

# The diagnostic value of exercise stress testing for cardiovascular disease is more than just ST segment changes: A review

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## Abstract

**Purpose:** The objectives of this review were to: (1) identify the acute cardiovascular responses to aerobic exercise used in an exercise stress test (EST), (2) identify when and how to best conduct an EST including the stopping point, (3) identify conditions that would preclude an EST, (4) define the limiting signs and symptoms associated with an EST (5), discuss what data are needed as part of an EST and how to interpret EST data.

**Methods:** We identify the cardiovascular responses to an EST and when an EST should or should not be used. Finally we analyze the components of an EST and potential sensitivities, significances and predictability of the changes in the outcome data that will provide diagnosis overt cardiovascular disease, and for purposes of exercise prescription and evaluation of rehabilitation effects in cardiac patients.

**Results:** Although most of the focus for performing an EST traditionally has been on the diagnostic value to identify ST-segment abnormalities, an EST provides other valuable diagnostic and prognostic data including maximal oxygen consumption (predicted or measured), exercise capacity and fatigability, blood pressure and heart rate responses to exercise and recovery.

**Conclusions:** This review identifies the most recent standards, and guidelines of EST, which include the acute physiological response of the cardiovascular system to aerobic exercise, the use of EST in evaluation of coronary artery disease, an updated diagnostic and prognostic variables of EST, and reporting of EST.

**Condensed abstract:** This review identifies the most recent standards, and guidelines of the exercise stress test (EST), which include the acute physiological response of the cardiovascular system to aerobic exercise, the use of EST in evaluation of coronary artery disease, diagnostic and prognostic variables of EST, and reporting of EST.

## Introduction

An exercise stress test (EST) is commonly used for the diagnosis and evaluation of cardiac disease. In addition, EST is often used to evaluate the effects of pharmacological medication on whole body function, and for exercise prescription in diseases and conditions that include but are limited to cardiac rehabilitation, obesity, diabetes and various neuropathies. EST is typically conducted using a treadmill or a cycle ergometer, while monitoring the electrocardiogram (ECG) [1], ventilatory threshold [2], blood pressure (BP) [3], heart rate (HR) [4], oxygen consumption [5], general patient self-reported effort (e.g., by a Borg Scale test) and physical appearance—including chest pain and dyspnea [6]. The American College of Cardiology (ACC), American Heart Association (AHA), American College of Sports Medicine (ACSM) and the American Society of Nuclear Cardiology all recommend an EST for diagnosing patients who are at risk for obtaining cardiovascular disease (CAD). An EST can be conducted on the majority of patients who can exercise, irrespective of age or sex [7], but some of the guidelines for athletes may need some modifications [8]. This review provides an overview of the most recent standards, and guidelines of EST, which include the acute physiological response of the cardiovascular system to aerobic exercise, the use of EST in evaluation of CAD, updated diagnostic and prognostic variables of EST, and

modern reporting of EST. These guidelines are intended for healthcare professionals who currently use or are considering incorporating EST as part of health care evaluation, and rehabilitative delivery to their patients.

## Review of relevant literature

### Acute cardiovascular response to aerobic exercise used in an exercise stress test

EST incorporates acute aerobic exercise, which induces a requirement for increasing oxygen delivery to meet the challenges of increasing work, and to match this with sufficient perfusion of blood to the working musculature to remove the metabolic byproducts that are generated as a result of substrate utilization to generate ATP [9]. The amount of oxygen delivered to and consumed by the working skeletal muscle increases with the intensity of the exercise. Furthermore,

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ventilation of expired gases increases with elevated workloads to both dispose of the greater levels of carbon dioxide, produced by increased metabolism, and to buffer lactic acid/hydrogen ions produced during the EST. Many cardiorespiratory and hemodynamic mechanisms function collectively to support increased aerobic requirement of exercise. To maximize oxygen delivery, blood flow to the working muscles increases while non-essential tissues experience a concomitant sympathetic vasoconstriction resulting in a reduction of blood flow [10]. This maximizes the distribution of cardiac output to the exercising muscles [11]. The overall effect of changes include modifications of heart rate, stroke volume, cardiac output, blood flow, blood pressure and arteriovenous oxygen difference [12-14].

#### (i) Heart rate (HR)

Increasing workloads in an EST require an increased cardiac output (CO). Heart rate is the most important factor increasing CO during exercise, and it increases in linear fashion with work rate and oxygen uptake [15]. HR increases from an elevated sympathetic nervous system drive and a subsequent decrease in parasympathetic nervous system activity (*i.e.*, decreased "vagal tone"). Furthermore, the elevated HR during exercise occurs primarily at the expense of diastolic rather than systolic blood flow [16]. Although an increase in stroke volume contributes to an increase in CO during strenuous exercise, it is the increase in HR that is largely responsible for the CO increase [16]. In contrast to systolic blood pressure (SBP), which increases with age, maximum HR along with HR and  $\dot{V}O_2$  kinetics decrease with age [17]. The maximum HR is commonly used to prescribe exercise training or to predict exercise testing endpoints. The predicted maximal heart rate can be estimated from one of several available equations, some of which are derived separately for men and women. A commonly used estimation for maximal heart rate is: [maximum predicted HR=220-age in years, +/- 12 bpm] [18]. Achievement of 85% of age-predicted maximal HR leads to an increase in coronary blood flow of 2-4-fold in non-stenosed coronary arteries, however, this endpoint has been challenged and as it could potentially underestimate the exercise capacity of patients [19]. Methods for an accurate evaluation of the level of effort during exercise testing is somewhat limited and, therefore should not be used as a sole criterion to determine when a test should be terminated [20]. A typical increase in HR during exercise is about 10 bpm per metabolic equivalent (MET), where 1 MET=3.5 ml O<sub>2</sub>/Kg/Min at least in persons who are not treated with beta blockers [21]. However, recent data suggests that the maximal heart rate is not a limiting factor for determining cardiovascular capacity in healthy patients [14].

#### (ii) Stroke volume (SV)

Stroke volume is the volume of blood ejected per heartbeat, which is equal to the difference between end-diastolic volume (EDV) and end-systolic volume (ESV) [22]. This is one of the most important components of evaluation of the efficiency of the myocardium [23], but it is difficult to measure directly without invasive approaches during a stress test or during acute exercise although indirect measures of stroke volume by electrical bioimpedance, or CO<sub>2</sub> rebreathing, provide a reasonable estimation of the hemodynamics [23]. The increase in SV from 70-75 ml/beat can increase to ~120 ml/beat in a healthy young adult. In general, SV is expected to increase steadily up to 50% of maximal oxygen uptake ( $\dot{V}O_{2\max}$ ), or aerobic capacity, and then tends to level off. The increase in SV is also dependent upon an elevation of venous return from skeletal muscles to the myocardium (Frank-Starling law) and a subsequent improvement in ventricle muscle contractility

as a result of heightened neurohormonal control (e.g., enhanced sympathetic activity, catecholamine hormones). Chronic exercise training may increase the left ventricular compliance and contribute to larger filling volumes leading to improved stroke volumes [24].

#### (iii) Cardiac output (CO)

Cardiac output provides the general description of cardiac function. It is calculated as the product of stroke volume and heart rate. In healthy adults, CO increases linearly with increased work rate and oxygen uptake. It can increase from basal value about 5 L/min to a maximum of about 20-40 L/min during strenuous exercise [25]. Maximum value of CO is dependent on several factors, including age, posture, level of physical conditioning, and presence of diseases. At 50% of  $\dot{V}O_{2\max}$ , the increase in CO is a direct reflection on maximal SV with a lesser emphasis on maximal HR. Once  $\dot{V}O_{2\max}$  is beyond 50%, the increase in CO due primarily to HR [26]. As a result, aged persons have a lower CO capacity, largely as a result of their lower maximal heart rate.

#### (iv) Blood pressure (BP)

Blood pressure is dependent on CO and peripheral vascular resistance, and as such, BP provides a noninvasive way to monitor the overall clinical "pumping" capacity of heart [20]. There is linear increase in a systolic blood pressure (SBP) with increasing levels of exercise as a result of increasing CO. Normal SBP response to exercise is dependent on both sex and age. The average rise in SBP is about 8-12 mmHg/MET and maximal values of SBP are up to 190-220 mmHg. SBP should not be allowed exceed 250 mmHg [27,28]. Diastolic blood pressure (DBP) may decrease or remain unchanged because of vasodilatation of the vascular bed and decrease of peripheral vascular resistance [29]. At the end of exercise, SBP usually decreases rapidly, largely from the decrease in CO that matches the reduction of the exercise load at the conclusion of the EST. Typically, systolic BP will return to basal levels and may drop below pre-exercise levels for several hours [30]. On the other hand, syncope which can occur suddenly during recovery from a maximal exercise stress test or even acute exercise, (*i.e.*, post-exercise syncope), represents a failure to maintain or regulate blood pressure appropriately, and may arise from reduced muscle pump augmentation of blood return to the right side of the heart along with vasodilation [31]. Manual assessment of both diastolic (DBP) and systolic blood pressure (SBP) during an EST requires a skilled evaluator because it is difficult to accurately identify the Korotkoff sounds as a result of the noise of the treadmill etc. Even measuring resting DBP, can be challenging due to auditory problems, the ability to recognize the fifth Korotkoff sound, or an auscultatory gap. The measurement of BP through automatic equipment, with the right technique, offers many advantages over the manual technique, having verified its utility and clinical validity [16].

#### (v) Blood flow (BF) response

At rest, 15-20% of CO is distributed to skeletal muscles; the remainder goes to the brain, heart, and visceral organs. With exercise, CO and BF increase 4-5 times. BF is directed to active skeletal muscles and respiratory muscles, blood supply to the brain is maintained at resting level, and 85-90% of CO is directed to exercising muscles and to skin in order to help dissipate heat production caused by the increase in metabolism, and it is directed away from the viscera. Increases in coronary blood flow with intensity during exercise (260 ml/min to 900 ml/min at max) is experienced. The redistribution of BF during

exercise is due to sympathetic and hormonal effect on smooth muscles of blood vessels [16,32].

#### (vi) Oxygen difference response

Normally oxygen content in arterial blood is approximately 20 ml/dl and oxygen content in venous blood is about 15 ml/dl [33]. Arteriovenous oxygen difference is about 5 ml/dl at rest, which is a coefficient of 25%. During acute exercise, oxygen extraction increases so that the arteriovenous oxygen difference is ~15 ml/dl with a coefficient of 75% [33,34]. However, while long-term training is associated with an increase in cardiac output, there is a modest or no increase in arteriovenous oxygen difference [33].

#### (vii) Oxygen uptake (Maximal oxygen consumption $\dot{V}O_{2\max}$ )

Maximal oxygen consumption is the maximal amount of oxygen that can be consumed in one minute and is reported in absolute terms as liters per minute or in relative terms as milliliters per kilogram of body weight per minute [35].  $\dot{V}O_{2\max}$  is equal to the product of maximum CO and maximum arteriovenous oxygen difference and it is influenced by age, sex, exercise habits, heredity, obesity levels and cardiovascular clinical status [22,36].  $\dot{V}O_{2\max}$  increases linearly with work intensity up to a point beyond which, an increase in work intensity will not elicit an increase in oxygen uptake. It is good indicator for cardiorespiratory fitness and it is the best single predictor of the amount of aerobic work one can perform. Typical oxygen uptake for a young male at rest is 250 ml/min and under maximal conditions and this can be increased to 3600 ml/min.  $\dot{V}O_{2\max}$  can be estimated from the peak work intensity achieved during an EST [29].

#### (viii) Myocardial oxygen consumption

Primary factors that determine myocardial oxygen consumption include HR, myocardial contractility, and ventricular wall stress (*i.e.*, the product of SBP and ventricular volume). Myocardial oxygen consumption is inversely related to myocardial wall thickness. It can be measured during an EST by the double product rate (also known as rate-pressure product), which is the product of HR and SBP [37]. Myocardial oxygen consumption is directly proportional to coronary artery blood flow. During exercise, coronary blood flow increases as much as 5-fold above the resting value. It should be noted that a patient with CAD will not have insufficient coronary blood flow to the affected myocardial tissue that is required to meet the metabolic demands of the cardiac muscle during exercise. Consequently, exercise induced angina, ST-segment depression and myocardial ischemia occur at the same rate-pressure product rather than at the same external workload in patients with coronary artery diseases (CAD) [37]. This suggests the existence of an ischemic threshold at which myocardial oxygen consumption exceeds myocardial oxygen supply. The rate pressure product can estimate the maximal workload that can be performed by the left ventricle.

### Approach for conducting an exercise stress test

Although a variety of personnel including physicians, exercise physiologists, nurses and rehabilitative technicians can conduct the EST. The American College of Physicians (ACP), American College of Cardiology (ACC), and American Heart Association (AHA) task force statement on clinical competence in EST, recommend that graded EST should be performed only by well-trained qualified professional with an adequate knowledge of exercise physiology and preferably certification (*e.g.*, Registered Clinical Exercise Physiologist) [38]. In addition,

they should have suitable life-saving skills including certification in advanced cardiopulmonary resuscitation, emergency medication, and a defibrillator should be immediately available at the exercise laboratory in the event of an emergency. Even though EST is considered a safe test, there are always risks associated with such evaluations. For example, there are reports of cardiac events and sudden death during an EST [39]. Surveys have shown that 0-6 deaths or cardiac arrests occur per 10,000 tests and 2-10 myocardial infarctions per 10,000 tests might be expected, but these estimates will vary markedly with the prevalence and severity of underlying heart disease in the tested population [40,41]. The evaluator should also be aware of other rare complications that could occur during an EST including arrhythmias, acute coronary syndromes, heart failure, hypotension, syncope, shock and death [29].

### Indication of exercise stress test for diagnosis or prognosis

EST may be used for diagnostic, prognostic, therapeutic, and functional applications especially in regards to exercise prescription [42]. The most common use of EST is the diagnosis and evaluation of suspected CAD. Understanding the purpose of the individual exercise test allows the test supervisor to determine appropriate methodology and to select test end points that maximize test safety and obtain the needed diagnostic and prognostic information. Cardiovascular risk assessment has great importance for exercise prescription with the goal of improving clinical outcomes [43]. Table 1 outlines the primary indications for considering EST as an evaluative tool [43,44].

### Contraindications to exercise stress test

As with any test there are risks and therefore it is no surprise that there are both absolute and relative contraindications to EST. The potential benefits of test results clearly need to be weighted against any potential negative outcomes for the patient with the idea that the EST is to “do no harm” to the patient. Pre-exercise test evaluation and taking medical history help identify potential contraindications and increase the safety of EST. Generally patients with absolute contraindications should not perform the EST until such conditions are stabilized. Patients with relative contraindications may be tested after evaluation of the risk/benefit ratio and it can be superseded if benefits outweigh risk of exercise, but they should be closely supervised and monitored throughout the test procedures. In addition, patients with relative contraindications to EST can be tested using low level end points. Table 2 outlines both absolute and relative contraindications to EST that cover most patients [43,45].

### Obtaining an adequate workload

To provide an accurate assessment of cardiovascular function, the EST should be conducted using parameters that include: 85% of age-predicted maximal HR 46, a pressure-rate product >20,000, where coronary artery blood flow increases up to 2-3 fold in non-stenosed coronary arteries [47], and am ischemia which includes angina and ST-segment changes 48. If a patient cannot achieve an adequate workload

**Table 1.** Primary indicators for ordering an exercise stress test.

Diagnostic	Therapeutic	Evaluation & Function Capacity
Evaluation of suspected CAD	Antianginal therapy	After myocardial infarction
Evaluation of high risk patients	Antiarrhythmic therapy	After coronary bypass
After myocardial infarction	Antihypertensive therapy	After cardiac surgery
After angioplasty	Bronchodilators agents	Exercise prescription
Arrhythmia provocation	Vasodilators agents	Cardiopulmonary
Peripheral vascular disease		Rehabilitation

**Table 2.** Contraindications to exercise stress test.

Absolute Contraindications	Relative Contraindications
Acute myocardial infarction (MI), within 2 days or other acute cardiac event	Known of left main coronary artery stenosis
A recent significant change in the resting ECG suggesting ischemia	Moderate aortic stenosis
Unstable angina	Resting hypertension with systolic or diastolic blood pressures >200/110 mm Hg
Uncontrolled cardiac arrhythmia causing hemodynamic compromise	Tachyarrhythmias or bradydysrhythmias
Acute myocarditis ,acute pericarditis and active endocarditis	Ventricular aneurysm
Symptomatic severe aortic stenosis	Complete heart block
Decompensated heart failure	Hypertrophic obstructive cardiomyopathy with severe resting gradient
Acute pulmonary embolism, pulmonary infarction, or deep vein thrombosis	Recent stroke or transient ischemic attack
Acute aortic dissection	Neuromuscular or rheumatoid diseases that are exacerbated by exercise
Acute systemic infection	Uncorrected medical disease (anemia, diabetes, and hyperthyroidism)
Physical disability	Chronic infectious disease (AIDS, hepatitis)
	Mental and physical impairment with limited ability to cooperate

**Table 3.** Determining the point for terminating the exercise stress test.

Absolute Indications	Relative Indications
ST-segment elevation (>1.0 mm) in leads without preexisting Q waves because of prior MI (other than aVR, aVL, and V1)	ST depression (>2 mm horizontal or downsloping ST-segment depression), in a patient with suspected ischemia
Drop in SBP of >10 mm Hg, despite an increase in workload when accompanied by any other evidence of ischemia	Drop in SBP of >10 mm Hg from baseline despite an increase in workload, in the absence of other evidence of ischemia
Moderately severe angina (defined as 3 on standard angina scale)	Increasing chest pain
Increasing nervous system symptoms (e.g., ataxia, dizziness, near syncope)	Fatigue, shortness of breath, wheezing, leg cramps, or claudication
Signs of poor perfusion (cyanosis or pallor)	Arrhythmias other than sustained VT, including multifocal ectopy, ventricular triplets, supraventricular tachycardia, heart block and bradyarrhythmias
Sustained ventricular tachycardia (VT) or other arrhythmia, including second- or third-degree atrioventricular (AV) block, that interferes with normal maintenance of cardiac output during exercise	Hypertensive response (SBP>250 mm Hg and/or DBP >115 mmHg)
Technical difficulties in monitoring the ECG or SBP	Development of bundle-branch block or intraventricular conduction delay that cannot immediately be distinguished from VT
The patient's request to stop	

and cardiovascular stress stimulus for any reason, the results of the EST are of limited utility [49].

### Termination of exercise stress test

The supervisor of the EST has an important role in determining when to stop the test and this is generally based upon the purpose of EST in patient. Symptom-limited testing is appropriate for general evaluation, but it can be modified in several situations. Absolute indications are clear, where relative indications may be superseded by the supervisor of EST. Table 3 outlines the indications of terminating EST [44,50].

### Interpretation of exercise stress test (EST) data

It is very important to collect and evaluate an accurate patient medical history because this may influence both the test results and the information collected in EST [51]. There are several medical conditions that can have an impact on EST interpretation including orthopedic diseases, lung diseases, neurologic diseases, and deconditioning or prolonged bedrest. Other things to consider include drug history, abnormal resting ECG, left ventricular hypertrophy [44,51]. Interpretation of EST data should include ECG, functional capacity, and the hemodynamic response to the graded exercise. A thorough understanding of the best interpretation of the EST will provide optimal diagnostic, prognostic and therapeutic evaluation and prescription of rehabilitative programs for the patient.

### The diagnostic variables of exercise stress test

1. The ECG changes during exercise stress test

The normal ECG findings and response to exercise include the following [29,44]:

- P wave increases in height and change in morphology
- R wave decreases in height
- J point becomes depressed
- ST segment becomes sharply upward sloping
- QT interval shortens
- T wave decreases in height in early exercise but increase in higher exercise
- High-frequency content of the QRS power spectrum increases with exercise and shortening of QRS duration.

Some changes of ECG wave morphology may be indicative of an underlying pathology. For example, although it is normal for the QRS duration to decrease with exercise, the QRS duration may increase in patients with angina and left ventricular dysfunction. Exercise induced P-wave changes are rarely seen and are questionable significance. Although R wave in aVL lead (RaVL) is strongly correlated with left ventricular mass index (LVMI) assessed by transthoracic echocardiography [52]. Many factors affect R-wave amplitude; consequently, such changes during exercise have no independent predictive power [53,54].

Abnormal ST-segment changes have been the standard criteria for diagnosis of CAD for more than half a century. The ST level is measured relative to the end of the PR segment (the P-Q junction) because the T(U)-P segment during exercise is difficult or impossible to measure

when HR are fast. Three or more consecutive beats in the same lead with a stable baseline, and the average magnitude and tangent direction of displacement at 60-80 ms after the J-point determined should be identified, either manually or by use of computer-averaged complexes [55,56]. The R wave in aVL lead (RaVL) is strongly correlated with left ventricular mass index (LVMI) assessed by transthoracic echocardiography [52,57].

ECG from an EST is not always straightforward to interpret. For example, ST-Segment changes may be affected by abnormal resting ECG (bundle branch block, left ventricular hypertrophy, digitalis drug) so resting ECG responses should be examined carefully. Healthy subjects may have J-point depression and an enhanced T-wave at high intensities exercise and also recovery. Depression of J-point that leads to marked ST-Segment upsloping may be caused by competition between normal repolarization and delayed terminal depolarization forces rather than by ischemia [58-60].

### ST-Segment depression

ST-segment depression is a lowered J-point and a slope that occurs 60-80 ms after the J-point. This is the most common indicator of CAD. The standard criterion for a positive test is more than 1 mm horizontal or downsloping ST-segment depression with the PR segment as the isoelectric baseline of the ECG [61-65]. It must be present in at least 3 consecutive beats in 2 or more contiguous ECG leads. ST-segment depression does not identify the ischemic region nor the coronary arteries involved, however, if it occurs during recovery after EST, this is predictive of cardiac death [66-70]. Having more leads with ST-segment depression indicates a greater severity of the disease. Downsloping ST-segment depression is a stronger predictor of CAD than horizontal depression and both are more predictive than upsloping depression. Upsloping ST-segment depression is not strongly predictive of existing CAD in general populations, although and it might be associated with increased risk of future coronary events, especially in higher-risk men [71-73]. Upsloping ST-segment depression is generally defined as an "equivocal" test response, which is a major reason for the reduced sensitivity of EST (more false positive results) [59,74]. In presence of abnormal resting ECG, ST-segment depression during EST is less specific for CAD. In patients with left bundle branch block, ST-segment changes during exercise are not diagnostic with respect to evidence of ischemia. In right branch bundle block, exercise induced ST-segment depression in leads  $V_1$ ,  $V_2$  and  $V_3$  are not diagnostic; on other hand, ST-segment changes in leads  $V_4$ ,  $V_5$ ,  $V_6$  (lateral leads) or leads II, III, aVF (inferior leads) may be indicative of CAD [75-78].

### ST-Segment elevation

The standard criterion for positivity is more than 1 mm horizontal or upsloping ST-segment elevation, measured 80 ms after the J-point, and seen in 3 or more consecutive beats [44,79-82]. ST-segment elevation in leads with Q wave consistent with a prior myocardial infarction may be indicative of wall motion abnormalities from an aneurysm, and is associated with akinesis of the left ventricular wall, and residual viability within an infarcted area [83-85]. Exercise induced ST-segment elevation in  $V_1$  and  $V_2$  leads, but not the aVR lead, is significant for diagnosis of CAD [1,79,86,87]. ST-segment elevation signifies severe transmural ischemia caused by multi-vessel CAD, or coronary artery spasm (Prinzmetal's angina) [29,88-90]. In contrast to ST-segment depression, ST-segment elevation does identify the ischemic region; further, the territory of ischemia is greater in patients with exercise-induced ST-segment elevation than with ST-segment depression

### Limiting signs and symptoms

Perceived symptoms are one of the most an important component of EST which includes angina, dyspnea, and perceived exertion [29,94-97]. Angina without ECG changes is predictive of CAD and is even more predictive with associated ST-segment depression [94,98,99]. About 30% of patients who have ST-segment changes develop chest pain [100-102]. Angina during EST correlates with the severity of CAD, with the exception of diabetic patients [103-107]. Dyspnea which limits the test is indicative of a poor prognosis as compared to angina or leg fatigue [108,109]. It is important to obtain a careful description of all perceived symptoms during EST from the patient, and to document what the patient considers to be the primary limiting factor and patient's general appearance should be carefully observed during EST. Signs of poor perfusion, such as cyanosis, pallor, and nervous system symptoms, such as ataxia, dizziness, and vertigo, serve as absolute test termination criteria [110]. Even though the diagnostic value has not been confirmed, cardiac auscultation during the recovery stage of EST, could be indicative of altered cardiac function. For example, "Gallop" sounds, a palpable precordial bulge, or the development of a mitral regurgitant murmur after exercise, could suggest left ventricular dysfunction [111-113].

### Diagnostic value of exercise stress test

The diagnostic value of an EST to detect CAD is influenced by the principle of conditional probability [114]. The probability of a patient having CAD is not estimated correctly from EST result alone [115]. It also depends on the likelihood of having disease before the test. Bayes' theorem states that the posttest probability of having CAD is determined by CAD probability before EST and the probability the test will provide a true result [29]. The probability of a patient having CAD before EST is related to the medical history (age, sex, risk factor of cardiovascular disease) and symptoms (chest pain). Diagnostic EST is most valuable in patients with an intermediate pretest probability group, because the test result has the largest potential effect on diagnostic outcome. Therefore, an EST cannot be used to rule in or rule out CAD unless the probability of CAD is taken into account [44]. Generally EST is not considered for asymptomatic patients but may be useful when multiple risk factors are present.

In low risk patients (as men aged  $\leq 30$  & women aged  $\leq 40$ ) a positive test result is more likely to be a false positive, and negative results add little new information. In a high risk population, such as those aged over 50 with typical angina symptoms, a negative result cannot rule out CAD, although the results may be of some prognostic value [44]. The factors that determine the predicative outcome of EST are the sensitivity and specificity of the test procedure and the prevalence of CAD in patients. Sensitivity and specificity determine how effective an EST is in making correct diagnoses, and separates patients with disease from healthy subjects without disease, respectively. From a meta-analysis of multiple studies, 1 mm of horizontal or downsloping ST-segment depression has been selected as the discriminating point and has a sensitivity of 68% and specificity of 77% [116]. Disease prevalence is an important determinant of the predicative value of EST. Moreover, non ECG variables (functional capacity, MET, hemodynamic, symptoms of angina and dyspnea) should be considered in the overall interpretation of EST results.

### Sensitivity

Sensitivity of EST represents the percentage of patients with CAD who have abnormal test results (significant ST-segment positive

changes). EST sensitivity for diagnosis of CAD regularly is based on consequent cardiac catheterization determined coronary artery stenosis of 70-75% at least one vessel [44]. A true positive test reveals 1.0 mm or more horizontal or downsloping ST-segment depression. False-negative test results show no any diagnostic ECG changes and fail to identify patients with CAD. EST sensitivity is decreased by inadequate myocardial stress, drugs that reduce myocardial ischemia ( $\beta$ -blockers, nitrates, calcium channel blockers) and insufficient ECG leads monitoring. EST is most accurate for diagnostic CAD by applying validated multivariate scores which include pretest risk markers, ST-segment changes and other EST responses [117-121]. However, pre-existing ECG change (left ventricular hypertrophy, left bundle branch block, Wolff-Parkinson-White syndrome) limit the ability to interpret EST results. Generally, an EST has a higher sensitivity in

patients with triple-vessel disease than in those with double-vessel disease, which in turn is higher than those with single-vessel disease [122,123]. Therefore, EST sensitivity will vary with the extent of disease, even though all patients will have a diagnosis of CAD.

### Specificity

Specificity of EST is indicative of the percentage of patients without CAD who have normal EST results (non-significant ST-segment negative changes) [44]. Specificity may be affected by drugs such as digoxin, by baseline ECG patterns, and by left ventricular hypertrophy. A true-negative test correctly identifies a patient without CAD. Specificity is higher than sensitivity when workup bias is removed and EST can have a lower specificity if it is used in patients who are more likely to have false-positive results [8,124,125].

Sensitivity and specificity are inversely correlated. All tests have a range of inversely related sensitivities and specificities that can be selected by specifying a discriminant or a diagnostic cutoff point [126]. The sensitivity and specificity of EST are limited by the general use of angiographic CAD as the diagnostic "gold standard," and hence most data are derived from studies in which patients underwent both EST and cardiac catheterization. Because patients selected for coronary arteriography are more likely to have obstructive CAD, these data are subject to an experimental bias that inflates the estimated sensitivity and deflates the specificity. The diagnostic accuracy of a test will also be influenced by criteria that are used to determine whether an adequate level of stress has been achieved. This often is defined as having attained 85% of maximal age-predicted heart rate. There are shortcomings to using this calculation for diagnostic purposes, and it should not be used as a sole reason to terminate the test [20,127,128].

### Predictive values

The predictive value of an EST is a measurement of how accurately a test result (positive or negative) correctly identifies whether or not the patient has CAD, and it also helps define the diagnostic value of the test itself. The predictive value of a positive test is the percentage of those patients with an abnormal test who have CAD. EST should never be classified as negative unless the patient has attained as adequate level of myocardial stress.

The predictive value cannot be estimated directly from sensitivity

or specificity, because it depends on the prevalence of CAD in patients who have been tested [44]. EST has a higher positive predictive value and lower negative predictive value when used in high-prevalence patients. For example, an EST that shows ST-segment depression in an older patient with angina will most likely have a true positive result, whereas a false-positive result is more likely to be found in a young asymptomatic subject that does not have cardiac risk factors.

Examination of interactions among sensitivity, specificity, and predictive values are necessary to improve the use of diagnostic EST. Clinical factors that affect the likelihood of CAD prior to the patient undergoing EST include age, sex, symptoms, and traditional risk factors —hyperlipidemia, diabetes mellitus and hypertension. Based on the patient's likelihood of disease and the performance characteristics of the outcome on EST, the posttest likelihood of obstructive CAD can be estimated for a given patient [29]. Table 4 outlines the equation of sensitivity, specificity, predictive value of EST.

### Causes of a false positive exercise stress test

A false positive EST indicates an exercise-induced ST-segment depression in the absence of significant obstructive CAD. It is associated with pathophysiology such as increased left ventricular mass, pressure overload, or higher oxygen consumption, and decrease blood flow to the subendocardium [129]. In addition, sympathetic nerve stimulation, drugs, electrolyte abnormalities may affect the ST-segment at high HR resulting in false positive results [130-135].

### Causes of a false negative exercise stress test

A false negative EST is associated with males, single vessel disease, failure to achieve adequate workload, drugs like  $\beta$ -blockers agents which decrease HR, and contractility of ventricles and increase coronary blood flow with exercise, and high probability of CAD [136]. To obtain accurate EST results, it is necessary for drugs that decrease HR or BP, such as  $\beta$ -blockers, be discontinued days before the test. This requires the consultation and supervision of the patient's cardiologist. Table 5 outlines the causes of false positive and false negative of EST.

## Discussion

### The prognostic variables of exercise stress test

EST has a very important role in prognosis of cardiovascular diseases, prediction of future cardiac events and mortality. Even as alternative diagnostic strategies such as imaging modalities and serologic markers become more common, the use of EST continues to increase and can give a complimentary perspective [29,137-142]. There are several prognostic variables that can be derived from EST which include HR adjustment of ST-segment depression, functional capacity, exercise duration, BP Abnormalities, chronotropic incompetence, HR recovery, and ventricular dysrhythmias.

### HR adjustment of ST-Segment depression

Exercise induced ST-segment depression occurs during high workloads when there is coronary artery obstruction and an increased oxygen demand. This is physiological principal of imbalance between oxygen supply and oxygen demand. HR changes are related to changes

**Table 4.** Defining: Sensitivity, Specificity, Predictive value of exercise stress test.

Sensitivity = TP/ (TP + FN) = % of patients with CAD who have a positive test Specificity = TN/ (TN + FP) = % of patients without CAD who have a negative test Positive predictive test = TP/ (TP + FP) = % of patients with a positive test who have CAD
Negative predictive test = TN/ (TN + FN) = % of patients with a negative test who do not have CAD

Abbreviations: TP, true positive; FP, false positive; TN, true negative; FN false negative

**Table 5.** Causes of false positive and false negative exercise stress test.

Aortic valve diseases Athletics	Inadequate workload or failure to reach an ischemic threshold
Digoxin agents Estrogen agent Female sex	B-Blocker agents Calcium-Blocker agents
Left bundle branch block Left ventricular hypertrophy Heart failure	Single vessel CAD Male gender
Hypertrophic cardiomyopathy Sever Hypertension	Left bundle branch block Nitrates
Mitral valve diseases Hyperventilation	Right bundle branch block
Intraventricular conduction defects Coronary spasm (Microvascular disease)	High exercise DBP
Right bundle branch block Supraventricular tachycardia	Technical or observer error

in myocardial oxygen demand, resulting from low coronary blood flow, and ST-segment depression changes that occur during graded EST as a result of coronary artery obstruction [143,144]. Therefore, it is physiologically important to adjust observed ST-segment depression for the change in HR associated with its production to derive indices of obstructive CAD [122,123,145]. Two methods of heart rate adjustment of ST-segment depression during EST have been proposed. The first is the ST/HR index is the ratio of maximum ST-segment change (measured in mV) to the maximal change in HR from rest to peak exercise (measured in beats.min<sup>-1</sup>) and it is considered to be abnormal if ST/HR exceeds 1.6  $\mu$ V/bpm [29,137-142]. The ST/HR index = (Peak exercise - upright control ST)/(Peak exercise - upright control HR). The ST/HR index increases the sensitivity for diagnosis of CAD and predicts mortality and cardiovascular events [29,146-149]. Data from Kingfield's group [137,142,150] suggest that the ST/HR index should be used in routine EST evaluation.

The second approach is to use the ST/HR slope, which is measured by linear regression analysis of the ST-segment depression in individual leads, to the HR at the end of each stage of exercise. An ST/HR slope more than 2.4  $\mu$ V/bpm is considered abnormal, and values more than 6  $\mu$ V/bpm is suggestive of anatomically extensive disease, including three vessels or left main CAD [151,152]. The slope is used with gradual increments exercise protocol in HR, such as the Cornell protocol, because large increments in rate between stages of the Bruce protocol limit the ability to calculate statistically valid ST/HR slopes by regression [153-156]. ST/HR slope increases sensitivity for diagnosis of CAD and for identification of anatomically and functionally severe CAD when markedly abnormal.

### Functional capacity

Functional capacity is a key predictor and prognostic marker of risk for adverse events in apparently healthy individuals, those at increased risk for cardiovascular disease, and all patient populations [3,157-160]. Functional capacity is an estimate of the maximal oxygen consumption for any given workload and is measured in units of metabolic equivalents (MET). Functional capacity is a valuable predictor of CAD in both men and women. It has been determined that higher functional capacity can indicate a lower prevalence of CAD [101,161-165]. Bourque et al. found that patients who achieved more than 10 METs had a very low prevalence of CAD compared with those who achieved less than 7 METs [71,166]. It has been shown that functional capacity in METs is a very strong independent predictor of all-cause and cardiovascular mortality [167-169]. Each 1-MET increase in functional capacity leads to 13-15% decrease in rates of

all-cause death and cardiovascular events [170,171]. However, the use of functional capacity in routine clinical care is problematic because of a lack of standardization. Functional capacity is strongly related to age and gender. Thus, an estimated functional capacity of 7 METs in a 40-year-old man would be prognostically more concerning than the same value in a 60-year-old woman [136,157,158,172-174]. Functional capacity is higher in men than women, and decreases with age for both genders [175-177]. Some investigators have characterized functional capacity as abnormal if it is less than 5 METs in women or less than 7 METs in men [136,157,158,172-174]. Regardless of angiographic findings, patients with CAD who achieve more than 10 METs have an excellent prognosis [178-182]. Poor functional capacity (< 5 METs) in patients with known CAD or prior MI is associated with an increased risk of cardiac events [178-183]. Further evaluation is required when there is a sudden reduction in patient's functional capacity.

### Exercise duration

In an EST, healthy well-trained subjects can complete the Bruce protocol, in a maximum of 27 minutes whereas, the average middle-aged adult takes 8-10 minutes to complete this test [184,185]. Exercise duration is a good measure of functional capacity and it is considered an independent and strong predictor for mortality and cardiac events on a standard protocol in patients with known or suspected cardiovascular diseases [184,185]. Functional capacity, which is normally lower in women than men, decreases with age, however, exercise duration keeps its prognostic value after adjusting for both age and sex. In subsets of patients with CAD, exercise duration has been shown to provide risk stratification. More than three decades ago, the Coronary Artery Surgery Study (CASS) first showed that survival at 4 years was 100% in patients with CAD and preserved left ventricular function who achieved stage 5 of EST and walk more than 12 minutes [186-191].

### Blood pressure (BP) abnormalities

In response to exercise, there is both diagnostic and prognostic value in evaluating BP abnormalities. Hypotensive and hypertensive BP to exercise have been defined in various ways [184,185]. Exercise induced hypotension occurs when there is a decrease in SBP below the resting value or an initial increase in SBP during early exercise followed by a decrease of more than 10 mmHg [192-195]. It is a potential indication to terminate exercise, especially in the presence of evidence for ischemia or other known heart disease [29]. The pathophysiology of exercise-induced hypotension is a failure of cardiac output to increase during exercise and is associated with severe CAD and left ventricular systolic dysfunction [196,197]. Exercise induced hypotension has been shown to be associated with a threefold higher risk of cardiac events over two years and it is a marker of increased risk of adverse events [198-200].

Exercise induced hypertension is defined as an increase in SBP >210 mmHg for men and >190 mmHg for women [192-195,201-205]. An increase of DBP more than 10 mmHg above the resting value or an absolute value of 90 mmHg also is considered abnormal and could predict increased likelihood of CAD. EST termination should be made when SBP is more than 250 mmHg and DBP more than 115 mmHg, respectively [202,206-208]. A resting SBP >200 mmHg and DBP >110 mmHg are considered relative contraindications to EST. Exercise induced hypertension may indicate an increased risk for future hypertension, left ventricular hypertrophy, and cardiovascular events [192-195,201-205,209]. In the Coronary Risk Development in Young Adults cohort, participants with exercise-induced hypertension were 1.7 times more likely to have developed hypertension at 5-year follow-

up than those with a normal response. Patients with an increase in SBP >20 mmHg/min during aerobic exercise or whose SBP did not decrease two minutes after exercise have a 5-fold increased risk of stroke [210,211]. Abnormally delayed decreasing of SBP during the recovery stage of EST is predictive of severe CAD [212]. An increase of SBP >10 mmHg/min for 2 minutes in recovery stage of EST was associated with risk of future myocardial infarction [40,213-215]. Exercise induced hypertension may cause ECG changes and ST-segment depression in the absence obstruction of the coronary artery [216,217].

### Chronotropic incompetence

Chronotropic incompetence occurs when the HR fails to increase with an increase in workload. It also occurs when a minimum of 85% of age-predicted maximum HR cannot be reached for patients who are not taking  $\beta$ -blocker agents [218-220]. However, 65-70% chronotropic incompetence cutoff points have been shown to stratify to heart failure patients with the works prognosis [221]. It is associated with cardiac disease, sick sinus syndrome, congestive heart failure, medications, and advanced age [29,137-142,222]. Regardless of whether or not a patient is taking  $\beta$ -blocker agents or calcium-channel blocker agents—chronotropic incompetence independently predicts cardiac event and all-cause mortality [223-226]. There are different measures for defining chronotropic incompetence were used in different studies, based on resting HR, exercise protocol, age, and drugs ( $\beta$ -blocker agents). Chronotropic response or index is calculated as: Chronotropic index =  $(HR_{peak} - HR_{rest}) / (220 - HR_{rest}) \%$  [29,49,137-142]. The difference between peak HR and resting HR is the HR reserve. It is abnormal if it is less than 80% and less than 62% for patients on  $\beta$ -blocker agents. There are challenges to the use of chronotropic response include calcium channel blockers, pacemakers, and atrial fibrillation.

### Heart rate recovery (HRR)

HR normally slows during the recovery stage of EST, as it is closely related to autonomic function and parasympathetic nervous system reactivation. Abnormal heart rate recovery HRR is failure of HR to decrease 12 beats or more during the first minute at recovery stage of EST while patients are standing [157,158,201,227-229]. An abnormal HRR is associated decreased parasympathetic reactivation (vagal tone), increased sympathetic activity and autonomic imbalance [198,230,231]. Excessive sympathetic activity, increases HR, BP, cardiac workload, hemodynamic stress, endothelial dysfunction, coronary artery spasm, left ventricular hypertrophy, serious arrhythmias, stroke, and cardiac mortality. In contrast, increased parasympathetic activity decreases HR, BP and myocardial oxygen consumption, so it is protective against ischemia related dysrhythmias [232-236]. Abnormal HRR is independently a predictor of all-cause mortality and cardiovascular events [101,157,158,201,227-229,237,238].

Difficulties in characterizing HRR represent a challenge for its use in routine EST. Several factors have influence on HRR—the type of recovery protocol of EST (complete cessation of exercise or cool-down) and body position (supine, sitting, standing). Suggested thresholds for abnormal responses include [29,137-142]:

- Standing position HR should slow down by at least 12 beats/minute at 1 minute
- Sitting position at least 22 beats/minute at 2 minutes
- Supine position at least 18 beats/minute at 1 minute

Both chronotropic incompetence and abnormal HRR can predict risk of death. HRR appears to be modifiable, as improvements in HRR

have been reported following exercise training of cardiac patients [11,165,239-241].

### Ventricular ectopy

Ventricular ectopy is the most common cardiac arrhythmia during exercise. In general, ventricular ectopy includes paired premature ventricular contractions (PVC), multiform PVC, and a run of ventricular tachycardia. It is of concern in patients with a family history of sudden death or medical history of cardiomyopathy, valvular heart disease, or CAD. Isolated PVCs occur during EST in 30-40% of healthy people and in 50-60% of patients with cardiovascular disease [44]. Although, the diagnostic and prognostic values of ventricular ectopy during exercise and recovery are still controversial [29, Frolkis et al. showed that frequent ventricular ectopy during recovery stage of EST is better a predictor of 5-year mortality than ventricular ectopy during exercise dose [242]. In addition, other studies have shown that ventricular ectopy during exercise and the recovery stage of EST was associated with an increased death rate. In addition, it was found to be an independent predictor of increased morbidity and mortality [243-246]. The exact relationship between exercise induced ventricular ectopy, ischemia, and left ventricular function are currently unclear.

### Application to practice

#### Integrated exercise stress test scores

Patient management decisions are based on risk and prognostic evaluation. The data obtained from an EST is most useful when used along with other clinical information, such as ECG data and other clinical hemodynamic variables [247-250]. There are several multivariate prognostic scores that can be measured based on traditional ECG data, functional and hemodynamic variables of EST, including the Duke Treadmill Score (DTS), the VA/ Froelicher score, and the Veteran Score [44]. The Duke Treadmill Score is the most common risk score used in labs and it has been developed from more than 2000 patients (30% women) with CAD who completed an EST using the Bruce protocol and this was followed by diagnostic cardiac catheterization [175,228,246]. The Duke Treadmill Score includes exercise duration, ST-segment depression, and the presence and nature of angina. The Duke Treadmill Score is calculated as follows:

- $DTS = \text{exercise time} - (5 \times \text{ST-segment deviation}) - (4 \times \text{angina score index})$
- Exercise time is measured in minutes when using the Bruce protocol.
- ST deviation is the net ST-segment deviation in any lead other than aVR, and angina score is given a value of (no angina = 0, non-limiting angina = 1, and test-limiting angina = 2).

The Duke Treadmill Score is classified into risk as follows: Low-risk ( $\geq 5$ ), Moderate risk ( $-10$  to  $+4$ ), and High-risk ( $\leq -11$ ). This score is applicable in providing valuable diagnostic and prognostic information in both men and women. It predicts cardiovascular mortality and all-cause mortality in symptomatic and asymptomatic men and women [175]. Alternatively, a score by Lauer et al. has been proposed that has integrated more clinical risk factors (age, sex, lipid level, and smoking history) with EST variables. For predicting all-cause mortality it may be superior to the Duke Treadmill Score [246].

#### Data to include in a current exercise stress report

Current standards for an EST report include diagnostic, prognostic



**Table 6.** Data that is needed in an EST report.

Variable	Response and result	Comment
ST-segment	Negative, positive, equivocal	Normal or abnormal
ST/HR index	≤1.6 V/bpm	*Consistent with absence of CAD
	>1.6 V/bpm	*Consistent with presence of CAD & ↑ cardiovascular risk
Functional capacity	Xx MET	high/low risk of all-cause mortality
Blood pressure	Normal, high, low	No /↑ risk of developing HTN
chronotropic index	0.xx if ≤ 0.8 or ≤0.62 on β-blockers	↑/↓ risk of death compared with DTS.
Heart rate recovery	xx bpm	↑/↓ risk of death
PVCs during recovery stage	Presence or absence	↑/↓ risk of death
DTS	xx	*Low, moderate, high risk *Predicts a cardiac mortality of X% / year over the next 5 years.

Abbreviation: CAD, coronary artery disease; HTN, hypertension; DTS, Duke Treadmill Score, ↑ increased; ↓, Decreased.

variables data and the reason for stopping the test. Also, if there is a presence of chest pain at peak exercise it is necessary to note that in the report. An EST has moved beyond solely evaluating the ST segment and thus, cardiac laboratories and clinicians should revise the former standard report (positive, negative and equivocal) to the new comprehensive report which includes all variables data of the test to evaluate patients with CAD. In Table 6 we list the minimal data that should be included in an EST report [29,137-142,175].

## Summary

Exercise stress testing for evaluation of cardiovascular dysfunction or disease has traditionally relied on ST-segment abnormalities to identify or predict cardiovascular disease. However, an exercise stress test provides the opportunity to obtain additional objective diagnostic and prognostic data and use these data to more completely evaluate the extent of cardiovascular disease. This includes obtaining maximal oxygen consumption (predicted or measured), exercise capacity and fatigability, as well as blood pressure and heart rate responses as well as a comprehensive analysis of ECG abnormalities. We have reviewed standards, and guidelines for exercise stress testing, that have included the acute physiological responses of the cardiovascular system to aerobic exercise. The use of exercise stress test can be used to evaluate the presence and extent of coronary artery disease and the data can be used to prescribe an appropriate exercise rehabilitative program by which to reduce the effects of the disease process. Finally, the exercise stress test can be used to evaluate the effectiveness of pharmacological or exercise interventions to improve the effects of cardiovascular disease. Thus, a comprehensive exercise stress test and not just a pharmacological stress test 96 should be used unless otherwise contraindicated, to provide a full cardiovascular assessment of a patient's cardiovascular function (Table 6).

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