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CHAIR OF THE FACULTY THERAPY

**FACULTY THERAPY**

(Methodics work out for foreign students, studying the course of faculty therapy)

Part 1

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**ANGINA PECTORIS**

Synonyms and related keywords: coronary artery disease, myocardial ischemia, chest pain

Angina pectoris is the result of myocardial ischemia caused by an imbalance between myocardial blood supply and oxygen demand. Angina is a common presenting symptom (typically, chest pain) among patients with coronary artery disease. A comprehensive approach to diagnosis and to medical management of angina pectoris is an integral part of the daily responsibilities of physicians.

**Frequency**

Approximately 6.3 million Americans are estimated to experience angina. An estimated 350,000 new cases of angina occur every year. Each year, 1.1 million new and recurrent cases of an acute coronary event occur in this country, of which more than 40% are fatal.

Coronary artery disease is the single most common cause of death in the United States, more than half of those who die suddenly from coronary artery disease have no previous symptoms.

The prevalence of angina pectoris increases with age.

Angina pectoris is more often the presenting symptom of coronary artery disease in women than in men. Women have a slightly higher rate of mortality from coronary artery disease compared with men, in part because of an older age at presentation and a frequent lack of classic anginal symptoms. The estimated age-adjusted prevalence of angina is greater in women than in men.

**Causes**

* Decrease in myocardial blood supply due to increased coronary resistance in large and small coronary arteries
* Significant coronary atherosclerotic lesion in the large epicardial coronary arteries (ie, conductive vessels) with at least a 50% reduction in arterial diameter
* Coronary spasm (ie, Prinzmetal angina)
* Abnormal constriction or deficient endothelial-dependent relaxation of resistant vessels associated with diffuse vascular disease (ie, microvascular angina)
* Syndrome X

**Risk factors**

***Major risk factors for atherosclerosis:***

a family history of premature coronary artery disease,

cigarette smoking,

diabetes mellitus,

hypercholesterolemia,

systemic hypertension.

Other risk factors: These include LV hypertrophy, obesity, and elevated serum levels of homocysteine, lipoprotein (a), plasminogen activator inhibitor, fibrinogen, serum triglycerides, or low high-density lipoprotein (HDL).

**Pathophysiology**

Myocardial ischemia develops when coronary blood flow becomes inadequate to meet myocardial oxygen demand. This causes myocardial cells to switch from aerobic to anaerobic metabolism, with a progressive impairment of metabolic, mechanical, and electrical functions. Angina pectoris is the most common clinical manifestation of myocardial ischemia. It is caused by chemical and mechanical stimulation of sensory afferent nerve endings in the coronary vessels and myocardium. These nerve fibers extend from the first to fourth thoracic spinal nerves, ascending via the spinal cord to the thalamus, and from there to the cerebral cortex.

Recent studies have shown that adenosine may be the main chemical mediator of anginal pain. During ischemia, ATP is degraded to adenosine, which, after diffusion to the extracellular space, causes arteriolar dilation and anginal pain. Adenosine induces angina mainly by stimulating the A1 receptors in cardiac afferent nerve endings.

Heart rate, myocardial inotropic state, and myocardial wall tension are the major determinants of myocardial metabolic activity and myocardial oxygen demand.

Increases in the heart rate and myocardial contractile state result in increased myocardial oxygen demand. Increases in both afterload (ie, aortic pressure) and preload (ie, ventricular end-diastolic volume) result in a proportional elevation of myocardial wall tension and, therefore, increased myocardial oxygen demand. Oxygen supply to any organ system is determined by blood flow and oxygen extraction. Because the resting coronary venous oxygen saturation is already at a relatively low level (approximately 30%), the myocardium has a limited ability to increase its oxygen extraction during episodes of increased demand. Thus, an increase in myocardial oxygen demand (eg, during exercise) must be met by a proportional increase in coronary blood flow.

Myocardial ischemia can result from

1) a reduction of coronary blood flow caused by fixed and/or dynamic epicardial coronary artery (ie, conductive vessel) stenosis,

2) abnormal constriction or deficient relaxation of coronary microcirculation (ie, resistance vessels),

3) reduced oxygen-carrying capacity of the blood.

**Atherosclerosis** is the most common cause of epicardial coronary artery stenosis and, hence, angina pectoris.

Patients with a fixed coronary atherosclerotic lesion of at least 50% show myocardial ischemia during increased myocardial metabolic demand as the result of a significant reduction in CFR. These patients are not able to increase their coronary blood flow during stress to match the increased myocardial metabolic demand, thus they experience angina.

Fixed atherosclerotic lesions of at least 90% almost completely abolish the flow reserve; patients with these lesions may experience angina at rest.

**Coronary spasm** can also reduce CFR significantly by causing dynamic stenosis of coronary arteries.

Prinzmetal angina is defined as resting angina associated with ST-segment elevation caused by focal coronary artery spasm. Although most patients with Prinzmetal angina have underlying fixed coronary lesions, some **have angiographically normal** **coronary arteries**. Several mechanisms have been proposed for Prinzmetal angina:

focal deficiency of nitric oxide production,

hyperinsulinemia,

low intracellular magnesium levels,

smoking cigarettes,

using cocaine.

**The microvascular angina**

Approximately 30% of patients with chest pain referred for cardiac catheterization have normal or minimal atherosclerosis of coronary arteries. A subset of these patients demonstrates reduced CFR that is believed to be caused by functional and structural alterations of small coronary arteries and arterioles (ie, resistance vessels).

Under normal conditions, resistance vessels are responsible for as much as 95% of coronary artery resistance, with the remaining 5% being from epicardial coronary arteries (ie, conductive vessels).

The former is not visualized during regular coronary catheterization. Angina due to dysfunction of small coronary arteries and arterioles is called **microvascular angina**. Several diseases, such as diabetes mellitus, hypertension, and systemic collagen vascular diseases (eg, systemic lupus erythematosus, polyarteritis nodosa), are believed to cause microvascular abnormalities with subsequent reduction in CFR.

**Types of Angina**

**Stable.** Intensity, character, and frequency of episodes can be predicted, and angina occurs in response to a known amount of exercise or other stress.

**Unstable.** Intensity, frequency, or duration of episodes is changed and can no longer be predicted. Pain is precipitated by less exercise or is of longer duration. This includes angina at rest and new-onset angina.

**Variant.** Pain, which may occur at rest, is secondary to vasospasm of coronary arteries.

**The Canadian Cardiovascular Society grading scale is used for classification of angina severity, as follows:**

Class I - Angina only during strenuous or prolonged physical activity

Class II - Slight limitation, with angina only during vigorous physical activity

Class III - Symptoms with everyday living activities, ie, moderate limitation

Class IV - Inability to perform any activity without angina or angina at rest, ie, severe limitation

**The New York Heart Association classification is also used to quantify the functional limitation imposed by patients' symptoms, as follows:**

Class I - No limitation of physical activity (Ordinary physical activity does not cause symptoms.)

Class II - Slight limitation of physical activity (Ordinary physical activity does cause symptoms.)

Class III - Moderate limitation of activity (Patient is comfortable at rest, but less than ordinary activities cause symptoms.)

Class IV - Unable to perform any physical activity without discomfort, therefore severe limitation (Patient may be symptomatic even at rest.)

Unstable angina is defined as new-onset angina (ie, within 2 mo of initial presentation) of at least class III severity, significant recent increase in frequency and severity of angina, or angina at rest.

**CLINICAL**

**History**

Ask patients about the frequency of angina, severity of pain, and number of nitroglycerin pills used during angina episodes.

* Most patients with angina pectoris report of retrosternal chest discomfort rather than frank pain. The former is usually described as a pressure, heaviness, squeezing, burning, or choking sensation.
* Classically described as substernal chest pressure or heaviness radiating to the left shoulder and arm, neck, or jaw, associated with nausea, diaphoresis, and shortness of breath.
* Typically, angina is precipitated by exertion, eating, exposure to cold, or emotional stress. It lasts for approximately 1-5 minutes and is relieved by rest or nitroglycerin. Sometime the pain may lasts 2 to 10 minutes and rarely 30 minutes. Chest pain lasting only a few seconds is not usually angina pectoris.
* Not all patients experience chest pain. Some present with only neck, the mandible (jaw), ear, arm, or epigastric discomfort. **Atypical presentations may include right arm pain.**
* Other symptoms, such as shortness of breath or severe weakness, may represent anginal equivalent symptoms.
* A patient may present to the emergency department because of a change in pattern or severity of symptoms. A new case of angina is more difficult to diagnose because symptoms are often vague and similar to those caused by other conditions (eg, indigestion, anxiety). **In the elderly, symptoms such as confusion, pallor, fatigue or dyspnea may be suggestive of ischemia. Ambulatory ECG monitoring reveals that at least 25% of ischemic episodes are silent even in patients with a history of typical angina.**

Patients may have no pain and may only complain of episodic shortness of breath, weakness, lightheadedness, diaphoresis, or nausea and vomiting.

Patients may complain of the following:

* Palpitations
* Pain, which is usually described as pressure, squeezing, or a burning sensation across the precordium and may radiate to neck, shoulder, jaw, back, upper abdomen, or either arm
* Exertional dyspnea that resolves with pain or rest
* Diaphoresis from sympathetic discharge
* Nausea from vagal stimulation
* Decreased exercise tolerance
* Patients with diabetes and elderly patients are more likely to have atypical presentations and offer only vague complaints, such as weakness, lightheadedness, and nausea.

**Stable angina**

* Involves episodic pain lasting 5-15 minutes
* Provoked by exertion
* Relieved by rest or nitroglycerin

**Unstable angina**

Patients have increased risk for adverse cardiac events, such as MI or death. Three clinically distinct forms exist, as follows:

* New-onset exertional angina
* Angina of increasing frequency or duration or refractory to nitroglycerin
* Angina at rest
* Variant angina (Prinzmetal angina)
* Occurs primarily at rest
* Triggered by smoking
* Thought to be due to coronary vasospasm

**Physical**

For most patients with stable angina, physical examination findings are normal. Diagnosing secondary causes of angina, such as aortic stenosis, is important.

A positive Levine sign (characterized by the patient's fist clenched over the sternum when describing the discomfort) is suggestive of angina pectoris.

Look for physical signs of abnormal lipid metabolism (eg, xanthelasma, xanthoma) or of diffuse atherosclerosis (eg, absence or diminished peripheral pulses, increased light reflexes or arteriovenous nicking upon ophthalmic examination, carotid bruit).

Examination of patients during the angina attack may be more helpful. Useful physical findings include third and/or fourth heart sounds due to LV systolic and/or diastolic dysfunction and mitral regurgitation secondary to papillary muscle dysfunction.

Pain produced by chest wall pressure is usually of chest wall origin.

**Imaging Studies**

**ECG** is useful for evaluating persons with angina pectoris; however, findings are variable among patients.

Approximately 50% of patients with angina pectoris have normal findings after a resting ECG.

During an attack of angina pectoris, 50% of patients with normal findings after resting ECG show abnormalities.

* **A 1-mm or greater depression of the ST segment below the baseline, measured 80 milliseconds from the J point, is the most characteristic change.**
* Reversible ST-segment elevation occurs with Prinzmetal angina.

Some patients with coronary artery disease may show pseudonormalization of the resting ECG ST-T–wave abnormalities during episodes of chest pain.

* Exercise with ECG monitoring alone is the initial procedure of choice in patients without baseline ST-segment abnormalities or in whom anatomic localization of ischemia is not a consideration.

Horizontal or down-sloping ST-segment depression of at least 1 mm, measured 80 milliseconds from the J point, is considered the characteristic ischemic response.

ST-segment depression of more than 2 mm at a low workload or that persists for more than 5 minutes after termination of exercise and a failure of blood pressure to rise or an actual drop in blood pressure are signs of severe ischemic heart disease and a poor prognosis.

* Withhold beta-blockers for approximately 48 hours before the stress test, whenever possible. Patients on digoxin and those with LV hypertrophy with repolarization abnormalities more often show positive results. Exercise stress tests have lower sensitivity and specificity in women and in patients with left bundle-branch block.
* Pharmacologic agents (eg, dobutamine, dipyridamole, adenosine) can be used in patients who are unable to exercise.
* Ambulatory ECG monitoring can be used for diagnostic purposes in patients with chest pain suggestive of Prinzmetal angina but is primarily used to evaluate the frequency of silent ischemia. Silent ischemia has been shown to be an independent predictor of mortality in patients with angina pectoris.
* Chest radiograph findings are usually normal in patients with angina pectoris. However, they may show cardiomegaly in patients with previous MI, ischemic cardiomyopathy, pericardial effusion, or acute pulmonary edema. Calcification of coronary arteries frequently correlates with major coronary artery disease.
* Graded exercise stress testing is the most widely used test for the evaluation of patients presenting with chest pain. In patients with established stable angina pectoris, it also can provide prognostic information about the extent of disease.
* Stress echocardiography can be used to evaluate segmental wall motion during exercise. It detects changes in regional wall motion that occur during myocardial ischemia. Normal myocardium becomes hyperdynamic during exercise; ischemic segments become hypokinetic or akinetic.
* Thallium Tl 201 and technetium Tc 99m sestamibi are the most frequently used myocardial perfusion scintigraphy tests. These tests are especially useful in patients with baseline ECG abnormalities, to localize the region of ischemia, and as prognostic indicators. The presence of increased lung uptake upon thallium imaging is associated with a poor prognosis. Increased lung uptake, together with poststress dilation of the LV and multiple perfusion defects, is suggestive of either left main coronary artery disease or severe 3-vessel disease. The number of affected myocardial segments is predictive of long-term survival. Smaller perfusion defects are usually associated with peripheral coronary artery lesions, which are associated with a better prognosis. The absence of perfusion defects even in the presence of symptoms indicates an excellent prognosis.

**Procedures**

1. Selective coronary angiography is the definitive diagnostic test for evaluating the anatomic extent and severity of coronary artery disease.
2. In patients in whom Prinzmetal angina is suggested, provocative testing with ergonovine maleate during coronary angiography may be useful.
3. Intra-aortic balloon counterpulsation can be used in patients who continue to have unstable angina pectoris despite maximal medical treatment. This procedure should be followed promptly by coronary angiography with possible coronary revascularization.

**TREATMENT**

***General measures***. Treat risk factors, including smoking, hypertension, diabetes mellitus, obesity, and hyperlipidemia.

Smoking cessation results in a significant reduction of acute adverse effects on the heart and may reverse, or at least slow, atherosclerosis. Strongly encourage patients to quit smoking, and take an active role in helping them to achieve this goal.

The level of activity that aggravates anginal symptoms is different for each patient. However, most patients with stable angina can avoid symptoms during daily activities simply by reducing the speed of activity.

Exercise training results in improvement of symptoms, increase in the threshold of ischemia, and improvement of patients' sense of well-being. However, before enrolling a patient in an exercise-training program, perform an exercise tolerance test to establish the safety of such a program.

***Medical Care***. The main goals of treatment in angina pectoris are to relieve the symptoms, slow the progression of disease, and reduce the possibility of future events, especially MI and premature death.

* **Sublingual nitroglycerin** has been the mainstay of treatment for angina pectoris. Sublingual nitroglycerin can be used for acute relief of angina and prophylactically before activities that may precipitate angina. No evidence indicates that long-acting nitrates improve survival in patients with coronary artery disease.
* Several clinical trials have shown that in patients with established coronary artery disease, reduction of low-density lipoprotein (LDL) with a beta-hydroxy-beta-methylglutaryl coenzyme A reductase inhibitor (ie, **statin)** is associated with significant reductions in both mortality rate and major cardiac events.
* Antiplatelet agents - Prevent thrombus formation by inhibiting platelet aggregation. Aspirin is proven beneficial in primary and secondary prevention of coronary artery disease. In patients with aspirin intolerance, use clopidogrel.

Clopidogrel is also used in combination with aspirin after coronary stent placement. Recently, clopidogrel use in addition to aspirin has been shown to be significantly superior to aspirin alone in patients with acute coronary syndrome without ST-segment elevation MI.

Consider enteric-coated **aspirin** at a dose of 80-325 mg/d for all patients with stable angina who have no contraindications to its use. Adult dose of Clopidogrel - 75 mg PO qd.

* **Beta-blockers** are also used for symptomatic relief of angina and prevention of ischemic events. They work by reducing myocardial oxygen demand and by decreasing the heart rate and myocardial contractility. Beta-blockers have been shown to reduce the rates of mortality and morbidity following acute MI.
* Long-acting heart rate–slowing **calcium channel blockers** can be used to control anginal symptoms in patients with a contraindication to beta-blockers and in those in whom symptomatic relief of angina cannot be achieved with the use of beta-blockers, nitrates, or both. **Avoid short-acting dihydropyridine calcium channel blockers because they have been shown to increase the risk of adverse cardiac events.**
* Anginal symptoms in patients with Prinzmetal angina can be treated with **calcium channel blockers with or without nitrates**. In one study, supplemental vitamin E added to a calcium channel blocker significantly reduced anginal symptoms among such patients.
* **Surgical Care -** revascularization therapy (coronary revascularization - percutaneous transluminal coronary angioplasty, with or without coronary stenting, coronary artery bypass grafting, laser transmyocardial revascularization).

**Prognosis**

Important prognostic indicators in patients with angina pectoris include LV function, severity and location of atherosclerotic lesions, and response of symptoms to medical treatment.

LV function is the strongest predictor of long-term survival. Elevated LV end-diastolic pressure and volume along with reduced LV ejection fraction (<40%) are poor prognostic signs.

Critical lesions of left main and proximal left anterior descending coronary arteries are associated with a greater risk. Mortality rates are also directly associated with the number of epicardial arteries involved.

Unstable angina, recent MI, or both is a sign of atherosclerotic plaque instability, which is a strong predictor of increased risk of short-term coronary events.

A number of signs during noninvasive testing are predictive of a higher risk of coronary events, including ST-segment depression of more than 2 mm at a low workload, ST-segment depression that persists for more than 5 minutes after termination of exercise, and failure of blood pressure to rise or an actual drop in blood pressure.

Patients who continue to smoke after an MI have a 22-47% increased risk of reinfarction and death.

In general, Prinzmetal angina and syndrome X are associated with excellent long-term prognoses.

**TREADMILL AND PHARMACOLOGIC STRESS TESTING**

Exercise testing is a cardiovascular stress test using treadmill or bicycle exercise with ECG and blood pressure monitoring. Pharmacologic stress testing, established after exercise testing, is a diagnostic procedure in which cardiovascular stress induced by pharmacologic agents is demonstrated in patients with decreased functional capacity or in patients who cannot exercise. Pharmacologic stress testing is used in combination with imaging modalities such as radionuclide imaging and echocardiography.

Exercise stress testing, which is now widely available at a relatively low cost, is currently used most frequently to estimate prognosis and determine functional capacity, to assess the probability and extent of coronary disease, and to assess the effects of therapy. Ancillary techniques, such as metabolic gas analysis, radionuclide imaging, and echocardiography, can provide further information that may be needed in selected patients, such as those with moderate or prior risk.

**Exercise physiology**

The initiation of dynamic exercise results in increases in the ventricular heart rate, stroke volume, and cardiac output due to vagal withdrawal and sympathetic stimulation. Also, alveolar ventilation and venous return increase as a result of sympathetic vasoconstriction. The overall hemodynamic response depends on the amount of muscle mass involved, exercise efficiency, conditioning, and exercise intensity.

In the initial phases of exercise in the upright position, cardiac output is increased by an augmentation in stroke volume mediated through the use of the Frank-Starling mechanism and heart rate. The increase in cardiac output in the later phases of exercise is due primarily to an increase in ventricular rate.

During strenuous exertion, sympathetic discharge is maximal and parasympathetic stimulation is withdrawn, resulting in autoregulation with generalized vasoconstriction, except in the vital organs (cerebral and coronary circulations).

Venous and arterial norepinephrine release from sympathetic postganglionic nerve endings is increased, and epinephrine levels are increased at peak exertion, resulting in an increase in ventricular contractility. As exercise progresses, skeletal muscle blood flow increases; oxygen extraction increases as much as 3-fold; peripheral resistance decreases; and systolic blood pressure (SBP), mean arterial pressure, and pulse pressure usually increase. Diastolic blood pressure (DBP) remains unchanged or may increase or decrease by approximately 10 mm Hg. The pulmonary vascular bed can accommodate as much as a 6-fold increase in cardiac output, with only modest increases in pulmonary arterial pressure, pulmonary capillary wedge pressure, and right atrial pressure; this is not a limiting determinant of peak exercise capacity in healthy subjects.

The maximum heart rate and cardiac output are decreased in older individuals, related in part to decreased beta-adrenergic responsiveness. Maximum heart rate can be calculated by subtracting the patient's age (y) from 220 (has a standard deviation of 10-12 beats per minute [bpm]). The age-predicted maximum heart rate is a useful measurement for safety reasons and as an estimate of the adequacy of the stress to evoke inducible ischemia. A patient who reaches 80% of the age-predicted maximum is considered to have a good test result, and an age-predicted maximum of 90% or better is considered excellent.

In the postexercise phase, hemodynamics return to baseline within minutes of discontinuing exercise. The return of vagal stimulation is an important cardiac deceleration mechanism after exercise and is more pronounced in well-trained athletes but blunted in patients with chronic congestive heart failure. Intense physical work or important cardiorespiratory impairment may interfere with achievement of a steady state, and an oxygen deficit occurs during exercise. The oxygen debt is the total oxygen uptake in excess of the resting oxygen uptake during the recovery period.

American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for exercise stress testing were revised in 1997 and were initially formed to create recommendations regarding the appropriate use of testing in the diagnosis, prognosis, and treatment of patients with known or probable cardiovascular disease.

Exercise testing is a well-established procedure that has been in widespread clinical use for decades, and, although it is generally a safe procedure, both myocardial infarction and death have been reported and can be expected to occur at a rate of 1 incident per 2500 tests. Therefore, use good clinical judgment when deciding which patients should undergo exercise testing.

When considering the use of exercise testing in individual patients, factors that are important in establishing good clinical outcomes include the quality, expertise, and experience of the professional and technical staff performing and interpreting the study to reduce observer error; the sensitivity, specificity, and accuracy of the technique to establish limitations of this procedure; and the cost and accuracy of the technique as compared with more expensive imaging procedures to establish the risk-to-benefit ratio, to determine the effect of positive or negative results on clinical decision making, and, lastly, to weigh the potential psychological benefits of patient reassurance.

**Contraindications to exercise stress testing**

The following contraindications are from the AHA/ACC guidelines published in 1997.

Absolute contraindications

* Acute myocardial infarction (within 2 d)
* Unstable angina not previously stabilized by medical therapy: Appropriate timing of tests depends on the level of risk of unstable angina as defined by the Agency for Health Care Policy and Research Unstable Angina Guidelines.
* Uncontrolled cardiac arrhythmias causing symptoms or hemodynamic compromise
* Symptomatic severe aortic stenosis
* Uncontrolled symptomatic heart failure
* Acute pulmonary embolus or pulmonary infarction
* Acute myocarditis or pericarditis
* Acute aortic dissection

Relative contraindications: Relative contraindications can be superseded if the benefits of exercise outweigh the risks.

* Left main coronary stenosis
* Moderate stenotic valvular heart disease
* Electrolyte abnormalities
* Severe arterial hypertension: In the absence of definite evidence, the committee suggests an SBP of greater than 200 mm Hg and/or a DBP of greater than 110 mm Hg.
* Tachyarrhythmias or bradyarrhythmias
* Hypertrophic cardiomyopathy and any other forms of outflow tract obstruction
* Mental or physical impairment leading to an inability to exercise adequately
* High-degree atrioventricular (AV) block

The vast majority of treadmill exercise testing is performed on adults with symptoms of known or probable ischemic heart disease. Candidates for exercise stress testing may have stable symptoms of chest pain, may be stabilized by medical therapy following symptoms of unstable chest pain, or may have already had a myocardial infarction or a vascularization procedure.

**Treadmill protocol**

Report exercise capacity in estimated metabolic equivalents (METs) of exercise. A MET refers to the resting volume oxygen consumption per minute (VO2) for a 70-kg, 40-year-old man. One MET is equivalent to 3.5 mL/min/kg of body weight. An example is the standard Bruce protocol, which starts at 1.7 mph and 10% grade (5 METs) with larger increments between stages than other protocols, such as the Naughton, Weber, and Asymptomatic Cardiac Ischemia Pilot (ACIP) study, which start at less than 2 METs at 2 mph and increase in 1- to 1.5-MET increments between stages. The Bruce protocol has 3-minute periods to allow achievement of a steady state before workload is increased.

Stage 1 is 1.7 mph at 10% grade (5 METs). Stage 2 is 2.5 mph at 12% grade (7 METs). Stage 3 is 3.4 mph at 14% grade (9 METs).

The modified Bruce protocol has two 3-minute warmup stages at 1.7 mph and 0% grade and 1.7 mph and 5% grade, and it is most often used in older individuals or those whose exercise capacity is limited by cardiac disease.

Other exercise protocols include **bicycle and arm ergometry**, both of which are used less often than treadmill stress testing in North America. The bicycle ergometer has the advantage of requiring less space than a treadmill. It is quieter, permits sensitive precordial measurements without much motion artifact, and is generally safer because the risk of falling from the machine is lower.

**Indications for terminating exercise testing**

According to the ACC/AHA guidelines, the following are indications for termination of exercise testing:

Absolute indications for termination of exercise testing

* Drop in SBP of greater than 10 mm Hg from baseline blood pressure, despite an increase in workload, when accompanied by other evidence of ischemia
* Moderate-to-severe angina
* Increasing nervous system symptoms (eg, ataxia, dizziness, near-syncope)
* Signs of poor perfusion (cyanosis or pallor)
* Technical difficulties in monitoring ECG tracings or SBP
* Subject's desire to stop
* Sustained ventricular tachycardia
* ST elevation (>1 mm) in leads without diagnostic Q waves (other than V1 or aVR)
* Relative indications for terminating exercise testing
* Drop in SBP greater than or equal to 10 mm Hg from baseline blood pressure, despite an increase in workload, in the absence of other evidence of ischemia
* ST or QRS changes such as excessive ST depression (>2 mm of horizontal or down-sloping ST-segment depression) or marked axis shift
* Arrhythmias other than sustained ventricular tachycardia, including multifocal premature ventricular contractions (PVCs), triplets of PVCs, supraventricular tachycardia, heart block, or bradyarrhythmias
* Fatigue, shortness of breath, wheezing, leg cramps, or claudication
* Development of bundle-branch block or intraventricular conduction delay that cannot be distinguished from ventricular tachycardia
* Increasing chest pain
* Hypertensive response (SBP of 250 mm Hg and/or DBP >115 mm Hg)

**Interpretation**

Interpretation should include exercise capacity and clinical, hemodynamic, and ECG response. The occurrence of ischemic chest pain consistent with angina is important, particularly if it forces termination of the test. The classic criteria for a positive stress test are J-point (defined as the junction of the point of onset of the ST-T wave and is normally at or near the isoelectric baseline of the ECG) and ST80 (defined as the point that is 80 ms from the J point) depression of 0.1 mV (1 mm) or more and/or an ST-segment slope within the range of ±1 mV/s in 3 consecutive beats.

The usefulness of exercise testing for the diagnosis of CAD is expressed most commonly by sensitivity and specificity. Sensitivity varies from 61-73% as reported by various analysts, and specificity varies from 59-81% depending on the study or article referenced. Results of correlative studies have been divided concerning the use exercise stress testing in patients with 50% or 70% luminal diameter occlusion.

**PHARMACOLOGIC STRESS TESTING**

Pharmacologic stress testing is generally instituted when contraindications to routine exercise stress exist or when the patient is unable to exercise because of debilitating conditions in various forms. These include the following general indications:

* Elderly patients with decreased functional capacity and possible CAD
* Patients with chronic debilitation and possible CAD

Younger patients with functional impairment due to injury, arthritis, orthopedic problems, peripheral neuropathy, myopathies, or peripheral vascular disease, in which a maximal heart rate is not easily achieved with routine exercise stress testing, usually because of an early onset of fatigue due to musculoskeletal, neurologic, or vascular problems rather than cardiac ischemia

Other cases, including patients taking beta-blockers or other negative chronotropic agents that would inhibit the ability to achieve an adequate heart response to exercise

Some centers prefer to use pharmacologic stress testing in conjunction with echocardiogram, MRI, or CT scanning because it avoids repositioning the patient, which may be necessary during nuclear imaging. Repositioning the patient may give a false-positive pharmacologic stress test result because of different degrees of attenuation of myocardial tissue imaging with changes in the breast positions as seen in women. Various pharmacologic agents are used for cardiovascular stress testing and are usually used in combination with radionuclide isotopes that are taken up by the myocardium during routine testing. The common ones are discussed below.

* Adenosine

Adenosine is a naturally occurring substance found throughout the body in various tissues. It functions to regulate blood flow in many vascular beds, including the myocardium. The mechanisms by which adenosine is produced intracellularly are the S-adenosyl homocysteine and the adenosine triphosphate pathways; the latter plays a role during ischemia.

Once transported across cell membranes, adenosine interacts and activates the A1 and A2 cell surface receptors. In the vascular smooth muscles, adenosine primarily acts by activation of the A2 receptor, which stimulates adenylate cyclase, leading to an increase in cyclic adenosine monophosphate (cAMP) production. Increased cAMP levels inhibit calcium uptake by the sarcolemma, causing smooth muscle relaxation and vasodilation. Activation of the vascular A1 receptor also occurs, which stimulates guanylate cyclase, inducing cyclic guanosine monophosphate production, leading to vasodilation.

This direct coronary artery vasodilation induced by adenosine is attenuated in diseased coronary arteries, which have a reduced coronary flow reserve and cannot further dilate in response to adenosine. This is not the case in healthy or less-diseased coronary arteries in the same patient, which produces relative flow heterogeneity throughout the coronary arteries, resulting in relatively more coronary blood flow in the healthy or less-diseased coronary arteries compared with the more-diseased coronary artery. In most cases, coronary blood flow in the diseased coronary arteries does not decrease.

In cases of severe vessel stenosis or total occlusions with compensatory collateral circulation, a decrease in coronary blood flow may occur in the diseased coronary artery, thus inducing ischemia via a coronary steal phenomenon. This regional flow abnormality also induces a perfusion defect during radionuclide imaging.

* Dipyridamole (Persantine)

Dipyridamole is an indirect coronary vasodilator that works by increasing intravascular adenosine levels. This occurs by the inhibition of intracellular reuptake and deamination of adenosine. However, the increase in coronary blood flow induced by dipyridamole is less predictable than that of adenosine. In one comparative study of dipyridamole and adenosine, 66% of patients (10 of 15) receiving dipyridamole versus 80% of patients (12 of 15) receiving adenosine had a maximal hyperemic response. However, this difference may not be apparent clinically. The mechanism of inducing a perfusion abnormality is similar to that of adenosine (see Adenosine) except true coronary steal occurs more frequently.

The standard dose of dipyridamole 0.56 mg/kg infused over 4 minutes.

Any physical limitation that prevents a patient from exercising maximally is an indication for vasodilator stress.

Patients taking beta-blockers or other negative chronotropic agents that would inhibit the ability to achieve an adequate heart rate response to exercise are also appropriate candidates for vasodilator stress.

* Dobutamine

Dobutamine is a synthetic catecholamine, which directly stimulates both beta-1 and beta-2 receptors. A dose-related increase in heart rate, blood pressure, and myocardial contractility occurs. As with physical exertion, dobutamine increases regional myocardial blood flow based on physiological principles of coronary flow reserve. A similar dose-related increase in subepicardial and subendocardial blood flow occurs within vascular beds supplied by significantly stenosed arteries, with most of the increase occurring within the subepicardium rather than the subendocardium. Thus, perfusion abnormalities are induced by the development of regional myocardial ischemia.

Dobutamine is infused in incremental doses starting at 5 mcg/kg/min for 3 minutes. Then, 10, 20, 30, and 40 mcg/kg/min are administered until the stress end point is reached. The end points are similar to those of exercise stress testing (eg, target heart rate, chest pain with ECG changes, hypotension).

Consider dobutamine as a second-line pharmacologic stressor to be used in patients who cannot perform exercise stress and have a contraindication to vasodilator stress.

A dose-related increase in both heart rate and SBP occurs with dobutamine. However, diastolic pressure falls as the dose of dobutamine increases. These hemodynamic changes are similar to those of exercise stress.