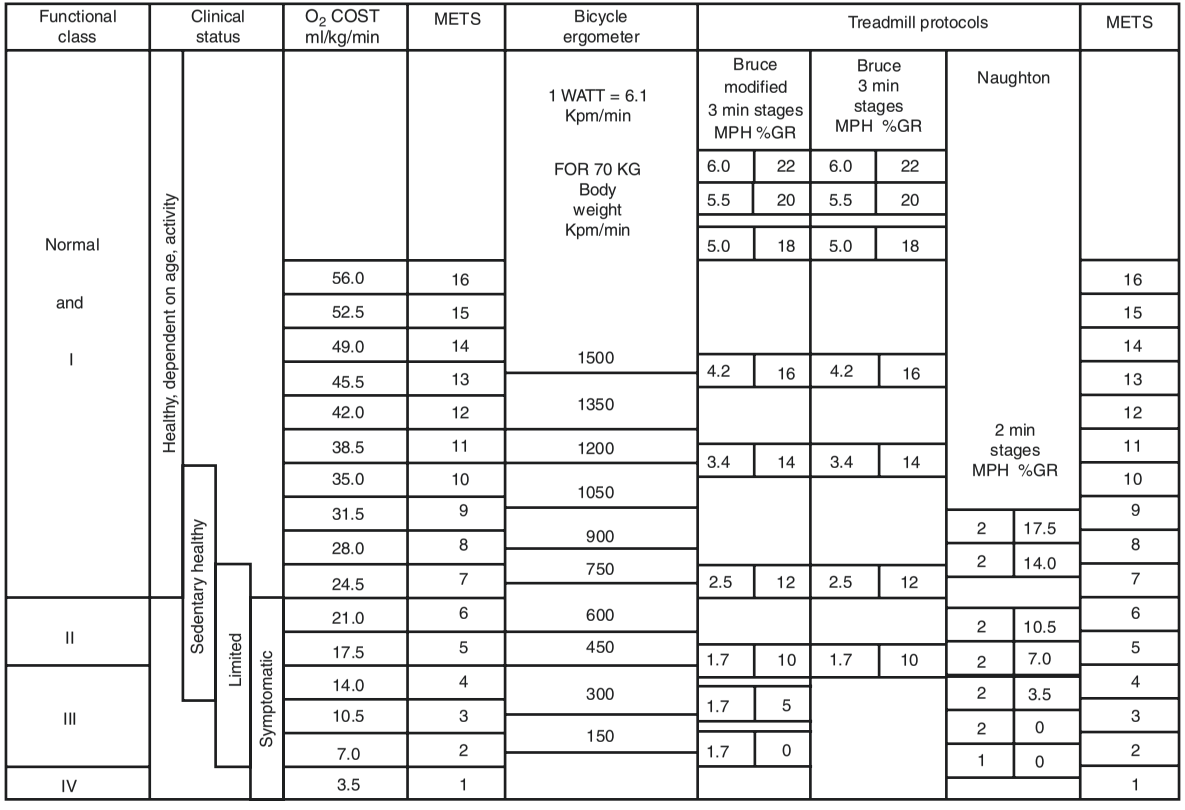


**Fig. 3** Protocols of several types of exercise tests. The relationship of exercise workload (total body $O_2$ cost) and metabolic equivalents (METs) to stages of the tests is shown. Functional class refers to New York Heart Association. (Reprinted from Fletcher et al. [1]. With permission from Wolters Kluwer Health, Inc.)

Several of the relationships in Table 2 warrant brief commentary: (1) The most frequently used terms to describe the diagnostic utility of EECG are sensitivity and specificity. (2) It is helpful to understand sensitivity and specificity as follows: the calculation of sensitivity includes only abnormal descriptors: proportion of positive tests in individuals with the disease in question. The calculation of specificity involves only normal descriptors: proportion of negative tests in individuals without disease. (3) However, to the clinician observing a negative or positive result of an EECG, the negative predictive value (NPV) and positive predictive value (PPV) are of more immediate interest than sensitivity or specificity because they reflect the probability that a given positive or negative test result is correct. (4) The foregoing terms "disease" and "no disease" pertaining to the coronary arteries are defined by the standards set for a specific study. Thus, physiologically significant CAD is commonly defined as ≥70% narrowing of coronary artery lumen diameter determined on coronary angiography. Less than 70% coronary narrowing is broadly considered not to be severe enough to cause ischemia at increased myocardial oxygen demand. The 70% coronary narrowing threshold that defines a significant coronary lesion is an over-simplification which has served reasonably well for clinical purposes. However, it omits important factors that contribute to the physiological significance of a coronary lesion such as its length, lesions in series, vasomotion, response to mediators, and the presence of collateral vessels. The term "specific" is frequently and incorrectly used in cases in which PPV is appropriate. For example, an EECG demonstrating >2.0 mm of ST depression should be described as having a high PPV for ischemia rather than being specific for ischemia.

## 3 Indications for Exercise Testing

There are numerous indications for EECG, of which the detection of exercise-induced myocardial ischemia, and thereby likelihood of CAD, is the most frequent [1–4, 11]. Symptoms of CVD are wide-ranging and varied, and for many of these, there is a role for EECG in ascertaining clinical impairment and evidence of the underlying condition. Relatively common indications for EECG, in addition to chest pain, include dyspnea, palpitations, fatigue, and syncope. EECG also has an important role in prognosis and management of established CVD. This noninvasive method can unmask symptoms of CVD and their thresholds, estimate extent of disability from estimated functional capacity, provide prognostic data, assess efficacy of medical and interventional therapy, and indicate the basis for an exercise prescription. In patients with established CAD, valvular disease, cardiomyopathy, or congenital heart disease, EECG offers quantitative data to help monitor disease course and the timing of interventional therapy based on both its ECG and non-ECG data.

However, the application of EECG in healthy, asymptomatic individuals has been a continuing concern because of the high rate of false positive tests in this population [1–4, 23]. Therefore, there should be specific indications for EECG in

asymptomatic persons, such as a high coronary risk profile and an early family history of CVD, or for sedentary middle-aged/elderly individuals prior to initiating an exercise program.

## 4 Administration of Exercise Electrocardiography

Serious complications of exercise treadmill testing are rare: the rate of serious complications is reported as ≤5 per 10,000 tests, and mortality is less than one-tenth the rate of these nonfatal complications [4]. Individuals undergoing EECG should be clinically stable, and a brief history and examination should confirm their capacity for engaging in the demands of the test. EECG is supervised by a physician (or other trained clinician, e.g., physician assistant, nurse practitioner). The ECG extremity leads should be placed on the subject's torso: lower extremity leads on the lower abdomen above the inguinal ligament and upper extremity leads on the infraclavicular areas slightly medial to the shoulders. In addition, EECG requires (1) a normal baseline ECG with isoelectric ST segments, especially if ischemia detection is the indication and (2) the subject's ability to perform an adequate level of exercise, which should be confirmed by a brief history and cardiopulmonary examination. The exercise laboratory should include an ECG workstation on which data can be continuously observed and recorded at the following points: standing rest, each test stage, occurrence of symptoms, or ECG abnormalities, and during the post-exercise period until data have returned to baseline. Communication with the subject during the test is essential in order to be cognizant of the subject's symptoms or need to discontinue the test. BP should be measured at rest and at least once during each stage of the test which should be initiated at a low intensity, "warm-up" level for a brief period (15–20 seconds) to ensure balance and steady gait.

Most EECG protocols comprise 2- or 3-min stages of progressive treadmill speed and grade (Fig. 3). The subject should be checked by brief communication at each stage and notified before the stress level is advanced to the next stage. During the test, subjects may hold the handrails lightly for balance, if necessary. Gripping the rails increases blood pressure and results in a falsely elevated measure of work capacity (METs) (Table 2). The test usually proceeds to volitional fatigue (maximum effort) unless there is need to discontinue it earlier because of symptoms or objective evidence of marked abnormality.

Endpoints include severe chest pain or dyspnea, dizziness, unsteady gait, major ST segment depression (>2.5 mm), sustained ventricular tachyarrhythmia, non-sustained ventricular tachycardia (≥3 consecutive beats, rate ≥100/min), and decrease in systolic BP of ≥10–15 mmHg or to less than the standing BP at rest. Because of its inaccuracy, there is usually little or no reason to use 85% of age-predicted maximum HR as a test endpoint, except in situations such as the early months following myocardial infarction. Subjects should be discharged following the test after HR, BP, and ECG have returned to baseline. Post-exercise BP may be

lower after, than before, the test; this is a normal response if the decrease is modest and the patient is stable.

## 5 Detection of Exercise-Induced Myocardial Ischemia

Among the multiple reasons for performing EECG, chest pain is the most frequent, typically to aid in the detection or exclusion of CAD by provocation of exercise-induced symptoms and/or signs of ischemia. A variety of exercise protocols are shown in Fig. 1 that are appropriate for differing patients' indications and estimated functional capacity. The initial stress test for evaluation of chest pain in low-risk patients has been EECG without imaging [24, 25] if the baseline ECG is normal, evaluation suggests that the subject can exercise adequately, and estimation of the site and size of an ischemic cardiac defect is not the goal. If the latter data are necessary, a stress imaging study is indicated.

Exercise-induced ST-segment depression in an ECG that is normal at rest has been the hallmark of ECG evidence of myocardial ischemia and thereby of significant CAD. The diagnostic implications of this finding are the same whether ST depression occurs during exercise or only in the post-exercise recovery phase [26]. Figure 4 displays examples of normal and ischemic ST-segment responses to exercise. The latter is defined as ≥0.1 mV ST-segment horizontal or downsloping depression (1.0 mm = 1.0 mV at normal ECG standardization) for a duration of 60–80 msec starting at the J point (1.0 mm = 1.0 mV at normal ECG standardization). With high HRs at which the ST segment joins the initial ascent of the T wave in <80 msec, ST depression for 60 msec is considered sufficient to indicate ischemia. The PPV of ST depression for obstructive CAD increases with greater degrees of exercise-induced abnormalities of the ST response as well as other EECG variables such as HR, BP, and FC. Figure 4 reveals the most obvious ST-segment abnormality (deep, downsloping depression) compared to examples in the figure with less aberration of the ST segment. Thus, it has the highest PPV for CAD, barring any of the multiple factors that can alter the ST segment in the absence of ischemia such as left ventricular hypertrophy, left bundle branch block, drugs, metabolic derangements, and nonspecific changes.

Ischemia is most frequently detected by the lateral precordial leads ($V_{5,6}$), likely related to their position on the chest in relation to the major mass of the left ventricle. Exercise-induced ST depression that is isolated to the inferior leads is associated with a high rate of false positive results that has been attributed to the effects of atrial repolarization on the ST segments in these leads [27, 28]. By contrast, the effect of atrial repolarization on the ST segments of the lateral leads is minimal. Figure 5 displays representative ECG strips at progressive stages of a patient's EECG. Notable findings in these tracings are the normal baseline ECG, ischemic ST depression prior to onset of chest pain, and marked ST depression at maximum exercise with return toward pre-exercise appearance in the posttest phase. The onset of ischemic ECG alterations prior to symptoms of ischemia is common and

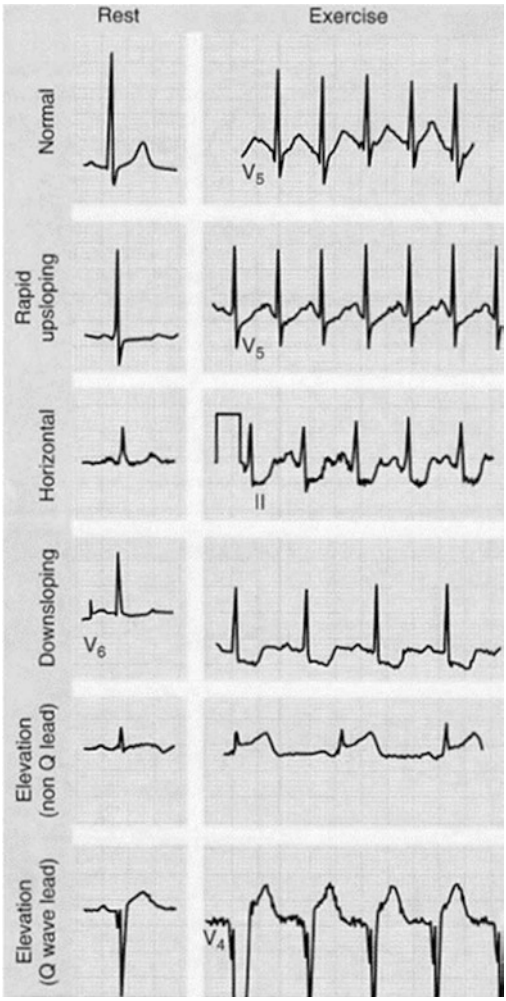


**Fig. 4** Examples of ST-segment responses during exercise testing. The top row shows a normal isoelectric ST segment in a resting electrocardiogram; the successive examples, from upper to lower, display increasingly abnormal ST responses during exercise. "Rapid upsloping" ST depression is a common, normal finding if the ST segment is depressed <1.0 mm at 60–80 msec after the J point. "Minor ST depression" shows a noninterpretable ST segment because of the baseline artifact. Ideally, a stable baseline with three consecutive complexes is standard for optimal test interpretation. In the "slow upsloping" example, the ST segment is minimally upsloping and is positive for ischemia with ~2.0 mm ST essentially horizontal depression. "Horizontal" demonstrates >3.0 mm ST depression that is also positive for ischemia, and "Downsloping" reveals J point depression of >2.0 mm with further depression of the ST segment after the J point. The last two examples demonstrate exercise-induced ST elevation in an ECG lead with and without a pathologic Q wave. The first is positive and consistent with coronary spasm occurring during exercise. The last reflects a left ventricular wall motion abnormality without ischemia. Note that the resting examples all show an isoelectric ST segment, allowing meaningful interpretation of ST deviation during exercise. (Reprinted from Chaitman [2]. With permission from Elsevier)

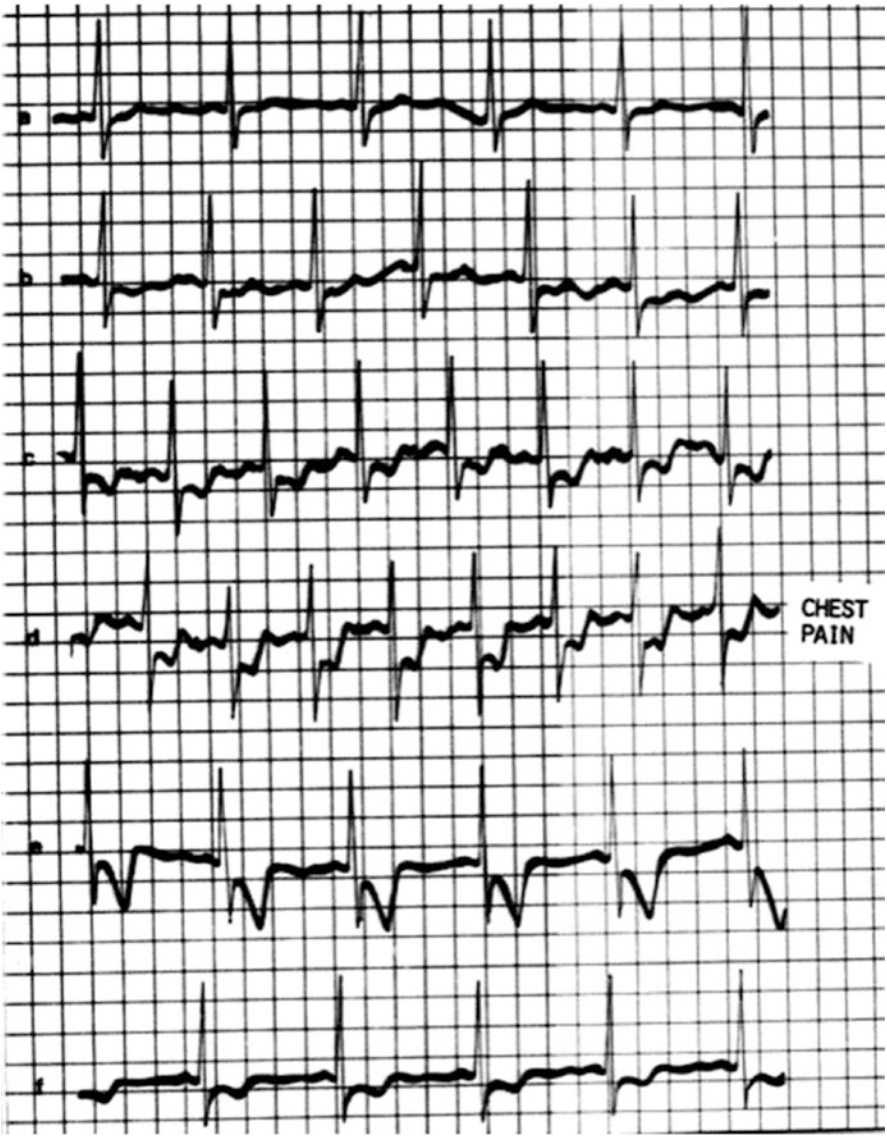


**Fig. 5** The electrocardiographic (ECG) record of a progressive exercise test of a middle-aged man. Top line of ECG strip (lead $V_5$): resting ECG, heart rate (HR) 68/min, isoelectric ST segment. 2nd line: HR has increased to 88/min; ST segment now shows mild depression. 3rd line: HR is 100/min, ST segment shows ischemic depression of 2–3 mm, and the test is positive for ischemia. 4th line: HR 107/min, ST segment depressed 4–5 mm, and chest pain has occurred. 5th line: post-test HR has decreased to 68/min, and there is marked T wave inversion which resolved in 5 minutes. The test shows several key points regarding exercise-induced myocardial ischemia: chest pain occurs later than ECG evidence ischemia, which is initially "silent." The test is markedly positive (4–5 mm ST depression) and accompanied by symptoms, suggesting a high positive predictive value for coronary artery disease or other cause of ischemia. This conclusion is supported by the relatively low HR (100/min) at which the test became positive for ischemia

is an example of "silent myocardial ischemia." It is recognized that in the ischemic cascade, symptoms usually occur after objective evidence of ischemia detected by imaging and ECG findings, suggesting that symptoms are usually less sensitive than ECG or imaging methods for detection of ischemia [29].

The diagnostic accuracy of EECG for detection of CAD based on the standard of coronary angiography in numerous studies has varied widely as reflected by a meta-analysis of 147 reports from over 47,000 patients [30]. The sensitivity of EECG for detection of significant CAD averaged 66% (range, 23–100%), and specificity was 84% (range, 17–100%). These results demonstrated that EECG was associated with relatively high rates of false negatives (about one-third) and lower rates of false positives (about 15%). By contrast, in over 800 patients specifically presenting with angina, all of whom underwent both angiography and EECG, sensitivity for CAD was only 45%, and specificity was maintained at 85%, indicating the effect of decreased referral bias that favors angiography in higher-risk patients [31]. If the ST segments in the baseline ECG are abnormal (depressed or elevated) and the indication for the test is detection of ischemia, it is prudent to choose a stress imaging study because baseline ST-segment deviation precludes reliable interpretation of further exercise-induced alterations. Special criteria for ischemia in ECGs with baseline ST abnormality have been proposed, but their reliability is inadequate for clinical use.

Many factors influence sensitivity and specificity of EECG including pre-test probability of CAD, abnormal baseline ECG, valvular heart disease, left ventricular hypertrophy, cardiac drugs, equivocal ST responses, and "referral bias." The latter refers to preferential angiography in patients with positive exercise tests or a history of a coronary event compared to lesser rates of angiography in low-risk patients. This practice increases sensitivity of EECG for CAD and reduces specificity. Extent of CAD also strongly influences EECG results. In patients with left main and three-vessel CAD, false negative results are unusual in contrast to results in patients with single right or left circumflex CAD, in which a majority of results are false negatives. By contrast, isolated left anterior descending CAD is usually associated with a sensitivity greater than 50%. Of note, many patients with ischemic ST depression on EECG whose functional capacity is $\geq$10 METs have an adequate-excellent prognosis, reflecting the predictive importance of functional capacity, a non-ECG variable of EECG [2, 4, 7–10].

## 6 Exercise-Induced ST-Segment Elevation

This is a potentially ominous finding that reflects transmyocardial ischemia/injury during exercise testing. It is reported to occur in 0.5–5.0% of exercise tests [32, 33], a variability that is likely attributable to factors such as the definition of ST elevation, inclusion of baseline ECGs with pathologic Q waves, and the number of ECG leads employed during testing. Our experience concurs with the rarity of exercise-induced ST elevation. The presence of pathologic Q waves in the resting ECG may be associated with exercise-induced ST elevation in those leads and usually indicates a left ventricular wall motion abnormality or aneurysm rather

than ischemia. In contrast to exercise-induced ST depression, ST elevation during EECG reliably localizes the ischemic area, which usually also affords identification of the involved coronary vessel. Ventricular arrhythmias and infarction also may occur during exercise-induced ST elevation. The pathophysiology of this finding is analogous to that of Prinzmetal angina, i.e., spasm of an angiographically normal or diseased coronary artery. Figure 6a, b depicts the distinctly rare observation of exercise-induced ST elevation with initial onset in the post-exercise phase of the

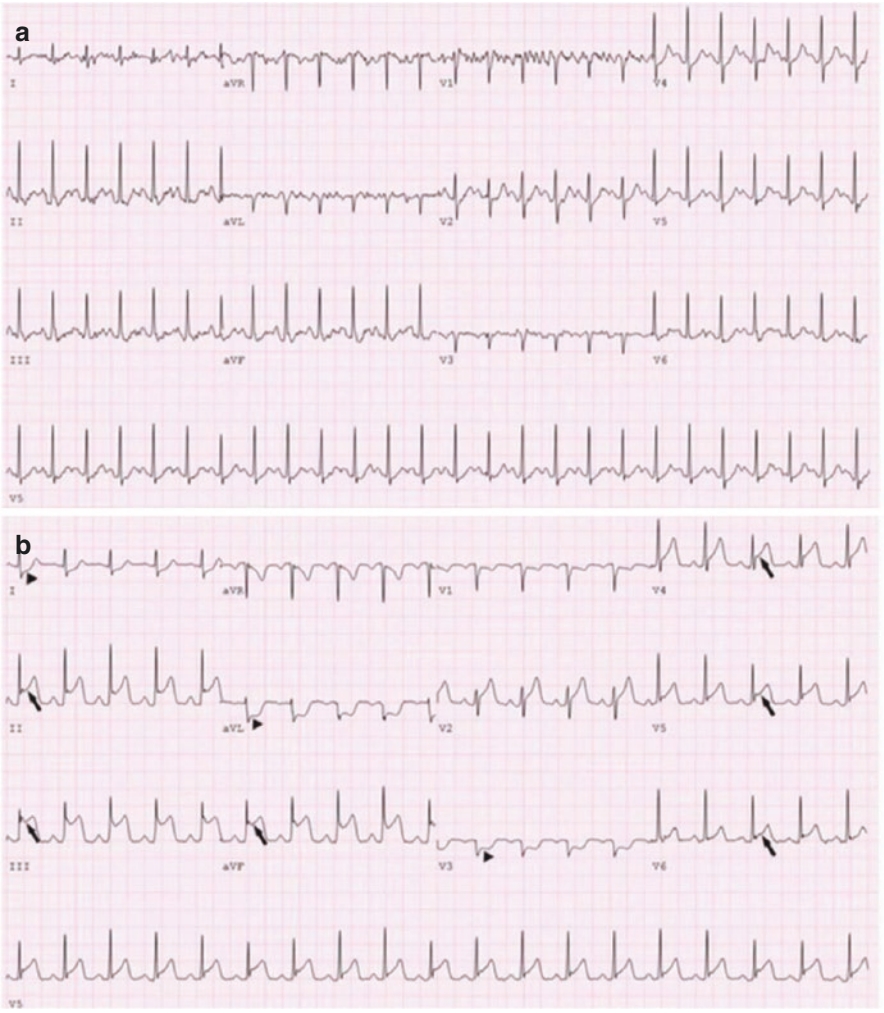


**Fig. 6** (**a**). 12-lead exercise electrocardiogram showing sinus tachycardia (maximum heart rate 153/min) and no exercise-induced abnormalities. (**b**). Post-exercise electrocardiogram (1.5 minutes of recovery) showing 3–4 mm ST elevation in leads 2, 3, and aVF (arrows) and 1–2 mm ST elevation in leads V4, V5, and V6 (arrows). There is also ST depression in I, aVL, and V3 (arrowheads). (Reprinted from Takahashi et al. [34]. With permission from Elsevier)

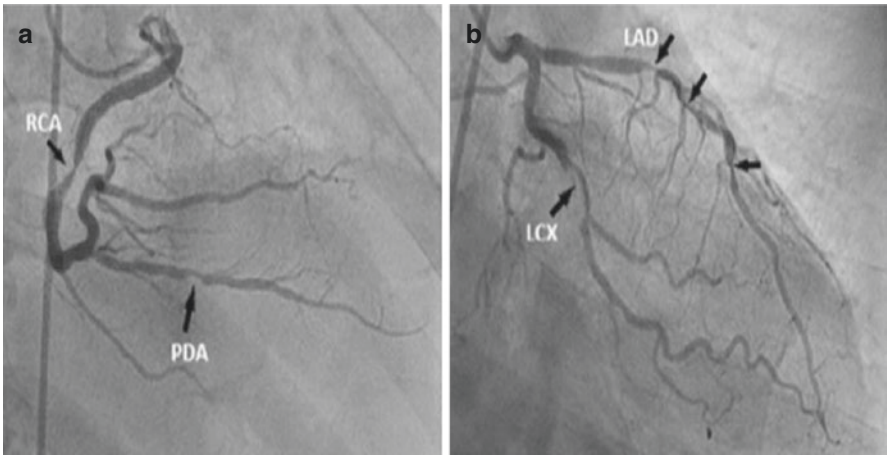


**Fig. 7** Coronary angiogram of the patient with the exercise test data shown in Fig. 6a, b. There are multiple coronary artery stenoses (arrows) in the left anterior descending coronary artery (LAD), left circumflex artery (LCX), and right coronary artery (RCA). (Reprinted from Takahashi et al. [34]. With permission from Elsevier)

EECG, which in this patient was associated with severe multi-vessel CAD [34] (Fig. 7). We do not usually perform provocative testing for coronary spasm in these patients because their management is apparent from angiography and testing with a coronary vasoconstrictor conveys unnecessary risk.

## 7 Pretest Probability of Disease and Bayes' Theorem

Pretest probability of disease has a powerful influence on posttest probability of disease [35], as reflected in Fig. 8. The impact of pretest probability is evident from the magnitude of increase or decrease in posttest probability based on a positive or negative test, respectively. There is minimal alteration of post-EECG probability of disease in association with a negative test and a very low pretest risk of CAD or a positive EECG in a patient with a very high pre-EECG risk of CAD.

The limitations and dilemmas that may result from indiscriminate EECG in asymptomatic, apparently healthy patients have been widely emphasized, as have admonitions concerning the use of EECG as a screening method for CAD in healthy, low-risk populations [9, 23, 35, 37–39]. Bayes' theorem specifies that the accuracy of a test is determined by its sensitivity, specificity, and the pretest probability of disease in the subject tested, or the prevalence of the disease in the population undergoing testing. Bayesian analysis demonstrates the importance of the latter factors on test results, as shown in Fig. 8. Further, if the exercise ECG has a sensitivity of ~60% and a specificity of ~70% for CAD, and the test is applied in a population with very low risk of CAD, the frequency of false positives can actually exceed that

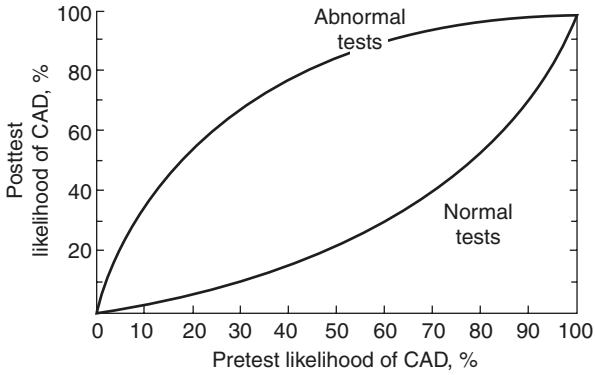


**Fig. 8** Graphic representation of the influence of pretest likelihood of CAD (coronary artery disease) (abscissa) on posttest likelihood of disease (ordinate) and its interaction with normal and abnormal tests. (Reprinted from Epstein [36]. With permission from Elsevier)

of true positives. The value of such testing can be counterproductive by resulting in a cascade of further testing, expense, and potential complications. Therefore, asymptomatic patients referred for EECG should usually have at least an intermediate pretest probability of disease and specific reason(s) for EECG.

There is a rationale for stress testing of selected asymptomatic persons such as those with multiple coronary risk factors and a strong family history of premature CAD or those middle-aged or older people who are beginning an exercise training program. Exercise testing provides a quantitative assessment of functional capacity upon which to base a formal exercise prescription or reveals exercise-induced abnormalities of HR, BP, ECG, and symptoms that can preclude vigorous exercise training, at least initially. In the absence of contraindications to exercise training, the exercise test provides a basis for prescribing training intensity, duration, and frequency at levels that can enhance functional capacity and exert a favorable effect on multiple cardiovascular risk factors.

## 8 Exercise Electrocardiography in Women

Early reports of EECG in women revealed a higher rate of false positive tests for CAD than in men [40]. Based on these findings, it was suggested that stress imaging tests were the most appropriate initial tests in women with chest pain, and this approach is still practiced by many clinicians. These stress imaging studies are costly, and some utilize ionizing radiation. This predicament can be accounted for by several factors. CAD occurs later in women (about 10 years) compared to men, and there was a high rate of premenopausal women in early EECG testing that contributed to the increased false positive rates [41]. With increasing age, the high false positive rate in women declines and is closer to that of men. Thus, as indicated by Bayesian analysis, a high prevalence of normal individuals in the early studies of EECG in women resulted in a high rate of false positive tests, as would occur in any group with an elevated prevalence of individuals without CAD [23]. The 2014 Consensus Statement of the American Heart Association on noninvasive testing of

symptomatic women includes the following recommendations for testing based on risk categories for ischemic heart disease: low-risk patient, no test or evaluation by EECG; low-intermediate or intermediate risk, EECG; and intermediate-high risk, stress imaging study [25]. The Duke treadmill score (DTS) (Table 2), which incorporates treadmill exercise testing, has been generally effective for evaluating diagnosis and prognosis in large cohorts of men and women [42].

Evidence of myocardial ischemia in patients with nonobstructive CAD presents a continuing challenge, and this condition is mainly encountered in women. Although this clinical presentation is not benign [43], a report in 348 women with nonobstructive CAD did not reveal an adverse effect of ischemia on all-cause mortality during a follow-up of 8.5 years [44]. Survival was greater than 95% in patients with and without evidence of ischemia. By contrast, survival was lowest (<85%) in patients with a prior myocardial infarction ($p = 0.05$). This report, therefore, of a limited patient cohort, did not confirm reduced survival on long-term follow-up in women with nonobstructive CAD and evidence of myocardial ischemia in contrast to the adverse effect of prior myocardial infarction. Additionally, we followed a group of 200 low-risk women who presented to the emergency department (ED) with chest pain and were found not to have acute coronary syndrome (ACS) or other serious condition. During a 5-year follow-up (100% of patients), none of these patients experienced ACS [45].

## 9 Exercise Electrocardiography in Chest Pain Units

EECG has played a major role in the evaluation of low-risk patients presenting to the emergency department (ED) with chest pain, who number more than six million annually in this country [45–51]. Extensive experience has established that an accelerated diagnostic protocol that confirms low risk by documentation of clinical stability, negative resting ECG, and normal cardiac injury markers, including cardiac troponin (sensitive or high sensitivity), provides a firm basis for safe, accurate, early, cost-effective patient discharge [45–51]. Experience with this approach in multiple centers in this country even before the advent of high-sensitivity cardiac troponin revealed no adverse effects of early EECG in more than 2400 patients [50]. We have utilized a symptom-limited, maximal EECG in this setting. Length of stay with this approach has been less than that reported for computed tomography coronary angiography in low-risk chest pain patients presenting to the ED [48]. An NPV of >99% for a cardiac event during 30-day follow-up of low-risk patients presenting to the ED with chest pain is based on numerous studies that have incorporated high-sensitivity cardiac troponin into the protocol, even without EECG [52]. Of considerable interest, we have observed negative EECGs in addition to absence of exercise-induced chest pain on maximal EECG in a large majority of low-risk patients who presented to the ED with the chief complaint of chest pain. All patients underwent EECG on no antianginal agents within an average of 10 hours from presentation.

The evaluation of low-risk patients presenting with chest pain continues to evolve, and the recent availability of high-sensitivity cardiac troponin in the USA,

which affords a more rapid, direct, and accurate means of excluding acute coronary syndrome, has reduced the necessity of advanced cardiac testing (including EECG) in many low-risk chest pain patients presenting to the ED [52].

## 10 Non-exercise Electrocardiographic Test Variables

The prognostic value of non-ECG exercise data has been recognized for decades [1–4, 53–60], but the interest of clinicians in these findings has not been comparable to that of their concern for exercise-induced ischemia. Non-ECG exercise test variables alone are potent predictors of cardiovascular and other diseases, and they can also be integrated with ECG findings of exercise testing, symptoms, and traditional risk factors to develop scores for refining prognosis, this regard, it is also essential to consider an individual's exercise capacity in the context of vital factors such as age and sex, as demonstrated by nomograms [13, 17] (Fig. 1).

### *10.1 Heart Rate*

This simple exercise factor correlates with prognosis as reflected by an investigation of 58,000 men and women aged 18–96 years [53]. Among multiple clinical and exercise factors assessed, after excluding age and sex, percent of maximum predicted HR achieved was second only to exercise capacity for predicting survival during a decade of follow-up. It was also shown, in a 7.7-year follow-up of almost 1600 men free of coronary heart disease, that chronotropic incompetence, defined as failure to achieve 85% of age-predicted maximum heart rate, was one of several rate-related factors associated with future all-cause mortality, including coronary heart disease and incident coronary heart disease [55]. An important limitation of the predictive capacity of maximum HR is that it is typically dependent on measures such as functional capacity.

### *10.2 Blood Pressure*

The typical response of this variable during EECG is a continuous rise to maximum systolic pressure, which occurs at peak exercise and may exceed 200 mmHg in healthy men with high functional capacity [56]. Diastolic BP remains unchanged or shows a small rise or fall at peak exercise. Peak systolic pressure is typically higher in men than in women. Exercise-induced hypotension, variably defined as a decline of ≥10–15 mmHg or a fall to less than standing BP [61], can indicate serious cardiac disease, onset of complications during the test, or measurement error. In a summary of 11 reports of 6693 exercise tests, the frequency of hypotension (defined

as ≥20 mmHg decrease) was 8.0% [61]. Importantly, almost 50% of patients with exercise-induced hypotension in this study had either left main or three-vessel CAD. However, it is emphasized that the PPV for these outcomes is also highly dependent on the pretest probability of severe disease.

In patients with cardiac valvular disease, functional capacity is a critical factor in determining the timing of valve replacement, and acquisition of this information by history alone may be challenging in some patients. Although previously prescribed in patients with severe aortic stenosis, judicious exercise testing is now recommended in selected patients with this disease to obtain objective evidence of functional capacity and BP response during a progressive exercise test [4]. This approach can document impaired functional capacity and/or inadequate BP response, both of which may be useful in determining the timing of valve replacement. Information of similar value is afforded by EECG in patients with hypertrophic cardiomyopathy [4].

## *10.3 Double Product*

Defined earlier in this chapter as the product of HR and systolic BP, this factor is closely related, in relative terms, to myocardial oxygen demand and thereby to relative changes in coronary blood flow [12]. Unless ambient conditions vary, myocardial ischemia usually occurs at the same double product in a given patient with coronary disease [12, 18]. Froelicher defined an adequate double product as >25,000 [58]. In our middle-aged and elderly patients, this value is rarely achieved, which may be related to age, sex, cardiovascular disease, or impaired physical fitness. More commonly, a double product of >20,000 is considered good-excellent and is attained in a relatively small proportion of cardiac patients. Although the double product affords insight into the balance between myocardial oxygen supply and demand, there are no universally accepted standards or normative values for this informative exercise-derived parameter.

## *10.4 Functional Capacity*

This factor is considered by many as the single most reliable indicator of prognosis obtained from exercise testing in women and men with or without cardiovascular disease, as documented in multiple large, long-term investigations [53–55, 57, 58]. The importance of functional capacity is reflected by the generally favorable prognosis of patients with CAD who have good-excellent functional capacity (>10 METs) and appropriate management of coronary risk factors, as we and others have reported [2, 7, 8, 10]. All-cause mortality and specific cause mortality were independently related to maximal treadmill exercise capacity in an investigation of

over 10,000 men and more than 3000 women during a follow-up of >8 years [53]. Age-adjusted all-cause mortality rates decreased across levels of functional capacity from least-fit to most-fit men (64 to 19 per 10,000 person-years) and declined similarly in women from 40 to 9 per 10,000 person-years. Not inconsequentially, mortality rates for cardiovascular disease and cancer were also lower in those with higher fitness levels. In a study of over 5800 men followed for more than 6 years, nomogram, developed from readily accessible pretest and exercise test variables, demonstrated the following advantages: it was significantly associated with mortality ($p < 0.001$), was able to correctly reclassify multiple patients with intermediate-high-risk Duke treadmill scores to low risk, and accurately predicted 3-year mortality [60]. In a subsequent investigation, a nomogram, developed to predict age-related exercise capacity in women [13], revealed that in both asymptomatic ($n = 5721$, follow-up 8.4 years) and symptomatic women (4471, follow-up 5.3 years), all-cause and cardiac mortalities were twice as high ($p < 0.001$) among those whose exercise capacity was <85% of age-predicted value compared to those whose exercise capacity was ≥85% of age-predicted level. A different perspective than that provided by the foregoing salutary results related to the value of excellent functional capacity has also been reported, indicating that the rate of high-risk CAD was 25% in men with intermediate-high coronary risk profiles and abnormal exercise ECG, despite high functional capacity [62]. However, no follow-up was reported in this retrospective investigation.

## *10.5 Prognostic Scores*

This approach utilizes multivariable analysis by integrating individual data elements that contribute to a numerical score that predicts occurrence of disease or clinical outcomes in symptomatic and asymptomatic individuals. One of the earliest of these methods is the Duke treadmill score (DTS) [63], which utilizes data obtained during exercise testing according to the Bruce protocol (Table 2). Application of the DTS demonstrated that 5-year survival was 72% for patients with a score of less than *minus* 11 (13% of patients) compared to 97% survival in patients with a score of greater than *plus* 5 (34% of patients). The value of this score is its ease of use and its contribution of prognostic information beyond that of standard clinical, anatomic, and ventricular function data. However, the DTS has several limitations: it does not include age, sex, or risk factors; it was developed in relatively young patients (males ≤55 years, females ≤62 years); and it was applied prior to current advances in CVD management. In this regard, we have found favorable survival in many contemporary patients despite a relatively high-risk DTS [7, 10]. Additionally, the DTS has been inconsistent regarding its prognostic utility in elderly patients (age ≥ 75 years), with both support [64] and rejection [65] in subsequent studies. However, in another study, the DTS had similar predictive utility in elderly men as in younger men [66]; but in elderly women, its predictive accuracy was surpassed by both METs and heart rate recovery [67].

### *10.6 Heart Rate Recovery*

Heart rate recovery (HRR) is a potent and independent predictor of risk and is based on the deceleration of cardiac rate following maximum EECG. Post-exercise decline in heart rate reflects vagal prominence associated with cessation of exercise [68]. However, multiple definitions of this parameter have impeded comparison of results from individual studies because methodology differs in the time and other factors related to measurement of post-exercise HRR. These include timing of the measurements (1 or 2 minutes post-exercise), activity state during data acquisition (cool down post-exercise or abrupt cessation), and position (upright or supine). However, the predictive power, consistency, and independence of HRR are consistent and impressive.

Most frequently, impaired HRR is considered a decline of <12 beats/min in the first minute after symptom-limited exercise; <22 beats/min in 2 minutes post-exercise has also been proposed. Impaired HRR is associated with increased risk of cardiac events and decreased survival. In an early study of over 2400 symptomatic persons aged 57 ± 12 years (63% men) followed for 6 years, median 1-minute HRR for the total cohort was 17 beats/min after symptom-limited EECG. In the 26% of patients whose HRR was <12 beats/min, there was a fourfold increase in relative risk of mortality ($p < 0.001$) [69]. Following adjustment for multiple clinical and exercise factors (age, sex, cardiac risk profile, medications, exercise workload, results of myocardial stress scintigraphy), the predictive significance of impaired HRR for mortality persisted (relative risk twofold, $p < 0.001$).

### *10.7 Combined Predictive Factors*

It was subsequently shown that prediction of outcome by Framingham risk scores (FRS) could be enhanced by combination with either functional capacity, HRR, or both of these measures. After adjustment for FRS in over 6100 asymptomatic individuals aged 45 years (46% women) with low functional capacity and low HRR, each of these methods was a significant predictor of 10-year cardiovascular mortality [70]. However, as depicted in Fig. 9, risk was higher when FRS was combined with either the low value for HRR or low functional capacity and highest if FRS was considered together with both of the low functional values.

## 11 Conclusions

EECG remains one of the most frequently utilized, informative, and safest non-cardiac tests. It provides essential information for diagnosis, prognosis, and management of cardiac disease by unique insight into all three of these areas. EECG

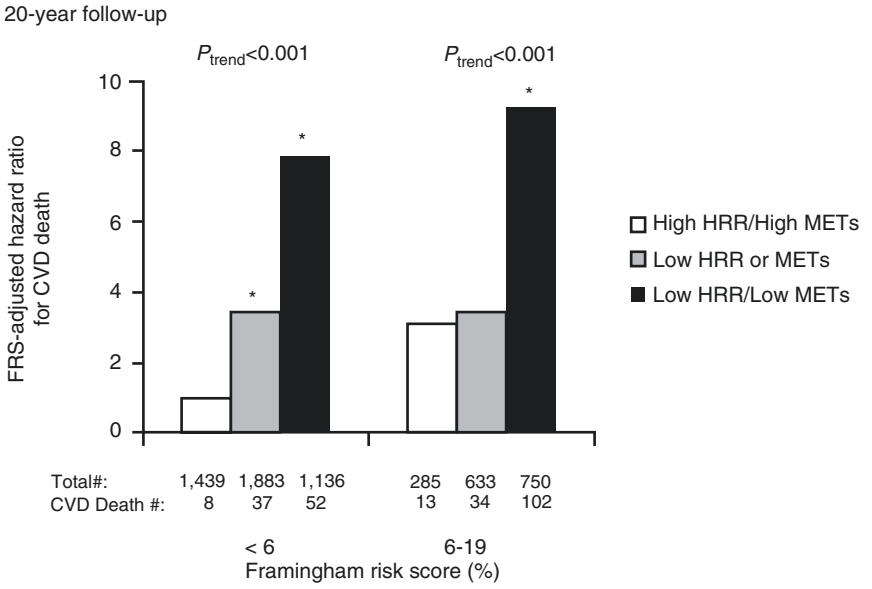


**Fig. 9** Enhancement of risk assessment by combining prediction methods. The graph demonstrates Framingham risk score (FRS)-adjusted hazard ratios for cardiovascular death (CVD) at 20 years by adding risk prediction with only one or with both low functional capacity (FC) and heart rate recovery (HRR) measures. Prediction of CVD mortality based on FRS (score of 6 on left, 6–10 on right) was greater when combined with low HRR or low FC and highest when prediction by both was added to FRS. Asterisks indicate significant ($p < 0.001$) increase in CVD. (Reprinted from Mora et al. [70]. With permission from Wolters Kluwer Health, Inc.)

utilizes safe induction of myocardial ischemia to help determine the presence or absence of obstructive CAD. Based on its ECG and non-ECG data, it has furthered understanding of normal and abnormal cardiovascular responses to physical stress and unmasked symptoms and provided objective evidence of myocardial ischemia and the presence of impaired function related to a variety of CVD. The value of the non-ECG variables of EECG, such as functional capacity and heart rate recovery, affords exclusive insights into prognosis. The diagnostic utility of EECG for CAD is comparable in men and women 10 years after menopause, but this test continues to be underutilized in these groups in favor of stress imaging tests, which are costly, some of which use ionizing radiation. Limitations of EECG include inability to localize ischemic myocardial regions and requirement of a normal baseline ECG if the goal of the test is estimation of exercise-induced myocardial ischemia. In addition, it is essential to appreciate that posttest probability of CAD is closely tied to pretest probability of CAD, which is the basis for continuing concerns of using EECG as a screening test for CAD in healthy, asymptomatic persons.

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