Overview of Exercise Stress Testing

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Exercise stress testing is a non-invasive, safe and affordable screening test for coronary artery disease (CAD), provided there is careful patient selection for better predictive value. Patients at moderate risk for CAD are best served with this kind of screening, with the exception of females during their reproductive period, when a high incidence of false positive results has been reported. Patients with a high pretest probability for CAD should undergo stress testing combined with cardiac imaging or cardiac catheterization directly. Data from the test, other than ECG changes, should be taken into consideration when interpreting the exercise stress test since it has a strong prognostic value, i.e. workload, heart rate rise and recovery and blood pressure changes. Only a low-level exercise stress test can be performed early post myocardial infarction (first week), and a full exercise test should be delayed 4 to 6 weeks post uncomplicated myocardial infarction. The ECG interpretation with myocardial perfusion imaging follows the same criteria, but the sensitivity is much lower and the specificity is high enough to overrule the imaging part.

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Exercise stress testing has been used for decades as a noninvasive test to diagnose and risk stratify coronary artery disease (CAD). However, it lacks adequate sensitivity, which nevertheless depends on the pretest probability of CAD in the population tested. The overall sensitivity has ranged from 60% to 70% with a specificity of 85%.[1,2,3] Due to the innumerable criteria set for the EKG stress test interpretation and reporting, a lot of confusion arises between institutions. To make it easier on the practitioner at our institution, we have adopted the criteria outlined in this review for interpretation of test results.

Indications and safety of exercise testing

Although exercise testing is generally a safe procedure, both myocardial infarction and death have been reported and can be expected to occur at a rate of up to 1 per 2500 tests. Good clinical judgment should therefore be used in deciding which patients should undergo exercise testing. Common indications and contraindications are listed in Table 1 The prognosis of the individual tested is not only linked to the result of the test whether it is positive or negative, but also depends on the exercise capacity, heart rate rise, heart rate recovery and blood pressure rise and recovery.

Exercise capacity is based on metabolic equivalents (MET) achieved, (one MET is defined as 3.5 mL O2 uptake/kg per min, which is the resting oxygen uptake in a sitting position). Less than 5 METS is poor, 5-8 METS is fair, 9-11 METS is good, and 12 METS or more is excellent. An inability to exercise >6 minutes on the Bruce protocol, or

Table 1. Common indications and contraindications for exercise stress testing.

Indications
• Evaluating the patient with chest pain or dyspnea with other findings suggestive, but not diagnostic of coronary artery disease (CAD)
• Risk stratification post-myocardial infarction
• Determining prognosis and severity of coronary artery disease
• Evaluating the effects of medical and surgical therapy
• Screening for latent coronary disease
• Evaluation of congestive heart failure
• Evaluation of arrhythmias
• Evaluation of functional capacity and formulation of an exercise prescription
• Evaluation of congenital heart disease
• Stimulus to a change in lifestyle

Contraindications (absolute)
• Very recent MI, < 3-4 days
• Unstable angina, not previously stabilized by medical therapy
• Severe symptomatic left ventricular dysfunction
• Life threatening dysrhythmias
• Severe aortic stenosis (relative?)
• Acute pericarditis, myocarditis or endocarditis
• Acute aortic dissection

Contraindications (relative)
• Left main coronary stenosis
• Moderate stenotic valvular heart disease
• Electrolyte abnormalities
• Severe arterial hypertension (SBP>200 mmHg or DBP>110 mmHg)
• Tachyarrhythmias or bradyarrhythmias
• Hypertrophic cardiomyopathy and other forms of outflow tract obstruction
• Mental or physical impairment leading to inability to exercise adequately
• High-degree atrioventricular block

an inability to increase heart rate (HR) to >85% of maximum predicted heart rate (MPHR) are significant indicators of increased risk of coronary events with a 5-year survival ranging from 50% to 72%. However, patients who attain >10 METS enjoy an excellent prognosis regardless of the test result even in the presence of known CAD, with a 5-year survival of 95%.

The heart rate should reach or exceed 85% of MPHR calculated according to the formulae, MPHR=220-age. The HR rises prortionately with the intensity of the workload. An excessive rise in rate results primarily from a reduced stroke volume, which in turn is often caused by physical deconditioning, cardiac disease or arrhythmias like atrial fibrillation or supraventricular tachycardias and other noncardiac abnormalities like anemia and hypovolemia. In these situations the HR reaches its peak early, which limits maximum exercise capacity. An impaired chronotropic response to exercise as defined by failure to achieve 85% of MPHR and/or a low chronotropic index (<0.8 of heart rate reserve at peak exercise) caused by sinus node dysfunction, medications like β–blockers, or ischemia, are occasionally associated with increased mortality and cardiac events even after adjusting for left ventricular function and the severity of exercise-induced myocardial ischemia.[4] The HR should decrease by at least 12 beats in the first minute of recovery, which is mediated through vagal reactivation. Otherwise, recovery is considered abnormal, which has a bad prognosis, with a 6-year mortality 2-3 times greater than those with normal recovery.[4,5]

BP should increase by at least 10 mm Hg during exercise except in patients on antihypertensive treatment where a blunted response is observed. Diastolic blood pressure (DBP) exhibits little or no change (<10 mm Hg) during exercise because of peripheral vasodilatation. A sustained drop of SBP>10 mm Hg, confirmed within 15 seconds, often indicates severe left ventricular dysfunction and severe CAD and is an indication to stop the test immediately and refer for further evaluation and treatment (Table 2). Failure to increase systolic blood pressure by 10 to 30 mm Hg during exercise testing is an independent predictor of adverse outcome in patients after myocardial infarction.[6] However, it is crucial to exclude other causes that could cause a drop in SBP with exercise without the presence of severe CAD or left ventricular dysfunction, i.e. vasovagal syncope, cardiac arrhythmias, left ventricular outflow obstruction or hypovolemia. In addition, an abnormal BP recovery, defined by the SBP at 3 minutes of recovery over an SBP at 1 minute of recovery >1, is associated with a greater likelihood of severe angiographic CAD.[7]

An abnormal rise of SBP to a level > 214 mm Hg in patients with a normal resting BP predicts an increased risk for future sustained hypertension, estimated at approximately 10% to 26% over the next 5 to 10 years.[8] However, in adults evaluated for CAD, exercise hypertension is associated with a lower likelihood of angiographically severe disease and a lower adjusted mortality rate on follow up.[9]
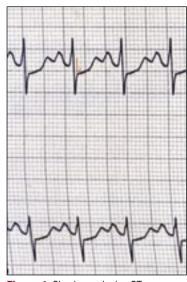
Interpretation of the electrocardiogram (ECG)

ST changes should be read at 60 to 80 ms from the J point,[16] and the test should be considered positive for ischemia if there is a 2 mm or more rapidly up-sloping ST depression (when the slope is more than 1 mV/s) ,[17,18] a 1.5 mm or more slowly up-sloping ST depression (when the slope is less than 1 mV/s) (Figure 1), or a 1 mm or more horizontal or down sloping ST depression (Figure 2, 3).

Ischemic ST-segment changes developing during recovery from treadmill exercise in apparently healthy individuals has adverse prognostic significance similar to those appearing during exercise. Resting ST-segment depression has been identified as a marker for adverse cardiac events in patients with and without known CAD.[19,20,21,22] Diagnostic end points of 2 mm of additional exercise-induced ST-segment depression or downsloping depression of 1 mm or more in recovery were particularly useful markers in these patients for diagnosis of any coronary disease (likelihood ratio 3.4, sensitivity 67 percent, specificity 80 percent).[22,23,24] Factors that preclude or interfere with proper interpretation of ECG are listed in Table 3.

In a recently published study, after 23 years of follow up, patients with frequent ventricular ectopy (a run of 2 or more consecutive premature ventricular contractions (PVC) making up more than 10% of all PVCs on any 30 seconds ECG) had an increased risk of death from cardiovascular causes by a factor of 2.5 times, similar to that observed in patients who had a positive ischemic response to exercise. Frequent PVCs at rest or during recovery were not associated with an increase in cardiovascular mortality in this study, but in another study a stronger association between ventricular ectopy during recovery and increased 5-year mortality was noted.[25]

Exercise-induced right bundle branch block (RBBB) or left bundle branch block (LBBB) is usually considered nonspecific unless it is associated with evidence of ischemia, i.e. angina, and then it is strongly suggestive of ischemia. Causes for a false positive test include left ventricular hyprtrophy (LVH), which is associated with decreased exercise testing specificity, but sensitivity is unaffected.[26] Digitalis causes exercise-induced ST depression in 25% to 40% of normal subjects.[27,28,29] Other diseases that might cause a false positive test include mitral or aortic valve dysfunction or mitral valve prolapse, pulmonary hypertension, pericardial constriction, hypokalemia, glucose ingestion prior to the test and

Figure 1. Slowly up-sloping ST depression.

Figure 2. Horizontal ST depression.

Figure 3. Down-sloping ST depression.

in females during reproductive years.

Causes of false negative test include use of β-blockers, which may reduce the diagnostic or prognostic value of exercise testing because of inadequate heart rate response, but the decision to remove a patient from β-blocker therapy for exercise testing should be made on an individual basis and should be done carefully to avoid a potential hemodynamic "rebound" effect, which can lead to accelerated angina or hypertension.[28,30] Acute administration of nitrates can attenuate the angina and ST depression associated with myocardial ischemia. Atrial repolarization waves are opposite in direction to P waves and may extend into the ST segment and T wave. Exaggerated atrial repolarization waves during exercise can cause downsloping ST depression in the absence of ischemia.[31,32]

The final Interpretation of the ECG is positive if the ST criteria are met at any heart rate, and there are no factors to preclude appropriate interpretation of the test. The interpretation is negative if no significant ST changes are noticed. The test is nondi-

Table 2. Indications for early termination of exercise stress testing

- Hypotension, with SBP drop > 10 mmHg
- Ventricular or Supraventricular arrhythmias other than PVC's or PACs
- Severe Hypertension, SBP >250 or DBP >120 mmHg
- ST elevation (> 1mm in leads without Q waves), if transient, often indicate severe proximal coronary stenosis and ominous prognosis[10,11,12,13]
- Angina with dynamic ST changes
- Excessive ST Depression, > 2 mm horizontal or downsloping
- Signs of poor perfusion, i.e. pallor or cyanosis
- Achieving 100% of MPHR

High-risk criteria:

- Hypotension with systolic BP drop > 20 mm Hg
- Early positivity, within the first or second stage of the Bruce protocol
- Late recovery
- Diffuse ST-T changes
- More than 2 mm ST depression in multiple leads
- ST elevation[10,11,12,13]

Table 3. Factors that preclude interpretation of exercise stress testing results.

- Left bundle branch block[14]
- Left ventricular hypertrophy with repolarization changes
- Digoxin therapy
- Right bundle branch block, cannot interpret leads V1-V3[15]
- Marked ST abnormalities at baseline with ST depression > 1 mm in at least two leads
- Paced ventricular rhythm
- Preexcitation syndrome (Wolff-Parkinson-White)

agnostic if the patient fails to achieve 85% of the MPHR and the test was negative. The results are indeterminate if the patient has baseline LBBB, a paced rhytm, LVH with repolarization changes and/or is on digoxin therapy. Patients with an abnormal exercise ECG, but a normal perfusion scan have a low risk for future cardiac events (<1%).[33]

Exercise testing in women

Numerous reports have demonstrated a lower diagnostic accuracy for exercise electrocardiography in women, in particular the occurrence of 1 mm of ST segment depression. The average sensitivity and specificity for the exercise electrocardiogram are 61% and 69%.[34,35,36] The increased age of presentation by

women, coincident with functional impairment, is associated with lower exercise capacity and an inability to attain maximal stress. Additional critical factors that have been reported to affect test accuracy in women include resting ST-T wave changes in hypertensive women and lower electrocardiographic voltage and hormonal factors. For the premenopausal woman, endogenous estrogen has a digoxin-like effect that may precipitate ST segment depression, resulting in a false positive test. Physicians who test pre-menopausal women with chest pain or established coronary disease should caution the use of exercise stress testing in a woman's mid-cycle where estrogen levels are highest. Reports have noted a reduced frequency of ischemic episodes and chest pain during this phase of the menstrual cycle. The accuracy of the exercise electrocardiogram in women is highly variable and is influenced by multiple factors, including exercise capacity and hormonal status. The current American College of Cardiology/American Heart Association (ACC/AHA) guidelines[6] for exercise testing recommend this test as a first-line test for those with a normal resting 12-lead ECG and for those capable of performing maximal stress. Although maximal stress may be defined by achieving 85% of predicted maximal heart rate, care should be taken when interpreting a woman's heart rate response. For deconditioned patients, a hyperexaggerated response to physical work may result in marked increases in heart rate. Thus, the test should be continued until maximal symptom-limited exercise capacity. Women incapable of performing a minimum of 5 METS of exercise should be considered candidates for myocardial perfusion imaging with pharmacologic stress.

Women with diabetes are a special population worthy of mention. They are at an increased risk for premature atherosclerosis and at significant risk for myocardial infarction and cardiac death. The unique pathophysiology of diabetes mellitus makes traditional symptoms less reliable and diagnosis of CAD more challenging. The ECG is often a less reliable indicator of significant CAD in the diabetic patient. Myocardial perfusion imaging has been shown to be accurate in the risk assessment and prediction of future cardiac events in the diabetic woman.

Stress testing following myocardial infarction (MI)

Exercise stress testing is an invaluable tool for risk stratification post-MI. In the early days post MI (days 3-7), a low level stress test limited to 5 METS,

75% of MPHR or 60% of MPHR on β–blockers, is very helpful in patients who were treated conservatively with no revascularization to assess for ischemia at low workload, arrhythmias, to start cardiac rehabilitation and gaining self confidence. Late post-MI (4-6 weeks), symptom limited stress testing is usually performed to assess revascularization, medical therapy or need for any further interventions.

EKG interpretation with pharmacologic stress testing

The same criteria in exercise stress testing applies, but the sensitivity of an adenosine and dipyridamole pharmacologic stress EKG is much lower than exercise stress testing (30% vs. 65% respectively). However, specificity (95% vs. 85% respectively) and PPV (90%) is much higher than exercise stress test-

ing.[37,38] Some authors recommend termination of the test and canceling of the imaging, but chest pain with pharmacologic stress testing is nonspecific. The finding of ischemic ECG changes with normal SPECT images during vasodilator infusion is uncommon, occurs primarily in older women, and is associated with a higher subsequent cardiac event rate than is customarily associated with normal images. With the dobutamine stress test, a 12-lead ECG had a sensitivity, specificity, PPV, and NPV of 52%, 64%, 72%, and 41%, respectively.[39,40]

In conclusion, exercise stress testing is noninvasive, safe, easy to perform and is available in most hospitals and clinics. It can be very helpful in diagnosing, risk stratifying or assessing cardiac patients provided appropriate patient selection is used to enhance its sensitivity and specificity.

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