

EXERCISE STRESS TESTING

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I. Capabilities of the Exercise Stress Test:

- Exercise stress testing (EST) may be used for three purposes:
 - To screen for, or to evaluate the current status of coronary artery disease.
 - To screen for exercise related cardiac dysrhythmias.
 - To predict all-cause mortality.

II. Hazards & Limitations of the Test:

- Either **acute myocardial infarction** or **death** occurs in about 1 of 2500 tests¹ the test is therefore performed by ACLS-trained personnel, at a site equipped with emergency IV medications & defibrillation equipment. The absolute and relative contraindications to performing the test are shown in Table 3¹.
- The majority of acute myocardial infarctions probably occur because of rupture of “**vulnerable plaque**” pouring thrombogenic cholesterol “gruel” from the plaque-core into the arterial lumen. Vulnerable plaques tend to be relatively flat, narrowing the arterial lumen < 50% prior to their rupture. Vulnerable plaques may therefore not cause exercise-induced ischemia, and may not be identified by exercise stress test until they rupture & occlude the lumen¹.
- Ischemia begins at the periphery of the “culprit artery”. For this reason the lead in which ST segment depression occurs does not localize the site of ischemia. Lead V₅ is the most reliable & leads II, III & AVF are not useful indicators of ischemia.

III. Indications & Contraindications:

- EST is not indicated in patients with baseline EKG changes that obscure the reading of ischemic ST segment changes (see Table !). An imaging study should be selected instead:

Table 1: Conditions Obscuring ST changes¹.

- Preexcitation (Wolff-Parkinson-White) Syndrome.
- Electronically paced rhythm.
- Greater than 1mm or resting ST depression.
- Complete left bundle branch block.

- Table 2 lists the ACC/AHA Guidelines' indications for EST. Class I indications are those for which there is evidence or agreement that the test is of value. Class IIa indications are those in which evidence/opinion is generally favorable. Class IIb are indications less well established Class III are indications for which there is evidence/agreement that the test is not useful and/or may be harmful¹. Table III lists contraindications:

Table 2: Indications for EST¹:

<p>Class I:</p> <ul style="list-style-type: none">• Adults with intermediate CAD risk & symptoms• Initial workup of suspected or known CAD• Known CAD with change in clinical status• Submaximal EST, 4-7 days post-MI followed by symptom-limited EST at 3-6 weeks• Symptom limited EST at 14-21 days post-MI <p>Class IIa:</p> <ul style="list-style-type: none">• Patients with vasospastic angina• For post-discharge rehab after PTCA or CABG• Evaluation of known or suspected exercise related arrhythmia, pre or post ablation. <p>Class IIb:</p> <ul style="list-style-type: none">• Patients with high or low probability of CAD• On digoxin with ≤ 1mm ST segment depression• LVH by EKG with ≤ 1mm ST segment depression. <p>Class III:</p> <ul style="list-style-type: none">• Severe comorbidity obviating revascularization.• EKG changes preventing interpretation of the test.
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Table 3: Contraindications¹:

<p>Absolute:</p> <ul style="list-style-type: none">• Acute MI within 2 days.• Unstable angina not yet stabilized medically.• Uncontrolled cardiac arrhythmias causing symptoms or hemodynamic compromise.• Severe symptomatic aortic stenosis.• Uncontrolled congestive heart failure.• Acute pulmonary embolism or pulmonary infarction.• Acute myocarditis or pericarditis.• Acute aortic dissection. <p>Relative:</p> <ul style="list-style-type: none">• Left main coronary artery stenosis.• Moderate stenotic valvular heart disease.• Electrolyte abnormalities.• Severe arterial hypertension.• Tachyarrhythmia or bradyarrhythmia.• Obstructive cardiomyopathy or outflow obstruction.• Mental or physical inability to perform the test.• High-degree A-V block

IV. Qualifications to Perform & Interpret the Test²:

- The ACP/ACC/AHA Statement on Clinical Competence in Stress Testing recommends that resident training for certification of competence in stress testing include four week’s training, during which the resident participates in at least 50 stress tests.
- Physicians without formal training who have had ≥ 3 years experience & ≥ 150 stress tests may qualify if they have mastered the cognitive skills shown in Table 4.
- It is recommended that a physician perform ≥ 25 tests yearly to maintain proficiency.
- These recommendations pertain only to EKG monitored exercise stress testing in adults. They do not include qualifications required to perform pharmacological stress testing, those required to perform stress echocardiography, those required for performing or interpreting radionuclide cardiac imaging studies, or stress testing in pediatric populations. Those qualifications are discussed in the current ACP/ACC/AHA Competence Statement².

Table 4: Cognitive Skills Required for EST²:

<p>I. Skills Required to supervise the test:</p> <ul style="list-style-type: none"> • Know the indications for the test • Knowledge of alternative physiological CV tests • Know the contraindications & risks of the test • Know how to use the test for risk assessment • Recognize & treat test complications • Currently ACLS certified • Know various exercise protocols & indications for each. • Understand the normal hemodynamic response to exercise • Recognize & treat serious arrhythmias • Knowledge of CV drugs & their effects on exercise performance, hemodynamics & the EKG • Know how age & disease effect hemodynamic & EKG responses to exercise testing • Understand proper lead placement & skin preparation • Know the end points of testing & indications to stop the test <p>II. Skills Required to Interpret the Test:</p> <ul style="list-style-type: none"> • Understand sensitivity, specificity & clinical accuracy in different patient populations • Know how to apply Bayes theorem to interpret test results • Know how hyperventilation, ischemia, hypertrophy, drugs & conduction or electrolyte abnormalities effect the EKG • Know the conditions & situations likely to cause false positive, false negative or indeterminate results • Know the prognostic value of exercise testing • Knowledge of alternative & supplemental diagnostic procedures to exercise testing and when to use them • Understand METS & how to use them to estimate exercise intensity in different types of exercise

V. Selecting the Correct Testing Protocol:

- When testing a younger reasonably fit patient it is conventional in the US to use the Bruce Treadmill Protocol, which is described in Table 5. In elderly or orthopedically impaired patients, the Modified Bruce or the Naughton protocols shown in Tables 6 & 7 may be more appropriate. Many other exercise protocols are also available.

Table 5: Bruce Protocol					Table 6: Modified Bruce Protocol					Table 7: Naughton Protocol				
Stage	Time	Speed	Elevation	METS	Stage	Time	Speed	Elevation	METS	Stage	Time	Speed	Elevation	METS
1	3	1.7	10%	3	1	3	1.7	0%	1.7	1	2	2.0	0%	1
2	3	2.5	12%	7	2	3	1.7	5%	2.8	2	2	2.0	3.5%	2
3	3	3.4	14%	10	3	3	1.7	10%	5.4	3	2	2.0	7.0%	3
4	3	4.2	16%	13	4	3	2.5	12%	7	4	2	2.0	10.5%	4
5	3	5.0	18%	16	5	3	3.4	14%	10	5	2	2.0	14.0%	5
6	3	5.5	20%	19	6	3	4.2	16%	13	6	2	2.5	14.0%	6
7	3	6.0	22%	22	7	3	5.0	18%	17	7	2	2.5	17.5%	7

- Exercise capacity is one of the major determinates of CV risk. It substantially effects the interpretation of a positive stress test. The unit of measurement of energy expenditure is the **MET (Metabolic EquivalentT)**. One MET is the energy expenditure per minute, of a healthy resting, 45 year old 70 kg male (equivalent to a VO₂ of 3.5mL/kg/minute). The energy expended each minutes by the end of each stage of the EST has been empirically measured³ & is expressed in METS. Expression in METS of the energy-per-minute attained at the end of each stage of different EST protocols permits comparison of EST performances no matter which exercise protocol is used. Thus, a post-MI patient who cannot exercise to 5 METS has a poor prognosis no matter which protocol is used or whether or not the ST segments become depressed.
- In patients who are too physically impaired to ambulate, a pharmacologically induced imaging study is the test of choice.

- Patients with baseline ST segment changes that prevent detection of ischemia-induced ST-segment changes are inappropriate for EKG-treadmill testing & should be tested with a cardiac imaging study (eg thallium, stress-ECHO, ect.) either exercise or pharmacologically induced. These conditions include²:
 - Complete left bundle branch block
 - Preexcitation (Wolff-Parkinson-White) Syndrome
 - 1mm or greater ST-segment depression on the baseline EKG.
 - Electronically paced ventricular rhythm

VI. Performing the Test^{1, 2}:

- Exercise stress testing should be performed in a setting in which emergency IV equipment and medications and defibrillation equipment is immediately available.
- A physician trained in ACLS should supervise the test and should remain in the immediate vicinity in case of emergency.
- The examiner's job is to encourage the patient while observing continuously for indications of physical distress or abnormal BP or pulse response, & observing the monitor for rhythm deterioration, ST segment elevation ≥ 1 mm or ST-segment depression greater than 2mm.
- Younger patients should not grip the handrail as this may reduce energy expenditure up to 20%. Older patients who pose fall risks & might best be allowed to rest their hands on the rail.
- The machine's computer portrays a continuous signal-averaged image of the V₅ lead compared with the V₅ baseline. Should the ST segment in another lead decrease below 1mm, that lead will be portrayed instead of V₅. Real-time images of leads V₁, V₅ & lead II are portrayed alongside their baseline images.
- A "criteria met" message appears on the monitor when the ST segment in any lead (except AVR or V₁) becomes depressed by 1mm or more.

Table 8: Indications for Terminating the Test¹

Absolute Indications to stop the test:

- Evidence of ischemia & > 10 mm drop in systolic BP.
- Moderate to severe angina.
- \uparrow CNS symptoms (eg. ataxia, dizziness, presyncope).
- Cyanosis or pallor.
- BP or EKG monitoring difficulties.
- Patient's desire to stop.
- Sustained ventricular tachycardia.
- ≥ 1 mm ST segment elevation in a non-Q wave lead other than V₁ or AVR.

Relative Indications to stop the test:

- \downarrow in systolic BP ≥ 10 mm Hg without ischemia.
- ST depression ≥ 2 mm or marked axis shift.
- Multifocal PVCs, PVC triplets, SVT, heart block or bradyarrhythmias.
- Fatigue, SOB, wheezing, leg cramps or claudication.
- LBBB or IVCD indistinguishable from V-tach.
- Increasing chest pain.
- Hypertensive response (systolic >250 , diastolic >115).

VII. Interpreting the Test¹:

- **Criteria for a Positive Test:** An **abnormal (ischemic) test** is one in which there is ≥ 1 mm of horizontal or downsloping ST-segment depression ≥ 80 milliseconds after the J-point (as compared to the level of the PQ interval)¹.
- **Significance of Exercise Induced ST-Segment Elevation:** Early repolarization on the baseline EKG is a common and benign cause of ST segment elevation so ST changes with exercise are always read from the patient's baseline. Exercise induced ST segment elevation indicates **transmural ischemia** induced by spasm of the artery serving the territory indicated by the location of the ST segment elevation. It occurs rarely ($\pm 0.1\%$). It indicates immediate termination off the test¹.
- The average **sensitivity and specificity** of the EST for CAD is 68% & 77% respectively¹. The likelihood that an individual patient will have CAD is a product of the test's sensitivity & specificity and the pre-test probability of CAD.
- Although there are many risk factors for coronary artery disease, the strongest predictors are age, the presence or absence of chest pain and the quality of the chest pain if present. The **pre-test probability** of CAD can be estimated from Table 9:

Table: 9 Pre-test Probability of CAD (in %) by Age, Sex & Presenting Complaint⁴:

Age	Asymptomatic		Nonanginal Chest Pain		Atypical Angina		Typical Angina	
	Male	Female	Male	Female	Male	Female	Male	Female
30-39	1.9%	0.3%	5.2%	0.8%	21.9%	4.3%	69.7%	25.8%
40-49	5.5%	1.0%	14.1%	2.8%	46.1%	13.3%	87.3%	55.2%
50-59	9.7%	3.2%	21.5%	8.44%	58.0%	32.4%	92.0%	79.4%
60-69	12.3%	7.5%	28.1%	18.6%	67.1%	54.4%	94.3%	90.6%

- **Definitions:** “Typical angina” is defined as consisting of three components^{1,5}:
 - Substernal chest pain or discomfort
 - Provoked by exertion or emotional stress
 - Relieved by rest or nitroglycerine
 “Atypical angina” is defined as chest pain/discomfort lacking one of the components.
- If your patient is a 39 year old man with **typical angina** with a **positive** stress test the probability that your patient actually has CAD is the **post-test probability**, it is calculated as follows:

	Disease Positive	Disease Negative	
# Test Positive.	68% 0.68 x 69.7=47.4	23% 0.23x30.3=7	47.4 + 7 = 54.4 47.4/54.4 = 87.1%
# Test Negative	N/A	N/A	N/A
Prevalence	69.7 are disease positive	30.3 are disease negative	100 (total population)

- If the same man had a **negative** stress test, this is how you calculate the probability that he does **not** have CAD (this is the **post-test probability**):

	Disease Positive	Disease Negative	
# Test Positive.	N/A	N/A	N/A
# Test Negative	32% 0.32 x 69.7 = 22.3	77% 0.77x30.3=23.3	22.3 + 23.3 = 45.6 23.3/45.6 = 51.1%
Prevalence	69.7 are disease positive	30.3 are disease negative	100 (total population)

- Since the probability that man has CAD remains greater than 50%, you will want to determine his mortality risk. If the risk is sufficiently high, the next step would be an imaging study.

VIII. Determining Mortality Risk:

- The prognostic implications of a positive stress vary dramatically depending on the individual patient’s exercise capacity. ST segment depression ≥ 1 mm that occurs in the first 2 stages of the Bruce Protocol indicates high mortality risk while patients who can exercise to stage 4 have a good prognosis regardless of the ST segment response^{1,6}. The **Duke treadmill exercise score**⁷ is a prognostic measure that combines measures of exercise performance with ischemia induced ST changes. It appears valid in both women and men¹ as well as those with or without known CAD⁷. “Exercise time” is the time in minutes on the Bruce protocol. ST depression is expressed in millimeters. The “Angina Index” is scored: 0 if no chest pain occurs, 1 if chest pain occurs, & 2 if chest pain is severe enough to stop the test:

Duke Treadmill Score = Exercise time – (5 x ST-segment depression) – (4 x Angina Index)

Low Risk ≥ 5 (Less than 0.5% annual CV mortality)

Intermediate Risk = +4 to –10 (CV mortality 0.5% to 5% per year)

High Risk ≤ -11 (annual CV mortality $\geq 5\%$)

- **Chronotropic Incompetence**⁸ is an established predictor of CV mortality. Chronotropic incompetence is present if less than 80% of the patient’s heart rate reserve is used at peak exercise. Heart rate reserve is calculated as: 220 – age – resting heart rate. Chronotropic

incompetence is expected among patients taking β -blockers & is not a valid predictor of CV mortality in that group.

- **Heart Rate Recovery⁹** after exercise is another independent predictor of CV mortality. Heart rate recovery is the difference in heart rate at peak exercise and the heart rate one minute after peak exercise, as measured during the 2-minute “cool-down” period when the treadmill is set at 1.5 mph & a 2.5% grade. Heart rate should slow by at least 12 beats/minute. Slower recovery indicates failure of parasympathetic activation (unless the patient is taking a β -blocker) and is a third independent predictor of CV mortality. Heart rate recovery is similar in magnitude to the Duke exercise treadmill score as a predictor of mortality. When both are abnormal the predictive values for CV mortality are additive.
- Among **post-MI** patients, **inability to achieve 5 METS** energy expenditure is a poor prognostic sign. **Failure to increase BP by 30mmHg** from baseline & **failure to maintain systolic BP above 110mmHg** are also predictors of adverse outcomes.
- The EKG-EST has a sensitivity of 84% and a specificity of 70% for CAD in **elderly patients** over the age of 75. ST segment depression alone does not predict high event rates in this population group unless accompanied by exercise intolerance < 5 METS, chronotropic incompetence, failure to maintain systolic BP > 110 or failure to elevate the systolic BP by at least 30mmHg from baseline. A predictive scoring system for ambulatory men averaging age 59 who were referred for EST to the Long Beach VA Hospital¹⁰ performed somewhat better than the Duke Score in that population group.

VA Treadmill Score = 5 x (Digoxin/CHF Score*) + mm ST depression + (SBP Score** – METs)

*Digoxin/CHF Score: yes = 1; no = 0.

**SBP Score: > 40mmHg increase in standing systolic BP = 0.

31 – 40mmHg increase = 1

21 – 31mmHg increase = 2

11 – 21mmHg increase = 3

0 – 11 mmHg increase = 4

Reduction below standing preexercise systolic BP = 5.

Low risk score <-2: (< 2% annual CV mortality).

Intermediate risk score = -2 to 2: (7% annual CV mortality).

High risk score \geq 2: (annual mortality > 15%)

IX. Pharmacological Testing^{2, 11, 12, 13}:

- The exercise stress test is the test of choice for patients who can exercise to 85% of their calculated maximum heart rate, because of the valuable contribution of exercise tolerance to the meaning of the ST ischemic response. Those who are orthopedically or medically disabled may be tested using one of two classes of pharmacological agents combined with an imaging study:
 - **β -agonists (Dobutamine)** stimulate contractility, BP & heart rate thereby increasing blood flow in healthy arteries and evoking ischemia in those obstructed. Dobutamine is infused IV at 5 μ g/kg/minute & increased by 5 μ g/kg/minute every 3 minutes to a maximum dose of 40 to 50 μ g/kg/minute or an endpoint or side effect occurs. Atropine 0.25mg can be given IV every 2 to 3 minutes up to a maximum dose of 1 to 2 mg if the maximum dose of dobutamine doesn't produce an adequate heart rate. Contraindications to dobutamine stimulation are shown in Table 10. Results obtained with dobutamine are more reliable than those obtained with the vasodilators.
 - **Vasodilators (Adenosine & Dipyridamole)** work by dilating the healthy coronary arteries thereby causing a relative local subendocardial ischemic “steal syndrome”. The usual dose of dipyridamole is 0.56mg/kg over 4 minutes when thallium imaging is planned. Somewhat higher doses (0.84mg/kg over 8 minutes) may be used during stress echocardiography. Contraindications to vasodilators are shown in Table 10. The effects of these drugs may be reversed with theophylline. Imaging of patients on antianginal drugs or preexisting left bundle branch block, seem less affected when vasodilators are used¹³.

Table 10: Contraindications to Pharmacological Stress Testing¹¹:

	Absolute	Relative
Dobutamine	Symptomatic aortic aneurysm Uncontrolled ventricular tachycardia	Uncontrolled atrial fibrillation Uncontrolled hypertension Recent ventricular arrhythmias
Dipyridamole or Adenosine	Active bronchospasm Current treatment with theophylline High degree AV block without pacemaker Hypotension	Bradycardia First degree AV block History of asthma Symptomatic carotid artery stenosis

X. Alternative Cardiovascular Stress Tests:

- Stress Echocardiography** adds valuable information to the exercise EKG treadmill test: (1) resting & exercise ejection fraction, (2) global & local wall abnormalities, (3) wall thickness, & (4) valve structure & function. The test is therefore valuable in localizing the site of ischemia, in diagnosing multivessel & left main coronary artery disease, & assessing global cardiac function. The overall average sensitivity is 80% for obstructive coronary artery disease $\geq 50\%$. The specificity is 86%¹². The specific advantages of stress ECHO over perfusion imaging are lower cost, immediate availability of results, & availability of valve & wall structure & function¹¹. The downside is that the test is heavily operator dependent so its quality varies among institutions. Combined with the data from exercise treadmill testing, it is probably the “second level” test of choice of the future. As with the radioisotope perfusion tests, echocardiography may be performed after pharmacological stimulation.
- Radioisotope Perfusion Imaging’s** big advantage is **Thallium-201’s** availability in most institutions, & the ease of interpretation of its results. Perfusion imaging may use either planar or single-photon emission computed tomography (SPECT). SPECT produces a 3 dimensional image & is therefore better at localizing underperfused vascular territories, diagnosing LAD, left circumflex & multivessel disease. Average sensitivity and specificity for the diagnosis of CAD are 83% & 88% by visual analysis of planar views¹³. Quantitative analysis of SPECT imaging improves sensitivity to 90% but decreased specificity to 70%. **Technetium-99m (Tc-99m) sestamibi** is a newer isotope available in many centers. It has about the same sensitivity & specificity as Tl-201 for the diagnosis of CAD¹³. Its advantages include slower diffusion of the isotope after IV administration, which allows scanning to occur up to 4 hours after administration, better imaging in obese patients and through breast artifact in women with heavy breasts. Sestamibi’s big advantage however is the clarity of the image. Its major disadvantage is that its slow redistribution impairs its ability to identify seriously ischemic myocardium. Thus sestamibi underestimates viable myocardium in CAD patients compared with thallium¹³. EKG gated acquisition of SPECT perfusion tomograms now make the evaluation of wall motion abnormalities & ventricular ejection fraction possible with either isotope¹⁶.
- EST with ventilatory gas analysis:** One of the problems with the exercise treadmill is that the METs assigned to each stage of the EST protocols are rather crude estimates of energy expenditure by ventilatory gas exchange analysis. METs are “close enough” unless you’re trying to differentiate COPD from CHF as the cause of dyspnea, or you’re assessing someone for possible heart transplant. In these cases direct measurement of exercise capacity is required^{1, 14}. Ventilatory gas exchange analysis is performed at 10-second intervals during EST. Oxygen uptake (VO_2), carbon dioxide production (VCO_2), minute ventilation (V_E) are measured & expressed in mL/kg/minute. The ventilatory/aerobic threshold (VAT) is noted. The VAT is the point at which V_E dramatically increases despite a linear increase in work rate¹. VO_2 is the best indicator of mortality. The 2-year life expectancy of a CHF patient whose exercise tolerance exceeds 14mL/kg/min is as favorable as post-transplant patients¹³; those with lower VO_2 ’s are not. Thus this VO_2 “cut-point” is useful in serially evaluating transplant candidates.

Expiratory gases measured during EST can^{2, 15}:

- Provide the best estimate of functional capacity (eg. the “true” maximal O₂ uptake).
- Grade the severity of cardiac impairment & CHF.
- Objectively assess the response to therapy.
- Track disease progression that impacts exercise tolerance.
- Differentiate between cardiac & pulmonary limitations

When energy expenditure is directly measured, the discrete stages of the conventional exercise protocols have less meaning. Hence there are advantages to using **ramp testing** instead of a staged protocol. Ramp testing is said to be better tolerated & to improve exercise tolerance, resulting in elicitation of higher VO₂'s & higher sensitivity for CAD¹⁴.

XI. Future Applications of EST:

- The principle application for EST in the past has been to identify patients with obstructive CAD who are appropriate candidates for revascularization. Perhaps the principle use of EST in the future will be in the assessment of prognosis so as to direct therapy with the ACE inhibitors, statin drugs, β-blockers, & antithrombotic agents to patients in high-risk population groups¹⁴.

XII. Bibliography:

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