15 Exercise Physiology and Exercise Electrocardiographic Testing

GARY J. BALADY AND PHILIP A. ADES

Exercise electrocardiographic testing is among the most fundamental and widely used tests for the evaluation of patients with cardiovascular disease (CVD). It is easy to administer, perform, and interpret; it is flexible and adaptable; and it is reliable, inexpensive, and readily available in hospital or practice settings. The exercise test has been used by clinicians for more than half a century, and its durability can be attributed to its evolution over time. Primarily developed to detect the presence of myocardial ischemia secondary to coronary artery disease (CAD), the exercise electrocardiogram (ECG) is now recognized for its power in predicting prognosis. Exercise test variables beyond the ST segment yield important information, particularly when used in combination with clinical information, to predict outcomes and guide therapy in a broad range of individuals, from the healthy to those disabled by heart disease. Emerging applications of exercise electrocardiography have demonstrated its usefulness in the evaluation and management of patients with a wide variety of cardiovascular conditions, including valvular heart disease, congenital heart disease, genetic cardiovascular conditions, arrhythmias, and peripheral artery disease (PAD). When used appropriately with adjunctive modalities to measure gas exchange and ventilation or with imaging techniques such as echocardiography or nuclear perfusion imaging (see Chapters 16 and 18), the power of the exercise ECG is greatly enhanced. The exercise ECG is the clinician's beacon that can guide optimal care for a great majority of patients with known or suspected CVD. This chapter provides a detailed foundation of information on the physiology of exercise testing and the exercise ECG. Other chapters address adjunctive imaging techniques and further discuss the use of exercise testing in patients with specific cardiovascular conditions.

EXERCISE PHYSIOLOGY

Total-Body Oxygen Uptake

Exercising muscles require energy to contract and relax. Most of this energy is derived from oxidative metabolism to generate adenosine triphosphate; thus, energy requirements at rest and for any given amount of physical activity *(work rate)* can be estimated from measurements of total-body oxygen uptake ($\dot{V}o_2$). The Fick equation (Fig. 15.1) demonstrates that $\dot{V}o_2$ is determined by the product of cardiac output and oxygen extraction at the periphery (i.e., arteriovenous oxygen difference). $\dot{V}o_2$ is easily expressed in multiples of resting oxygen requirements (metabolic equivalents [METs]), with 1 MET being resting energy expenditure and defined as approximately 3.5 mL O_2/kg body weight/min. This convenient system indexes the amount of energy used during any given physical activity against that used at rest. Accordingly, 5-MET activity requires five times the energy expenditure at rest. $\dot{V}o_2$ max is the peak oxygen uptake achieved during performance of the highest level of dynamic exercise involving large muscle groups and by definition cannot be exceeded despite increases in work rate. It is related to age, sex, heredity, exercise habits, and cardiovascular status. Cardiac output can increase as much as four to six times resting levels in the upright position. Maximum cardiac output is the result of a twofold to threefold increase in heart rate (HR) from resting levels and an increase in stroke volume. Stroke volume in healthy persons generally plateaus at 50% to 60% of $\dot{V}o_2$ max. Oxygen extraction at the periphery can increase as much as threefold, and the maximum arteriovenous O_2 difference has a physiologic limit of 15 to 17 mL O_2/100 mL blood. During clinical exercise testing, patients are prompted to exercise not until they attain $\dot{V}o_2$ max but rather to the $\dot{V}o_2$ that is attained during symptom-limited, maximum tolerated exercise; this level is termed the $\dot{V}o_2$ peak.[1]

Myocardial Oxygen Demand and Supply Relationships During Exercise

Myocardial ischemia occurs when the supply of oxygenated blood to myocardial cells is inadequate to meet demands. Many factors affect the delicate balance of supply and demand (Fig. 15.2). Exercise testing is performed to stress these relationships and observe the physiologic responses that ensue. This enables the clinician not only to assess for the development of myocardial ischemia, but also to evaluate at what level of myocardial oxygen demand and physical activity (work rate) ischemia occurs.[1]

MYOCARDIAL OXYGEN DEMAND

Myocardial oxygen demand is related to HR, blood pressure (BP), left ventricular (LV) contractility (myocardial shortening per beat), and LV wall stress. The latter is related to LV pressure, wall thickness, and cavity size. Changes in any of these interdependent factors can affect myocardial need for oxygenated blood. Of these parameters, HR and BP are the easiest to measure and monitor. The product of HR and systolic BP, termed the *rate-pressure product*, is a reliable index of myocardial oxygen demand and can be readily assessed clinically.

During acute endurance (high-repetition/low-resistance) exercise (e.g., walking or cycling), cardiac output rises in response to the

$$\text{Resting } VO_2 = \text{C.O.} \times \text{A-}VO_2 \text{ Difference}$$

$$\text{Maximal Exercise } VO_2 = \text{C.O.} \times \text{A-}VO_2 \text{ Difference}$$

$$= \text{HR (2-3x resting)} \times \text{SV (2x resting)} \times \text{A-}VO_2 \text{ Difference (3x resting)}$$

FIGURE 15.1 Fick equations at rest and during exercise. See text for details. A-VO_2 Difference, arteriovenous oxygen difference; *C.O.*, cardiac output; *HR*, heart rate; *SV*, stroke volume; *Vo_2*, total body oxygen uptake.

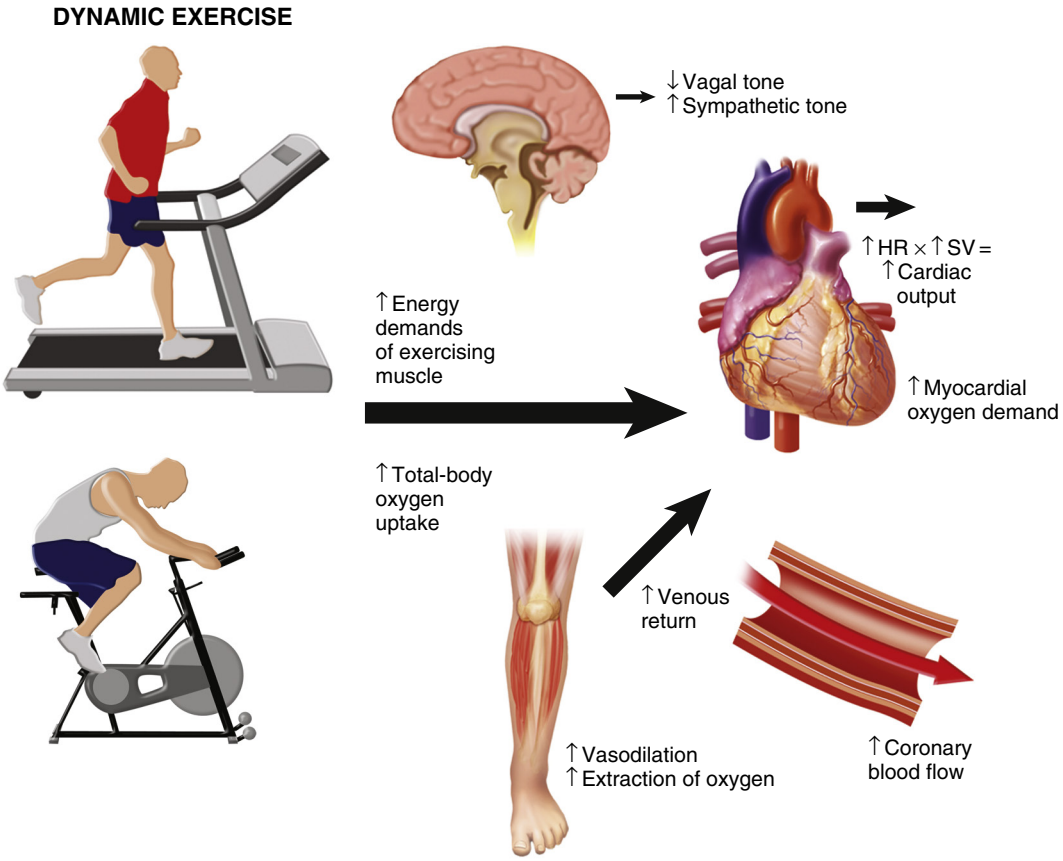

FIGURE 15.2 Physiologic responses to acute exercise. See text for details.

metabolic needs of the exercising muscles (estimated by measured $\dot{V}O_2$). Diminution of vagal tone and a rise in sympathetic tone lead to an increase in HR and LV contractility. Stroke volume also rises because of increases in venous return of blood from exercising muscles, and blood flow is redistributed from the renal, splanchnic, and cutaneous circulation to the exercising muscles. Accumulation of metabolites in the actively contracting muscles causes vasodilation of muscle arterioles, which increases skeletal muscle blood flow up to four times that of resting levels and results in a reduction in aortic outflow impedance. This in turn allows more complete systolic ejection, thereby further increasing stroke volume. Systolic BP increases mostly because of the rise in cardiac output, whereas diastolic BP either remains constant or falls as a result of the reduction in vascular resistance. The size and location of the exercising muscle groups will have different effects on the hemodynamic response to exercise. Dynamic arm exercise elicits higher HR and BP responses at any given work rate than does dynamic leg exercise. Arm work yields differences in sympathetic output, peripheral vasodilation, venous return, and metabolic requirements, which are influenced not only by the exercising muscle mass but also by the stabilizing muscles recruited during arm exercise.[1]

Resistance (low-repetition/high-load) exercise (e.g., weightlifting) is not generally used during graded exercise testing but may be used in work simulation testing or exercise training regimens. This type of exercise generates an increased sympathetic response, leading to an increase in HR; however, venous return, especially during straining, may decrease. Therefore, the rise in cardiac output is relatively small in comparison to that achieved with endurance exercise and is primarily caused by increases in HR. Muscle contraction during resistance exercise generates compressive force on muscle capillaries that leads to elevated peripheral resistance. This rise in vascular resistance coupled with an increase in cardiac output yields an increase in both systolic and diastolic BP. Elevations in systolic BP from rest to exercise are proportionally greater than the elevations in HR during resistance exercise than during endurance exercise. Therefore, both endurance exercise and resistance exercise increase myocardial oxygen demand because of variable increases in HR, BP, LV contractility, and LV wall stress (the latter caused by increases in LV pressure and/or volume during exercise).[1]

MYOCARDIAL OXYGEN SUPPLY

Coronary blood flow increases during exercise in response to neurohumoral stimulation (primarily sympathetic beta receptor stimulation) and as a result of the release of endothelial substances, including nitric oxide. In healthy persons during acute exercise, coronary arteries dilate and coronary blood flow rises in response to the increases in myocardial oxygen demand. Most often, coronary flow is compromised as a result of atherosclerotic plaque within the lumen of the coronary artery (see Chapter 36). Plaque may cause minimal stenosis or complete occlusion of the artery. Several factors influence the significance of a given luminal stenosis, including the degree of luminal obstruction, the length of the obstruction, the number and size of functioning collateral vessels, the magnitude of the muscle mass supplied, the shape and dynamic properties of the stenosis, and the autoregulatory capacity of the vascular bed. In general, a 50% to 70% reduction in luminal diameter will impair peak reactive hyperemia, whereas 90% or greater stenosis will reduce resting flow. However, exercise stimulates local changes in vasomotor tone as a result of neuromodulation, endothelial dysfunction, and local factors, and these changes can further influence the supply of oxygenated blood to the myocardium. Atherosclerotic arteries often fail to dilate and may actually constrict with exercise, thus further reducing the supply of blood in the setting of increased demand.[1]

TECHNICAL COMPONENTS OF EXERCISE TESTING

Patient Preparation

Patient Assessment

It is important to clinically assess the patient before performing the exercise test to evaluate the indications for the test, the appropriateness of the specific test that has been ordered to answer the question posed, the ability of the patient to perform exercise, and whether the patient has any contraindications to exercise testing (Table 15.1). Information from the medical history as provided by the patient, chart review, and the ordering provider and/or the patient's primary care physician or cardiologist can be most useful in this pretest evaluation. A brief physical examination that addresses the components outlined in Table 15.2 can also be helpful. A current standard resting 12-lead ECG is useful in assessing HR, rhythm, conduction abnormalities, and evidence of previous myocardial infarction (MI) and should be compared with the most recent previous ECG, if available.

Diagnostic exercise testing in patients without known CAD is best performed by withholding cardioactive medications on the day of the test to better assess for an ischemic response. On the other hand, functional testing in patients with known CAD is best performed with patients taking their usual medications to evaluate the effects of the medications on HR, BP, symptoms, and ischemia during exercise (see "Pharmacologic Influences on Interpretation").

In patients with permanent cardiac pacemakers, it is important to obtain information from the patient's cardiologist regarding the type of pacemaker (single or dual chamber), programmed mode, rate responsiveness, and pacing HR limits before the test. Similarly, in patients with implantable cardioverter-defibrillators (ICDs), information regarding ICD rhythm detection and treatment algorithms should be obtained so that the peak HR during the exercise test is maintained at least 10 beats/min below the programmed HR threshold for anti-tachycardia pacing and defibrillation.[2] Additional details of patient assessment are provided elsewhere.[1]

Symptom Rating Scales

Before exercising, patients should be made familiar with the symptom rating scales that might be used during testing. These are described further elsewhere[3] and may include the Borg Scale of Perceived Exertion.[3]

Electrocardiographic Lead Systems

As the technology of exercise electrocardiographic testing has evolved, several different types of lead systems have been developed and used. Details regarding these lead systems, along with skin preparation techniques, are provided elsewhere.[1] The importance of adequate skin preparation cannot be overstated; this is essential to optimize the quality of the exercise ECG. To obtain a high-quality 12-lead ECG during testing, electrode placement on the torso is standard for routine testing. Torso electrodes are placed under the lateral aspect of the clavicles for the arm leads and on the lower end of the rib cage or high under the rib cage for the leg leads. A standard 12-lead ECG should be performed before placement of the torso limb leads because such lead placement may alter the inferior lead complexes and result in previous Q waves being either mimicked or hidden. A standing ECG is then used as the basis for determining the presence of exercise-induced ECG changes.

TABLE 15.1 Contraindications to Exercise Testing

Absolute Contraindications
Acute myocardial infarction, within 2 days
High-risk unstable angina
Uncontrolled cardiac arrhythmia with hemodynamic compromise
Active endocarditis
Symptomatic severe aortic stenosis
Decompensated heart failure
Acute pulmonary embolism or pulmonary infarction
Acute myocarditis or pericarditis
Physical disability that precludes safe and adequate testing
Relative Contraindications
Known left main coronary artery stenosis
Moderate aortic stenosis with uncertain relation to symptoms
Tachyarrhythmias with uncontrolled ventricular rates
Acquired complete heart block
Hypertrophic cardiomyopathy with severe resting gradient
Mental impairment with limited ability to cooperate

From Fletcher GF, Ades PA, Kligfield P, et al. Exercise standards for testing and training: a scientific statement from the American Heart Association. *Circulation*. 2013;128:873–934.

TABLE 15.2 Patient Assessment for Exercise Testing

History

1. **Medical diagnoses and past medical history**—a variety of diagnoses should be reviewed, including cardiovascular disease (known existing CAD, previous myocardial infarction, or coronary revascularization); arrhythmias, syncope or pre-syncope; pulmonary disease, including asthma, emphysema, and bronchitis, or recent pulmonary embolism; cerebrovascular disease, including stroke; peripheral arterial disease; current pregnancy; musculoskeletal, neuromuscular and joint disease
2. **Symptoms**—angina; chest, jaw or arm discomfort; shortness of breath; palpitations, especially if associated with physical activity, eating a large meal, emotional upset, or exposure to cold
3. **Risk factors for atherosclerotic disease**—hypertension; diabetes; obesity; dyslipidemia; smoking
4. If patient is without known CAD, determine the pre-test probability of CAD (see Table 15.11)
5. **Recent illness, hospitalization, or surgical procedure**
6. **Medication dose and schedule**
7. **Ability to perform physical activity**

Physical Examination

1. Pulse rate and regularity
2. Resting blood pressure sitting and standing
3. Auscultation of the lungs, with specific attention to uniformity of breath sounds in all areas, particularly in patients with shortness of breath, a history of heart failure or pulmonary disease
4. Auscultation of the heart, particularly in patients with heart failure or valvular disease
5. Examination related to orthopedic, neurologic, or other medical conditions that might limit exercise

Exercise Test Modality and Protocols

The testing modality and protocol should be selected in accordance with the patient's estimated functional capacity based on age, estimated physical fitness from the patient's history, and underlying disease. Several exercise test protocols are available for both treadmill and stationary cycle ergometers. Patients who have low estimated fitness levels or are deemed to be at higher risk because of underlying disease (e.g., recent MI, heart failure) should be tested with a less aggressive exercise protocol. Treadmill and cycle ergometers may use stepped or continuous ramp protocols. Work rate increments (stages) during stepped protocols can vary from 1 to 2.5 METs. Ramp protocols are designed with stages that are no longer than 1 minute and for the patient to attain peak effort within 8 to 12 minutes. Accordingly, ramp protocols must be individualized and selected to accommodate the patient's estimated exercise capacity. Because there are no widely published or standard sets of ramp protocols, individual exercise testing laboratories usually develop their own customized protocols that

TABLE 15.3 Boston Medical Center Treadmill Ramp Protocols

STAGE*	VERY LOW RAMP			LOW RAMP			MODERATE RAMP			HIGH RAMP			ATHLETE'S RAMP		
	MPH	% GRADE	METS	MPH	% GRADE	METS	MPH	% GRADE	METS	MPH	% GRADE	METS	MPH	% GRADE	METS
1	1.0	0.0	1.8	1.0	0.0	1.8	1.5	1.5	2.5	2.1	3.0	3.5	1.8	0.0	2.4
2	1.1	0.2	1.9	1.1	0.5	1.9	1.6	2.0	2.7	2.2	4.0	3.9	2.1	0.5	2.7
3	1.2	0.4	2.0	1.2	1.0	2.1	1.7	2.5	2.9	2.3	4.5	4.2	2.4	1.0	3.2
4	1.3	0.6	2.1	1.3	1.5	2.3	1.8	3.0	3.1	2.4	5.5	4.6	2.7	1.5	3.6
5	1.4	0.8	2.2	1.4	2.0	2.5	1.9	3.5	3.4	2.5	6.0	5.0	3.3	2.0	4.1
6	1.5	1.0	2.3	1.5	2.5	2.7	2.0	4.0	3.6	2.6	7.0	5.5	3.3	2.5	4.6
7	1.6	1.2	2.5	1.6	3.0	2.9	2.1	4.5	3.9	2.7	7.5	5.8	3.6	3.0	5.2
8	1.7	1.4	2.6	1.7	3.5	3.1	2.2	5.0	4.2	2.8	8.5	6.4	3.9	3.5	6.1
9	1.8	1.6	2.8	1.8	4.0	3.4	2.3	5.5	4.5	2.9	9.0	6.8	4.2	4.0	7.3
10	1.9	1.8	2.9	1.9	4.5	3.6	2.4	6.0	4.8	3.0	10.0	7.4	4.5	4.5	8.4
11	2.0	2.0	3.1	2.0	5.0	3.9	2.5	6.5	5.1	3.1	10.5	7.8	4.8	5.0	9.5
12	2.1	2.2	3.2	2.1	5.5	4.2	2.6	7.0	5.5	3.2	11.5	8.5	5.1	5.5	10.6
13	2.2	2.4	3.4	2.2	6.0	4.5	2.7	7.5	5.8	3.3	12.0	8.9	5.4	6.0	11.5
14	2.3	2.6	3.6	2.3	6.5	4.8	2.8	8.0	6.2	3.4	13.0	9.7	5.7	6.5	12.2
15	2.4	2.8	3.8	2.4	7.0	5.1	2.9	8.5	6.6	3.5	13.5	10.1	6.0	7.0	13.0
16	2.5	3.0	3.9	2.5	7.5	5.5	3.0	9.0	7.0	3.6	14.5	10.9	6.3	7.5	13.8
17	2.6	3.2	4.1	2.6	8.0	5.8	3.1	9.5	7.4	3.7	15.0	11.4	6.6	8.0	14.7
18	2.7	3.4	4.3	2.7	8.5	6.2	3.2	10.0	7.8	3.8	16.0	12.2	6.9	8.5	15.5
19	2.8	3.6	4.5	2.8	9.0	6.6	3.3	10.5	8.3	3.9	16.5	12.6	7.2	9.0	16.4
20	2.9	3.8	4.7	2.9	9.5	7.0	3.4	11.0	8.7	4.0	17.5	13.3	7.5	9.5	17.3

METs, Metabolic equivalents.
*Stages are each 30 seconds in duration.

accommodate a wide range of fitness levels. Table 15.3 provides examples of such protocols. The American College of Sports Medicine (ACSM)[2] details a variety of treadmill and cycle ergometer testing protocols.

Exercise tests may be submaximal or maximal relative to the patient's effort. In addition to common indications for stopping the exercise test (Table 15.4), submaximal exercise testing has a predetermined endpoint, often defined as a peak HR (e.g., 120 beats/min or 70% of predicted maximum HR) or an arbitrary MET level (e.g., 5 METs). Submaximal tests are used in patients early after MI before discharge from the hospital because they can provide prognostic information to guide management. They can also be useful in the evaluation of a patient's ability to engage in daily activities after discharge and can serve as a baseline for cardiac rehabilitative exercise therapy (see "Physical Activity and Exercise Prescription"). Symptom-limited tests are designed to continue until the patient demonstrates signs and/or symptoms necessitating termination of exercise (see Table 15.4). Whatever modality or protocol is used, standard patient monitoring and measurements are made during and early after exercise (Table 15.5).

TREADMILL

Treadmill testing provides a more common form of physiologic stress (i.e., walking) in which patients are more likely to attain a higher oxygen uptake and peak HR than during stationary cycling. Cycling may be preferable when orthopedic or other specific patient characteristics limit treadmill testing or during exercise echocardiographic testing to facilitate acquisition of images at peak exercise. The most frequently used stepped treadmill protocols are the Naughton, Bruce, and modified Bruce (Table 15.6).[3]

During treadmill exercise, patients should be encouraged to walk freely and use the handrails for balance only when necessary. Excessive handrail gripping and support alter the BP response and decrease the oxygen requirement (METs) per given

TABLE 15.4 Indications for Terminating the Exercise Test

Absolute Indications

- ST elevation (>1.0 mm) in leads without Q waves due to prior MI (other than aVR, aVL, or V1)
- Drop in systolic BP of >10 mm Hg, despite an increase in workload, when accompanied by any other evidence of ischemia
- Moderate to severe angina
- Central nervous system symptoms (e.g., ataxia, dizziness, or near syncope)
- Signs of poor perfusion (cyanosis or pallor)
- Sustained ventricular tachycardia or other arrhythmia that interferes with normal maintenance of cardiac output during exercise
- Technical difficulties monitoring the ECG or systolic BP
- Patient's request to stop

Relative Indications

- Marked ST displacement (horizontal or downsloping of >2 mm) in a patient with suspected ischemia
- Drop in systolic BP of >10 mm Hg (persistently below baseline) despite an increase in workload, in the absence of other evidence of ischemia
- Increasing chest pain
- Fatigue, shortness of breath, wheezing, leg cramps, or claudication
- Arrhythmias other than sustained ventricular tachycardia, including multifocal ectopy, ventricular triplets, supraventricular tachycardia, atrioventricular heart block, or bradyarrhythmias
- Exaggerated hypertensive response (systolic blood pressure >250 mm Hg and/or diastolic blood pressure >115 mm Hg)
- Development of bundle branch block that cannot be distinguished from ventricular tachycardia

BP, Blood pressure; *ECG*, electrocardiogram; *MI*, myocardial infarction.
From Fletcher GF, Ades PA, Kligfield P, et al. Exercise standards for testing and training: a scientific statement from the American Heart Association. *Circulation*. 2013;128:873–934.

workload, thereby resulting in an overestimation of exercise capacity (**eFig. 15.1**) and an inaccurate HR-and BP-to-workload relationship. Exercise capacity (peak METs) can be estimated for treadmill exercise by using data provided by ACSM,[3] as long as the equipment is calibrated regularly. When precise determination of oxygen uptake is necessary, such as assessment of patients for heart transplantation (see Chapter 60), evaluation by expired gas analysis is preferred over estimation (see "Cardiopulmonary Exercise Testing"). Normal values for exercise capacity in healthy adults at different ages are available and may serve as a useful reference in the evaluation of a patient's exercise capacity.[3]

TABLE 15.5 Patient Monitoring During Exercise Testing

During the Exercise Period

- 12-lead ECG during last minute of each stage, or at least every 3 min
- Blood pressure during last minute of each stage, or at least every 3 min
- Symptom rating scales as appropriate for the test indication and lab protocol

During the Recovery Period

- Monitoring for a minimum of six minutes after exercise in sitting or supine position, or until near baseline heart rate, blood pressure, ECG and symptom measures are reached. A period of active cool-down may be included in the recovery period, particularly following high levels of exercise in order to minimize the post-exercise hypotensive effects of venous pooling in the lower extremities.
- 12-lead ECG every minute
- Heart rate and blood pressure immediately after exercise, then every one or two minutes thereafter until near-baseline measures are reached.
- Symptomatic ratings every minute as long as they persist after exercise. Patients should be observed until all symptoms have resolved or returned to baseline levels.

ECG, Electrocardiogram.

TABLE 15.6 Bruce Protocol for Treadmill Testing

STAGE	TIME	SPEED (MPH)	GRADE (%)	METS
REST	00.00	0.0	0.0	1.0
1	03.00	1.7	10.0	4.6
2	03.00	2.5	12.0	7.0
3	03.00	3.4	14.0	10.1
4	03.00	4.2	16.0	12.9
5	03.00	5.0	18.0	15.1
6	03.00	5.5	20.0	16.9
7	03.00	6.0	22.0	19.2

METS, metabolic equivalents.
Modified Bruce Protocol employs two initial low level 3–min stages at a speed of 1.7 mph and grades 0% and 5%, respectively, and then continues into the full Bruce protocol.
Data from American College of Sports Medicine Guidelines for Exercise Testing and Prescription. 10th ed. Philadelphia: Wolters Kluwer; 2018.

STATIONARY CYCLE

A cycle ergometer is smaller, quieter, and less expensive than a treadmill. Because a cycle ergometer requires less movement of the arms and thorax, quality electrocardiographic recordings and BP measurements are easier to obtain. However, stationary cycling may be unfamiliar to many patients, and its success as a testing tool is highly dependent on patient skill and motivation. Thus, the test may end before the patient reaches a true cardiopulmonary endpoint. Unlike treadmill testing, in which the work being performed involves movement of the patient's body weight at a given pace, stationary cycle work involves cycling at a given pace against an external force and is generally independent of the patient's body weight, which is supported by the seat. As shown in Table 15.7, the MET level attained at a given work rate varies with the patient's body weight. Accordingly, at the same given cycle ergometer work rate, a lighter person will attain higher METs than will a heavier person. Mechanically braked ergometers require that the patient's cycling speed be kept constant. Electronically braked cycle ergometers automatically adjust external resistance to the cycling speed to maintain a constant work rate at a given stage. Electronically braked cycle ergometers allow simple programming of ramp protocols. As with treadmill ramp protocols, customized cycle ergometer ramp protocols that accommodate a wide range of fitness levels need to be established by individual exercise testing laboratories.

ARM CYCLE ERGOMETRY

Arm ergometry is an alternative method of exercise testing for patients who cannot perform leg exercise. Although this test has diagnostic usefulness, it has been largely replaced by nonexercise pharmacologic stress techniques.

SIX-MINUTE WALK TEST

The 6-minute walk test can be used as a surrogate measure of exercise capacity when standard treadmill or cycle testing is not available. Distance walked is the primary outcome of the test. It is not useful in the objective determination of myocardial ischemia and is best used in a serial manner to evaluate changes in exercise capacity and the response to interventions that may affect exercise capacity over time. The 6-minute walk test protocol is discussed in detail elsewhere (Table 15.8).[4]

CARDIOPULMONARY EXERCISE TESTING (EXERCISE TESTING WITH GAS EXCHANGE ANALYSIS)

Because of the inaccuracies associated with estimating oxygen uptake ($\dot{V}o_2$) and METs from work rate with the treadmill or cycle ergometer, many laboratories perform cardiopulmonary exercise testing (CPX), which uses ventilatory gas exchange analysis during exercise to provide a more reliable and reproducible measure of $\dot{V}o_2$. Peak $\dot{V}o_2$ is the most accurate measure of exercise capacity and is a useful reflection of overall cardiopulmonary health. Measurement of expired gases is not necessary for all clinical exercise testing, but the additional information can provide important physiologic data that can be useful in both clinical and research applications. Measures of gas exchange primarily include $\dot{V}o_2$, carbon dioxide output ($\dot{V}co_2$), and minute ventilation. Use of these variables in graphic form provides further information on the ventilatory threshold and ventilatory efficiency.[5]

CPX is well established as useful in the following situations:

- Evaluation of exercise capacity in selected patients with heart failure, to assist in estimation of prognosis, evaluate the response to medications and other interventions, and assess the need for cardiac transplantation.

TABLE 15.7 Approximate MET Levels During Cycle Ergometer Testing

BODY WEIGHT		EXERCISE RATE (KP • M • MIN^{-1} AND WATTS)						
KP	LB	KPMS 300 WATTS 50	450 75	600 100	750 125	900 150	1050 175	1200 200
50	110	5.1	6.9	8.6	10.3	12.0	13.7	15.4
60	132	4.3	5.7	7.1	8.6	10.0	11.4	12.9
70	154	3.7	4.9	6.1	7.3	8.6	9.8	11.0
80	176	3.2	4.3	5.4	6.4	7.5	8.6	9.6
90	198	2.9	3.8	4.8	5.7	6.7	7.6	8.6
100	220	2.6	3.4	4.3	5.1	6.0	6.9	7.7

Kpm, kilopond-meter; *METs*, metabolic equivalents.
Data from *American College of Sports Medicine Guidelines for Exercise Testing and Prescription.* 9th ed. Philadelphia: Lippincott, Williams & Wilkins, 2013.

A

Start exer	Speed	Grade	Heart rate	VO_2	METs	RER
6:00	2.1	2.9	73	8.4	2.4	0.65
6:30	2.2	3.9	88	8.6	2.5	0.74
7:00	2.2	4.4	89	10.8	3.1	0.65
7:30	2.4	5.4	89	11.8	3.4	0.73
8:00	2.5	5.9	93	11.2	3.2	0.75
8:30	2.5	7.0	93	12.6	3.6	0.76
9:00	2.7	7.5	98	11.7	3.3	0.82
9:30	2.7	8.5	100	14.6	4.2	0.80
10:00	2.9	9.1	102	13.2	3.8	0.89
10:30	3.0	10.0	106	16.0	4.6	0.84
11:00	3.0	10.5	107	15.1	4.3	0.98
11:30	3.2	11.5	109	15.6	4.4	0.94
AT						
12:00	3.3	12.0	113	16.2	4.6	1.00
12:30	3.4	13.0	116	18.2	5.2	1.04
13:00	3.5	13.5	120	17.7	5.0	1.11
13:30	3.5	14.5	123	18.7	5.4	1.06
14:00	3.7	15.0	127	19.4	5.5	1.14
14:30	3.8	16.0	130	19.7	5.6	1.19
15:00	3.9	16.5	133	18.4	5.2	1.20
V02 Max						
15:30	4.0	17.5	136	21.9	6.2	1.20
Start reco						
16:00	0.0	0.0	137	18.9	5.4	1.28
16:30	0.0	0.0	23	14.5	4.2	1.33

B

Exercise test summary

Phase name	Stage name	Time in stage	Speed (mph)	Grade (%)	HR (bpm)	BP (mmHg)	Comment
PRETEST	SUPINE	36:41	0.00	0.00	76	108/78	0:27 spo2 99% 35:07 standing sp02–96
MANUAL	STAGE 1/2	00:26	2.00	0.00	70		
EXERCISE	STAGE 1	00:30	2.10	3.00	79		
	STAGE 2	00:30	2.20	4.00	89		
	STAGE 3	00:30	2.30	4.50	89		
	STAGE 4	00:30	2.40	5.50	93		
	STAGE 5	00:30	2.50	6.00	93		
	STAGE 6	00:30	2.60	7.00	96		
	STAGE 7	00:30	2.70	7.50	103		
	STAGE 8	00:30	2.80	8.50	101		
	STAGE 9	00:30	2.90	9.00	106	130/74	4:24 sp02–99
	STAGE 10	00:30	3.00	10.00	103		
	STAGE 11	00:30	3.10	10.50	110		
	STAGE 12	00:30	3.20	11.50	109		
	STAGE 13	00:30	3.30	12.00	115		
	STAGE 14	00:30	3.40	13.00	118		
	STAGE 15	00:30	3.50	13.50	123		
	STAGE 16	00:30	3.60	14.50	125	148/74	
	STAGE 17	00:30	3.70	15.00	130		
	STAGE 18	00:30	3.80	16.00	133		
	STAGE 19	00:30	3.90	16.50	137		
	STAGE 20	00:30	4.00	17.50	139		
	STAGE 21	00:04	4.10	18.00	139		
RECOVERY		00:30			131		
		00:30	0.00	0.00	116		
		07:25	0.00	0.00	85	124/70	2:03 spo2 99%

The patient exercised according to the HIGH RAMP for 10:03 min:s, achieving a work level of Max. METS: 13.60. The resting heart rate of 70 bpm rose to a maximal heart rate of 141 bpm. This value represents 87% of the maximal, age-predicted heart rate. The resting blood pressure of 131/85 mmHg, rose to a maximum blood pressure of 160/77 mmHg. The exercise test was stopped due to fatigue.

EFIGURE 15.1 Handrail support during treadmill exercise overestimates exercise capacity. **A,** Cardiopulmonary test results demonstrate peak measured VO_2 (*red rectangle*) and metabolic equivalent (MET) level (*blue rectangle*) during treadmill ramp protocol with patient using handrail support during treadmill exercise test. **B,** Estimated peak MET level (*blue rectangle*) during this same test using standard prediction equations. Note large difference between measured METs and estimated METs.

- Evaluation of exertional dyspnea. Such testing can provide useful information for differentiating cardiac from pulmonary limitations as a cause of exercise-induced dyspnea or impaired exercise capacity when the cause is uncertain.
- Evaluation of the patient's response to specific therapeutic interventions (e.g., medications; programmed pacing; cardiac rehabilitation) in which improvement in exercise tolerance is an important goal or endpoint.

Emerging evidence demonstrates that CPX can provide valuable clinical information in patients with hypertrophic cardiomyopathy (HCM), suspected or confirmed pulmonary hypertension, suspected myocardial ischemia, suspected mitochondrial myopathy, and confirmed chronic obstructive pulmonary disease or interstitial lung disease. More recently, utility of CPX has been demonstrated in the assessment of perioperative risk and valvular heart disease.

The technical aspects of CPX have become simplified with contemporary metabolic carts, but meticulous maintenance and calibration of these systems are required for optimal use. The personnel involved in administering and interpreting the test must be trained and proficient in this technique. The test also requires additional time, as well as patient cooperation. CPX used in combination with Doppler echocardiography can provide complementary information regarding cardiac output, myocardial contractile function, and valvular function.[5]

Exercise Test Supervision

Over the past 30 years since the American Heart Association (AHA) published its first set of *Standards for Adult Exercise Testing Laboratories*, the role of the physician in ensuring that the exercise laboratory is properly equipped and appropriately staffed with qualified personnel who adhere to a written set of policies and procedures specific to that laboratory has not changed. In subsequent iterations of their respective guidelines, the AHA, ACSM, American College of Cardiology (ACC), and American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR) have consistently addressed this issue. In 2000 the ACC/AHA/American College of Physicians/American College of Sports Medicine Competency Task Force focused its efforts on outlining the specific cognitive and training requirements for personnel involved in supervising and interpreting exercise ECGs and was the first to look beyond the specific professional type (e.g., physician, nurse, exercise physiologist) and focus on specific competencies of the individual staff member (see "Classic References"). In 2014 these recommendations were updated to define further the roles of each staff member involved with exercise testing.[6] This statement clearly defined different levels of supervision as follows: (1) "personal supervision" requires a physician's presence in the room; (2) "direct supervision" requires a physician to be in the immediate vicinity, on the premises or the floor, and available for emergencies; and (3) "general supervision" requires the physician to be available by phone or by page. Common to every guideline is the recommendation that patients be screened before exercise testing to assess their risk for an exercise-related adverse event, so that the most appropriate personnel to supervise the test can be provided. Exercise testing may be supervised by nonphysician staff members who are deemed competent according to the criteria outlined in the ACC/AHA statement.[6] In all such cases the physician should be immediately available to assist as needed (i.e., provide direct supervision). In high-risk patients the physician should personally supervise the test (i.e., provide personal supervision).

TABLE 15.8 Six Minute Walk Test Protocol

Testing Site
The Six Minute Walk Test Protocol should be performed indoors, along a long, flat, straight, enclosed corridor with a hard surface that is seldom traveled. The walking course must be 30 m in length. A 100-ft (30.4 m) hallway is required and its length should be marked every 3 m. The turnaround points should be marked with a cone (such as an orange traffic cone). A starting line, which marks the beginning and end of each 60-m lap, should be marked on the floor using brightly colored tape.
Measurements
Assemble all necessary equipment (lap counter, timer, clipboard, worksheet) and move to the starting point. Set the lap counter to zero and the timer to 6 min. Position the patient at the starting line. You should also stand near the starting line during the test. Do not walk with the patient. As soon as the patient starts to walk, start the timer. Do not talk to anyone during the walk. Use an even tone of voice when using the standard phrases of encouragement. Each time the patient returns to the starting line, click the lap counter once (or mark the lap on the worksheet). At the end of 6 min, tell the patient to stop walking, and measure the total distance traveled (meters). Heart rate, blood pressure and oxygen saturation should be measured at rest and at the end of exercise as well. The main outcome of this test is total distance traveled.
Patient Instructions
Standardized scripted patient instructions should be used, and are provided elsewhere

Data from American Thoracic Society: ATS statement: Guidelines for the six-minute walk test. *Am J Respir Crit Care Med*. 2002;166:111.

Risks of Exercise Testing

Exercise is associated with increased risk for an adverse cardiovascular event, and details regarding the safety of exercise testing and emergency preparedness in exercise laboratories are addressed in depth in guidelines from the AHA[1,5] and the ACSM.[3] Nonetheless, the safety of exercise testing is well documented, and the overall risk for adverse events is quite low. In several large series of individuals with and without known CVD, the rate of major complications (including MI and other events requiring hospitalization) was less than 1 to as high as 5 per 10,000 tests, and the rate of death was less than 0.5 per 10,000 tests. The incidence of adverse events depends on the study population. Patients with recent MI, reduced LV systolic function, exertion-induced myocardial ischemia, and serious ventricular arrhythmias are at highest risk.[1,7] A report of 5060 CPX studies performed in patients with severe functional impairment and a variety of high-risk cardiac diseases, including heart failure, HCM, pulmonary hypertension, and aortic stenosis, further supports the safety of exercise testing. The adverse event rate was 0.16%, and the most common adverse event was sustained ventricular tachycardia (VT). No fatal events were reported.[8]

Maintenance of appropriate emergency equipment, establishment of an emergency plan, and regular practice in carrying out the plan are fundamental to ensuring safety in an exercise testing laboratory (see "Classic References").

EXERCISE TESTING IN CORONARY ARTERY DISEASE

Exercise-Induced Symptoms

Any chest pain produced during the exercise test needs to be factored into the exercise test conclusion and report.

First, are the symptoms reported during the test the same or similar to the reported historical symptoms that prompted the exercise test? If the answer is yes, the provider can assess the objective test responses and discern whether they support the presence of CAD. If the answer is no, differences between the produced and historical symptoms need to be clarified. In addition, the symptoms produced need to be categorized according to whether they are consistent with angina. Distinguishing anginal from nonanginal chest pain is important at the time of occurrence of the chest pain. Angina is not well localized, pleuritic, or associated with palpable tenderness (see Chapters 13 and 35), and the only opportunity to define these qualities may be at the exercise test.

Second, exercise-induced angina is an important clinical predictor of the presence and severity of CAD, equal to or greater than ST-segment depression. Consideration of limiting versus nonlimiting chest pain, in addition to any induced angina, has been incorporated into the Duke Treadmill Score, as well as into other treadmill scores (see later). These factors will have an impact on the prognostic and diagnostic assessment of the test results, and ultimately the next step in the clinical evaluation.

Third, exercise-induced typical angina predicts an adverse prognosis and is worthy of further evaluation regardless of the ST-segment response or the exercise capacity. In a series of 3270 patients without

known coronary disease referred for exercise testing, Christman and colleagues[9] found that typical angina defined by physicians and exercise physiologists at the exercise test was a predictor of adverse events, including death, nonfatal MI, and revascularization. This was found irrespective of the presence or absence of a positive ST-segment response or good exercise capacity.

Lastly, if the patient stops exercise earlier than anticipated because of dyspnea, careful consideration should be given as to whether an anginal equivalent is present. If the presenting symptom was dyspnea with exertion, this becomes even more relevant.

Functional Capacity

Functional capacity is a strong predictor of mortality and nonfatal cardiovascular outcomes in both men and women with and without CAD.[10] Even though exercise capacity is most accurately measured by CPX, a reasonable estimate can be obtained from treadmill testing alone. The best methods for estimating predicted METs are the following simple regression equations.[1]

$$\text{Men}: \text{Predicted METs} = 18 - (0.15 \times \text{Age})$$

$$\text{Women}: \text{Predicted METs} = 14.7 - (0.13 \times \text{Age})$$

The reported exercise time can be translated into METs or METs based on the exercise test protocol. The reported METs can then be expressed as a percentage of the predicted METs. Table 15.9 provides an alternative qualitative classification of functional capacity that adjusts for age and sex.

In addition to clinical factors, functional capacity can be related to familiarity with the exercise equipment, level of training, and environmental conditions in the exercise laboratory. Patients who cannot adequately perform an exercise test or who undergo a pharmacologic stress test have a worse prognosis than do those who can perform an exercise test.[9]

Functional capacity should always be incorporated into the results, conclusions, and/or recommendations of the exercise test report. Functional capacity can be incorporated into available multivariable scores such as the Duke Treadmill Score or the Cleveland Clinic Prognostic Score to classify the prognosis as low, intermediate, or high risk (see Prognostic Value).

HEART RATE RESPONSES

Peak Heart Rate

The maximum HR with exercise is a fundamental physiologic parameter that provides the clinician relevant information concerning the intensity of exercise, the adequacy of the exercise test, the effect of medications that influence HR, the potential contribution to exercise intolerance, and the patient's prognosis.[11] The maximum achievable HR (HRmax) is unique for each patient but can be estimated by using regression equations that adjust for the patient's age. The most familiar equation, which was developed principally in middle-aged men, is:

$$\text{HRmax} = 220 - \text{Age}$$

Although easy to apply and calculate, there is considerable variability with this equation, especially in patients with CAD who are taking beta blockers. Newer equations[3] have been proposed to more accurately replace the "220 – age" rule to generate the maximum age-predicted HR (MPHR):

$$\text{Men}: \text{HRmax} = 208 - (0.7 \times \text{Age})$$

$$\text{Women}: \text{HRmax} = 206 - (0.88 \times \text{Age})$$

Chronotropic Incompetence

The inability of the heart to increase its rate to meet the demand placed on it is termed chronotropic incompetence. It is considered an independent predictor of cardiac or all-cause mortality, as well as other adverse cardiovascular outcomes.[11]

A *submaximal* study is assigned when the peak HR achieved is below the MPHR. An *inadequate* study is defined by failure to achieve a predefined goal, such as 85% of MPHR. If a patient without known CAD has an inadequate study, the term *nondiagnostic* study is often applied. As usual, this "nondiagnostic" status is relative. In the presence of any other diagnostic endpoints, such as 2-mm or greater ST-segment depression, exercise-induced hypotension, or exercise-induced anginal chest pain, the HR adequacy question becomes irrelevant.

Chronotropic incompetence typically has been defined by the adjusted HR reserve, incorporates both resting and peak HRs, as well as the age-adjusted HRmax. However, before "chronotropic incompetence" is applied, consideration should be given to the effort exerted in performing exercise, present medications, in particular beta blockers, and the reason for termination of the exercise test. Effort applied to the exercise is often defined by the symptoms produced or by indices of perceived exertion (e.g., Borg scale).[1,3] These work well in most settings but can also be defined quantitatively by using CPX parameters such as the respiratory exchange ratio. For the usual non-CPX application, the following formula defines the chronotropic index:

$$[(\text{HRmax} - \text{HRrest}) / (220 - \text{Age} - \text{HRrest})] \times 100$$

Failure to achieve a chronotropic index higher than 80% defines the presence of chronotropic incompetence and this predicts a poor prognosis.[11] Criteria for assessing chronotropic incompetence in patients with atrial fibrillation (AF) have not been established.

Heart Rate Recovery

The HR increases during exercise because of an increase in sympathetic tone and a decrease in vagal tone. At the cessation of exercise, under

TABLE 15.9 Estimated Functional Capacity Relative to Age and Sex

	ESTIMATED FUNCTIONAL CAPACITY (METS)				
AGE (YR)	POOR	FAIR	AVERAGE	GOOD	HIGH
Women					
≤29	<7.5	8–10	10–13	13–16	>16
30–39	<7	7–9	9–11	11–15	>15
40–49	<6	6–8	8–10	10–14	>14
50–59	<5	5–7	7–9	9–13	>13
≥60	<4.5	4.5–6	6–8	8–11.5	>11.5
Men					
≤29	<8	8–11	11–14	14–17	>17
30–39	<7.5	7.5–10	10–12.5	12.5–16	>16
40–49	<7	7–8.5	8.5–11.5	11.5–15	>15
50–59	<6	6–8	8–11	11–14	>14
≥60	<5.5	5.5–7	7–9.5	9.5–13	>13

METs, metabolic equivalents (1 MET = 3.5 mL/kg/min of oxygen consumption).
From Snader CE, Marwick TH, Pashkow FJ, et al. Importance of estimated functional capacity as a predictor of all-cause mortality among patients referred for exercise thallium single-photon emission computed tomography: Report of 3,400 patients from a single center. *J Am Coll Cardiol*. 1997;30:641–648.

normal circumstances, the reverse process occurs. In athletes and normal persons, there is a biexponential response, with an initial steep 30-second fall in HR followed by a shallower decline thereafter. This biexponential response disappears with the administration of atropine and becomes similar to the response in patients with heart failure. Thus, the initial steep phase is due to parasympathetic activation. Abnormal *HR recovery* (HRR) has been defined by many methods, but the most commonly accepted include less than 12 beats/min decrement after 1 minute with post-exercise slow walking cool-down, less than 18 beats/min after 1 minute with immediate cessation of movement into either the supine or sitting position, and less than 22 beats/min after 2 minutes. In healthy individuals, short-term reproducibility has been demonstrated (see "Classic References").

Abnormal HRR is associated with an increase in all-cause mortality in both asymptomatic individuals and patients with established heart disease.[12] This association is independent of the chronotropic index, beta blockade, CAD severity, LV function, Duke Treadmill Score, and ST-segment depression. HRR adds to the prognostic ability of peak $\dot{V}O_2$. When considered in a multivariable format assessing prognosis, HRR has been found to be an independent predictor of adverse outcomes even when combined with nuclear variables.[13]

BLOOD PRESSURE RESPONSES

Exercise BP responses, as with those for HR, reflect the balance between sympathetic and parasympathetic influences. Systolic BP, pulse pressure (difference between systolic and diastolic BP), HR-BP product (also called the *double product*), and double-product reserve (change in double product from peak to rest) all increase steadily as work rate increases. Diastolic BP increases only minimally or may fall. In most normal individuals, systolic BP will increase to well above 140 mm Hg and the double product to higher than 20,000.

Hypertensive Systolic Pressure Response

This response is usually defined as greater than 210 mm Hg in men and greater than 190 mm Hg in women. Even though these exercise responses are considered abnormal, they are not generally reasons to terminate exercise. Such responses may be indicative of the future development of hypertension or adverse cardiac events.[14]

Exercise-Induced Systolic Hypotension

This has been variably defined but most frequently as systolic pressure during exercise falling below resting systolic pressure.[1] Another definition is a 20 mm Hg fall after an initial rise. Either of these definitions would be an absolute reason to terminate the exercise test. The former definition is more predictive of a poor prognosis and is often related to severe multivessel CAD with LV dysfunction, especially when noted with other signs of ischemia, such as ST depression or angina at a low workload. Its positive predictive value (PPV) is higher in men than in women. Its presence usually warrants consideration of prompt invasive evaluation. Exercise-associated hypotension may also be seen in patients with cardiomyopathy, LV outflow tract obstruction, enhanced vagal tone, hypovolemia, antihypertensive medications, and arrhythmias. In addition, one study of 57,442 patients suggests that exercise-induced hypotension may be a predictor of future AF.[15]

One systolic BP response that needs to be appreciated might be called "pseudo–exercise-induced hypotension." This response occurs in patients who are anxious about the exercise study and begin exercise with a somewhat elevated systolic pressure. As exercise proceeds in the first stage, this elevated BP usually settles down or "falls" toward its customary resting level and the patient looks well. As exercise continues, continued observation reveals a gradual upward trend in BP. Considerable judgment needs to be used when interpreting this response.

Blunted Systolic Pressure Peak

A normal rise in systolic BP is approximately 10 mm Hg per MET increase. A blunted BP rise during exercise may be due to cardioactive medications, or may indicate underlying heart conditions that limit the normal increase in cardiac output during exercise (e.g., cardiomyopathy; aortic stenosis).[3]

ST-Segment Changes

For decades, the change in ST segments was the principal factor considered in the analysis of exercise ECG results (Fig. 15.3). However, the diagnostic value of ST-segment depression has been recognized to be only moderately helpful by current noninvasive test standards, with a sensitivity and specificity of 60% to 70% and 70% to 80%, respectively, based on coronary angiography. When adjusted for referral or workup bias, its sensitivity is lower (45% to 50%) and specificity higher (85% to 90%).[1] Accordingly, the overall prognostic value of ST-segment changes has been appropriately placed behind the prognostic value of non–ST-segment variables, such as functional capacity and HR responses. Despite these issues, it is still appropriate to consider ST-segment changes, but only in the context of other clinical and non–ST-segment data.

ST Depression

When considering ST-segment depression, it is important to use standards that allow application of uniform criteria. The usual criterion applied to raw data is 1 mm or greater or 0.1 mV or greater of horizontal or downsloping (i.e., <0.5 mV/sec) ST-segment depression in three consecutive beats.[3] This assumes that the PQ point (not the TP segment) is used as the isoelectric reference and that the point of ST-segment measurement is 60 to 80 milliseconds after the J point. The 60-millisecond post–J point criterion is used at HR higher than 130 beats/min. This criterion should be added to and not included with existing resting ST-segment depression. ST-segment changes in the presence of early repolarization should be measured from the isoelectric line and not the baseline ST elevation. Unlike ST-segment elevation, exercise-induced ST-segment depression does not localize ischemia to a precise region or vascular bed. The lateral precordial leads (especially lead V_5) are the best for defining positive responses. However, the inferior leads can be helpful in assessing the extent of ischemia when the lateral leads are abnormal as well. Isolated inferior ST depression is frequently falsely abnormal because of the influence of atrial repolarization in these leads.

Although raw data should always be examined, the use of signal-averaged data can be useful, especially when moderate baseline wandering or motion artifact is present. Particular care must be taken to avoid signal averaging that incorporates gross distortions as a result of motion and transient ventricular aberrations such as premature ventricular contractions and intraventricular conduction defects.

Post-exercise recovery responses are also important to assess. First, positive responses are occasionally limited to the recovery period, and these have equal significance to changes that occur at peak exercise. Second, positive changes during exercise that resolve within 1 minute of recovery are associated with a favorable prognosis and low downstream diagnostic test yield.[9] In addition, compared to ST changes longer than 1 minute, early-recovery ST changes are associated with significantly smaller summed stress scores on myocardial perfusion imaging and a lower prevalence of CAD.[16]

Upsloping ST Depression

Rapidly upsloping ST depression that resolves quickly is rarely a true-positive response and is less specific than horizontal or downsloping ST depression. However, ST-segment depression that is slowly upsloping (0.5 to 1.0 mV/sec) may be considered abnormal, especially if it occurs at low workloads. Its presence during exercise may presage horizontal or downsloping depression in recovery. HR adjustment can be applied to upsloping ST segments (see later).

Lead aVR ST Elevation

Emerging literature suggests that 1-mm or greater ST-segment elevation in lead aVR may be a significant predictor of left main CAD, proximal left anterior descending (LAD) artery disease, or at least multivessel CAD.[17] As an isolated marker, it appears to be sensitive, have moderate specificity, and a high negative predictive value (NPV). What is yet unclear is where it fits into the multivariate approach for assessing prognosis.

ST Adjustments

HR adjustments of ST segments have been proposed as an alternative way to analyze ST-segment depression.[1] However, comparative studies have not shown an increase in accuracy. Nevertheless, HR adjustments can be helpful for borderline cases in which ST depression is upsloping or barely abnormal, or traditional criteria and other clinical or exercise data suggest a false-positive result (e.g., low pretest probability or very high HR or workload achieved during exercise). HR adjustment

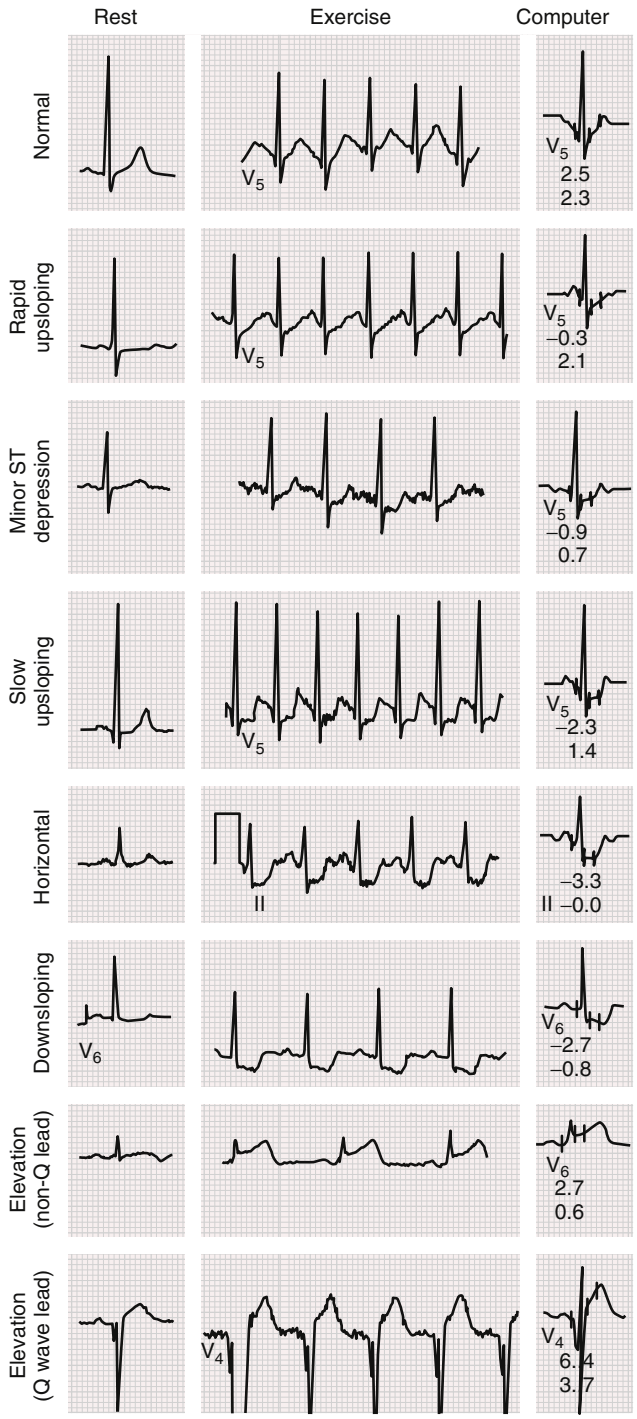

FIGURE 15.3 Eight typical exercise electrocardiographic patterns at rest and at peak exertion. The computer-processed incrementally averaged beat corresponds with the raw data taken at the same time point during exercise and is illustrated in the last column. The patterns represent worsening ECG responses during exercise. In the column of computer-averaged beats, ST80 displacement (*top* number) indicates the magnitude of ST-segment displacement 80 milliseconds after the J point relative to the PQ junction or E point. ST-segment slope measurement (*bottom* number) indicates the ST-segment slope at a fixed time point after the J point to the ST80 measurement. At least three non–computer-averaged complexes with a stable baseline should meet criteria for abnormality before the exercise ECG result can be considered abnormal. The *normal* and *rapid upsloping ST-segment* responses are normal responses to exercise. J point depression with rapid upsloping ST segments is a common response in an older, apparently healthy person. *Minor ST-segment depression* can occur occasionally at submaximal workloads in patients with coronary artery disease (CAD); in this figure, the ST segment is depressed 0.09 mV (0.9 mm) 80 milliseconds after the J point. The *slow upsloping ST-segment pattern* may suggest an ischemic response in patients with known CAD or those with a high pretest clinical risk of CAD. Criteria for slow upsloping ST-segment depression include J point and ST80 depression of 0.15 mV or more and ST-segment slope of more than 1.0 mV/sec. This pattern may also precede horizontal or downsloping ST-segment depression that will occur in recovery. *Classic criteria for myocardial ischemia* include horizontal ST-segment depression observed when both the J point and ST80 depression are 0.1 mV or more and the ST-segment slope is within the range of 1.0 mV/sec. Downsloping ST-segment depression occurs when the J point and ST80 depression are 0.1 mV and the ST-segment slope is –1.0 mV/sec. *ST-segment elevation in a non–Q wave noninfarct lead* occurs when the J point and ST60 are 1.0 mV or higher and represents a severe ischemic response. *ST-segment elevation in an infarct territory (Q wave lead)* indicates a severe wall motion abnormality and, in most cases, is not considered an ischemic response. (From Chaitman BR. Exercise electrocardiographic stress testing. In: Beller GA, ed. *Chronic Ischemic Heart Disease*. In: Braunwald E, series ed. *Atlas of Heart Diseases*. Vol 5. Philadelphia: Current Medicine; 1995:2.1–30.)

can be accomplished by two methods (complicated and simple). The complicated method, known as *ST/heart rate slope*, is automated and available on most stress testing machines as an option to be toggled on or off. It plots ST depression as a function of HR at numerous points during exercise and generates the terminal ST/HR slope for each lead. The criterion for abnormality is 2.4 μV/beat/min. Depending on the protocol used and the duration of exercise, the ST/HR slope will not always be calculated because of insufficient data points. The developers of the method proposed a modification of the standard Bruce protocol to increase the points available for analysis. The slightly less intensive Cornell protocol uses 2-minute rather than 3-minute stages and is useful in patients who are not anticipated to exercise beyond stage 2 of the Bruce protocol. The simple method, known as *ST/HR index*, can easily be calculated by dividing the maximum ST-segment depression in microvolts by the difference in resting and peak HR. The criterion for abnormality is 1.6 μV/beat/min.

ST Elevation

The usual criterion applied to raw data is 1 mm or greater or 0.1 mV of ST-segment elevation above the PQ point at 60 milliseconds after the J point in three consecutive beats. The J point may or may not be elevated as well. Without pathologic Q waves, exercise-induced ST elevation usually indicates either significant proximal coronary stenosis or epicardial coronary spasm. In either case the ST-segment elevation precisely localizes the transmural ischemia to a particular vascular region (e.g., anterior = LAD) and thus, coronary angiography is an appropriate next step. In most cases, coronary angiography should be performed in an expedited fashion. In contrast, when pathologic Q waves are present, ST-segment elevation is usually indicative of an LV aneurysm or significant wall motion change. Ischemia may be involved in this process, and myocardial perfusion imaging is generally required to determine this.

OTHER ELECTROCARDIOGRAM CHANGES

QRS Duration

During exercise there is a normal shortening of the QRS complex, as well as the PR and QT intervals. Exercise-induced bundle branch block (BBB) is rare and occurs at a frequency of 0.5% or less. Exercise-induced left BBB (EI-LBBB) has been reported.[1] When EI-LBBB occurs at HRs higher than 125 beats/min, this finding is not likely to reflect underlying CAD. However, the incidence of CAD does increase when EI-LBBB occurs at progressively lower HRs. One study suggested an increased association of EI-LBBB with death and major cardiac events.[18] The ST-segment changes before onset of the LBBB are still interpretable, but they become uninterpretable once the LBBB begins. Onset and offset of the LBBB usually occur at different HRs.

In contrast, exercise-induced right BBB (EI-RBBB) from one recent large Veterans Affairs series correlated with age, and was not associated with added incremental risk.[19] Limited data are available in women. EI-RBBB does not invalidate interpretation of the ST segment for the inferior (II, III, aVf) and lateral leads (V_5, V_6). However, ST-segment changes limited to V_1 to V_4 are nondiagnostic.

Exercise-Induced Rhythm Changes

Ventricular ectopic activity is noted in up to 20% of patients during exercise testing. It varies from isolated ventricular premature beats to nonsustained VT, to sustained VT. However, frequent ventricular ectopy, which is variably defined, occurs during exercise or recovery in only 2% to 3% of patients. Suppression of resting ventricular ectopic activity during exercise is essentially a normal finding that can occur with or without CAD. In clinical populations referred for testing because of symptoms, ventricular ectopic activity during exercise was predictive of mortality in most studies.[20] In addition, ventricular ectopic beats occurring during exercise or recovery increase the likelihood of future cardiac death.[1]

Exercise-induced supraventricular arrhythmias are not predictive of ischemia or any cardiovascular endpoint. However, they may be a marker for the later occurrence of AF or supraVT.

Pharmacologic Influences on Interpretation

Digitalis Glycosides

That digitalis can have an adverse effect on ST-segment interpretation is generally common knowledge. The principal issue has been false-positive results and reduced specificity. The absence of ST-segment change at rest does not eliminate the effect occurring during exercise. Sensitivity is not affected by digitalis. Therefore, a negative ST-segment response with digitalis is still reliable. For most patients taking digitalis, stress imaging is appropriate as an initial test if the goal of the test is to assess for myocardial ischemia.

Beta Adrenoreceptor Blockers

Beta blockers clearly reduce the rate-pressure product in most patients receiving adequate doses. Evidence indicates that the diagnostic sensitivity and NPV of exercise testing are adversely affected.

For those without established CAD who are undergoing a diagnostic-level exercise ECG, beta blockers should ideally be withheld to allow an adequate HR response. For those undergoing supplemental stress imaging, the issue is less critical given the availability of conversion to pharmacologic stress if the patient fails to achieve the desired HR response.

For those with established CAD, the situation is less clear and it depends on the indication for the stress test. For most patients with CAD, beta blockers are part of their standard medical therapy and have significant effects on both quality and quantity of life (i.e., their prognosis). Therefore, many laboratories do not discontinue these medications. Discontinuing beta blockers in patients with CAD creates a clinical state that is unlike their usual day-to-day existence. We are unaware of any reported studies in patients with established CAD indicating that beta blockers adversely affected the ability of exercise testing (with or without imaging) to detect prognostically important myocardial ischemia such that it would have significantly altered their clinical management. Therefore, discontinuation of beta blockers before exercise testing may be left to the discretion of the referring provider.

Diagnostic Value

Sensitivity and Specificity (see also Chapter 10)

Table 15.10 outlines the diagnostic characteristics of stress testing. Sensitivity and specificity define how effectively a test discriminates individuals with disease from those without disease. *Sensitivity* is the percentage of individuals with a disease who have abnormal test results and, in the case of CAD, is influenced by disease severity, effort level, and the use of anti-ischemic drugs. *Specificity* is the percentage of those without disease who have normal test results, and it may be affected by resting ECG patterns (e.g., LV hypertrophy, ST-T abnormalities, interventricular conduction delay) and drugs such as digoxin or flecainide. All tests have a range of inversely related sensitivities and specificities such that when sensitivity is the highest, specificity is lowest, and vice versa. These can be affected by specifying a *discriminant* or diagnostic cut point. The standard exercise test cut point of 0.1 mV (1 mm) of horizontal or downsloping ST-segment depression in three consecutive beats of at least a single lead has been selected as the discriminating cut point and has a sensitivity of 68% and specificity of 77% (see "Classic References").

TABLE 15.10 Diagnostic Characteristics of the Exercise Electrocardiogram Test

TERM	DEFINITION
True-positive (TP)	Abnormal test result in individual with disease
False-positive (FP)	Abnormal test result in individual without disease
True-negative (TN)	Normal test result in individual without disease
False-negative (FN)	Normal test result in individual with disease
Sensitivity	Percentage of patients with CAD who have an abnormal result = TP/(TP + FN)
Specificity	Percentage of patients without CAD who have a normal result = TN/(TN + FP)
Predictive value of a positive test	Percentage of patients with an abnormal result who have CAD = TP/(TP + FP)
Predictive value of a negative test	Percentage of patients with a normal result who do not have CAD = TN/(TN + FN)
Test accuracy	Percentage of true test results = (TP + TN)/total number tests performed

Modified from Chaitman BR. Exercise stress testing. In Bonow RO, Mann DL, Zipes DP, Libby P, eds. *Braunwald's Heart Disease*. 9th ed. Philadelphia: WB Saunders: 2012.

Once a discriminant value that determines a test's specificity and sensitivity is chosen, the population tested must be considered. If the population is skewed toward individuals with a greater severity of disease, the test will have higher sensitivity. Thus the exercise test has higher sensitivity in individuals with triple-vessel disease than in those with single-vessel disease.[1] The sensitivity and specificity of stress testing are limited by the use of angiographic CAD as the diagnostic "gold standard," so most data are derived from studies in which patients underwent both exercise testing and cardiac catheterization. The data are therefore subject to workup bias, which inflates the estimated sensitivity and deflates the specificity, because patients selected for coronary arteriography are more likely to have obstructive CAD[1] and in some studies, patients with a positive test result were more likely to be referred for angiography.

The *diagnostic accuracy* of a test is the percentage of true test results (total true positives plus total true negatives) among all tests performed. Diagnostic accuracy is additionally influenced by the criteria used to determine whether an adequate level of stress has been achieved. This is currently defined as having attained 85% of the maximum age-predicted HR, with HRmax estimated as "220 – age" (see earlier, "Heart Rate Responses"). Despite many limitations in using this equation for diagnostic purposes, it remains a standard criterion for test adequacy but should not be used as a reason to terminate the test.

Positive and Negative Predictive Values

Predictive values further define the diagnostic value of a test (see Table 15.10). The predictive value of a test is heavily influenced by the prevalence of disease in the group being tested. Bayes' theorem states that the probability of a person having the disease after the test is performed is the product of the probability of the disease before testing and the probability that the test provided a true result. Thus, a test has a higher PPV and lower NPV when used in a population with a high prevalence; conversely, a higher NPV and lower PPV occur in a population with a lower prevalence. For example, an exercise ECG that

demonstrates ST depression in an elderly person with typical anginal symptoms is most likely a true-positive result, whereas that in a young asymptomatic person without cardiac risk factors is most likely a false-positive result.

Pre-Test and Post-Test Probability of Disease

An important part of patient evaluation prior to exercise testing is the assessment of the pre-test probability of obstructive CAD. This can guide the clinician in deciding whether any testing is needed, and if so, what type of test might be the most helpful. This key step can affect the accuracy, yield, and cost-effectiveness of downstream diagnostic testing.[21] Table 15.11 provides a chart of the pre-test likelihood of obstructive CAD (Diamond/Forrester Score) that is contained or cited in most AHA/ACC guidelines,[22] and is widely used**.** It demonstrates the pretest probability of obstructive CAD based on age, sex, and symptoms. However, these data are derived from a cohort of patients who underwent diagnostic invasive coronary angiography, and as such, are subject to significant work-up bias. Hence, the probabilities listed in Table 15.11 overestimate CAD prevalence. More recently, the *CAD Consortium Clinical Score* (Fig. 15.4)[23] which is derived from data that use CT coronary angiography (≥50% stenosis) as the basis to define obstructive CAD, and take into account age, sex, type of pain, and the presence of atherosclerotic risk factors, has been shown in several studies to have significantly greater predictive accuracy regarding the likelihood of obstructive CAD than the Diamond/Forrester Score.[24] Accordingly, the CAD Consortium Clinical Score, which is now readily available (https://qxmd.com/calculate/calculator_287/pre-test-probability-of-cad-cad-consortium) can more reliably assist the clinician in pre-test patient assessment.

There are no widely used and validated calculators that assess the post-test likelihood of obstructive CAD, but several that evaluate post-test prognosis (see "Prognostic Value"). However, using exercise ST-segment criteria and knowledge of the sensitivity and specificity of the test when applied to the pre-test likelihood of disease in a given patient, the post-test likelihood of obstructive CAD can be estimated. This is further discussed in detail elsewhere.[22]

Assessment of Anatomic and Functional Extent of Disease

As discussed earlier, several factors influence the hemodynamic significance of a given coronary artery luminal stenosis, such as the length and complexity of a coronary lesion, and these factors may affect the presence and extent of myocardial ischemia relative to exercise-induced increases in myocardial oxygen demand. Furthermore, exercise-induced ST-segment depression does not provide a reliable assessment of the extent of disease or the specific coronary vessel or vessels involved. ST-segment elevation in leads without Q waves, although an uncommon response, generally reflects transmural ischemia that can be localized by the leads involved: leads V_2 to V_4 reflect LAD disease; lateral leads reflect left circumflex and diagonal vessel disease; and leads II, III, and AVF reflect right CAD (in a right-dominant circulation) (see **"**Classic References"). Other factors related to the probability and severity of CAD include the degree, time of appearance, duration, and number of leads with ST-segment depression or elevation. It is important to realize, however, that prognostically important CAD may be present in the absence of obstructive lesions. Therefore, the use of diagnostic ST-segment analysis alone during exercise testing is inadequate and should be done with consideration of several non–ST-segment variables, as discussed later (see "Prognostic Value").

Testing in Women

Identification of ischemic heart disease in women can be a diagnostic challenge because of several factors, including the lower prevalence of obstructive CAD in women younger than 65, more atypical manifestations of ischemic symptoms, and more frequent resting ST changes. In women with a low pre-test likelihood of CAD, exercise electrocardiographic testing results in a minimal change in assessment from pretest levels. Premenopausal women with one or fewer risk factors for CAD and with nonanginal or atypical symptoms will have a high rate of false-positive tests owing to the lower likelihood of obstructive disease in these low-risk patients. Thus, the exercise ECG in such low-risk women is of little value, except perhaps in selected cases to reassure women with atypical symptoms regarding their low likelihood of obstructive CAD when they have no exercise-induced ischemic ST changes and a low-risk Duke treadmill score.

The reported sensitivity and specificity of exercise electrocardiographic testing in symptomatic women vary greatly depending on the study characteristics and range from 31% to 71% and 66% to 86%, respectively.[25] However, exercise testing has similar diagnostic characteristics in women with an intermediate probability of CAD as it does for men. Thus, exercise testing has the greatest incremental value in intermediate-risk women, particularly when coupled with the Duke treadmill score (see "Prognostic Value"). In a series of 976 symptomatic women referred for exercise testing and coronary angiography, a low-, intermediate-, and high-risk score was associated with obstructive CAD (>75% luminal narrowing) in 19%, 35%, and 89% of women, respectively. Moreover, 2-year cardiac mortality rates in this same cohort of women with low-, moderate-, and high-risk Duke treadmill scores were 1%, 2%, and 4%, respectively. Non–ST-segment variables, including peak exercise capacity (METs), chronotropic response, HRR, and BP response, have prognostic value in women (Table 15.12),[25,26] and are most useful when incorporated into the prognostic scores discussed next. The usefulness of exercise stress testing in the assessment of ischemic heart disease in women has been reviewed and updated in detail by the AHA (Fig. 15.5).[26] The exercise ECG remains the recommended test of first choice for the assessment of symptomatic, intermediate-risk women who can exercise and have normal findings on a resting ECG. A negative and

TABLE 15.11 Pretest Likelihood of Coronary Artery Disease in Symptomatic Patients According to Age and Sex (Combined Diamond/Forrester and CASS Data)

	NONANGINAL CHEST PAIN		ATYPICAL ANGINA		TYPICAL ANGINA	
AGE (YR)	MEN	WOMEN	MEN	WOMEN	MEN	WOMEN
30–39	4	2	34	12	76	26
40–49	13	3	51	22	87	55
50–59	20	7	65	31	93	73
60–69	27	14	72	51	94	86

CASS, Coronary Artery Surgery Study.

From Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients with Stable Ischemic Heart Disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiology Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation*. 2012:126:e354–e471.

Adapted from Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary artery disease. *N Engl J Med*. 1979;300:1350–1358; and Chaitman BR, Bourassa MG, Davis K, et al. Angiographic prevalence of high-risk coronary artery disease in patient subsets (CASS). *Circulation*. 1981;64:360–367.

Consortium prediction model to estimate presence of CAD	
Age	**53**
Sex (M=1, F=0)	**0**
Quality of chest pain (if non-specific, enter 0 for both below)	
Atypical chest pain (Yes=1, No=0)	**1**
Typical chest pain (Yes=1, No=0)	**0**
Diabetes (Yes=1, No=0)	**0**
HTN (Yes=1, No=0)	**0**
HL (Yes=1, No=0)	**0**
Any current or prior smoking history? (Yes=1, No=0)	**0**
CCS available? (Yes=1, No=0)	**0**
Coronary calcium score	
Probability of obstructive CAD in at least 1 vessel	**Results**
CAD consortium basic	**5.0%**
CAD consortium clinical	**3.0%**
Clinical + CCS	

FIGURE 15.4 CAD consortium prediction model to estimate the presence of CAD. Calculator available at https://qxmd.com/calculate/calculator_287/pre-test-probability-of-cad-cad-consortium. In this example, the calculated predicted likelihood of obstructive CAD in a 53-year-old woman with atypical chest pain, no atherosclerotic risk factors, and no available coronary artery calcium score using clinical variables is 3%. *CAD*, Coronary artery disease; *CCS*, coronary calcium score; *F*, female; *M*, male.

TABLE 15.12 Electrocardiogram and Non-Electrocardiogram Variables Associated with an Elevated Ischemic Heart Disease Risk from Exercise Testing in Women

STRESS TESTING VARIABLES	METHOD OF ASSESSMENT	HIGH-RISK VALUE
Exercise capacity	Estimated by ETT protocol (speed and grade)	<5 METs
		<100% age-predicted METs = 14.7–(0.13 × age)
HR recovery	Difference between peak HR at 1 min of recovery	≤12 bpm after 1 min recovery (upright cool-down period)
ST-segment changes	Difference in ST segment Δs (at 60 msec after the J point) between peak exercise (or recovery) and resting ECG	ST-segment depression ≥ 2 mm
		ST-segment depression ≥ 1 mm at <5 METs or >5 min into recovery
		ST-segment elevation ≥ 2 mm (not in q-wave lead or aVR)
DTS	DTS = exercise time (5× STΔ) – (4× angina index)	High-risk DTS less than or equal to –11
BP response	Assessment of BP response to exercise, change in SBP from rest to peak exercise	Decrease in SBP >10 mm Hg from rest
Ventricular arrhythmias		Persistent ventricular tachycardia/fibrillation

BP, blood pressure; *DTS*, Duke Treadmill Score, *ETT*, exercise treadmill testing; *HR*, heart rate; *METs*, metabolic equivalents; *SPB*, systolic blood pressure.
From Mieres JH, Gulati M, Bairey Merz N, et al. Role of noninvasive testing in the clinical evaluation of women with suspected ischemic heart disease: a consensus statement from the American Heart Association. *Circulation*. 2014;130:350–379.

diagnostically adequate test, particularly when associated with low risk scores, makes the likelihood of obstructive CAD very low. A positive or inconclusive test generally requires further evaluation with either a stress imaging test or coronary angiography.

Prognostic Value

Predictive Variables

The strongest predictor of prognosis derived from the exercise test is functional capacity. A weaker predictor is ST-segment depression. All other variables, such as the HR achieved, HRR, BP response, ventricular arrhythmias, and exercise-induced angina, fall between these two extremes. This prognostic hierarchy is similar in both men and women. Table 15.13 provides a summary of the available prognostic scores that use variables derived from the exercise-ECG test.

Multivariable scores are the best way to distill the relative prognostic values of many variables into a single indicator of risk that can be expressed as both continuous (e.g., 0 to 100) and ordinal variables (e.g., low, intermediate, and high). To date, three scores have been developed and validated and are worthy of consideration in analyzing exercise tests.

DUKE TREADMILL PROGNOSTIC SCORE

This score has been available since 1987 (see "Classic References") and is the most widely recognized, used, and validated score. It was cited in the 1997 and subsequent updates of the ACC/AHA exercise test guidelines. It incorporates three treadmill variables: exercise time (Bruce protocol), millimeters of any ST-segment deviation (except aVR), and angina score index (1 = nonlimiting angina and 2 = exercise-limiting angina). It is simple enough to present as the following equation:

$$\text{Score} = \text{Exercise time} - (5 \times \text{ST deviation}) - (4 \times \text{Angina index})$$

ST deviation is the largest net ST-segment displacement in any lead. It is equally valid in men and women, and its prognostic value

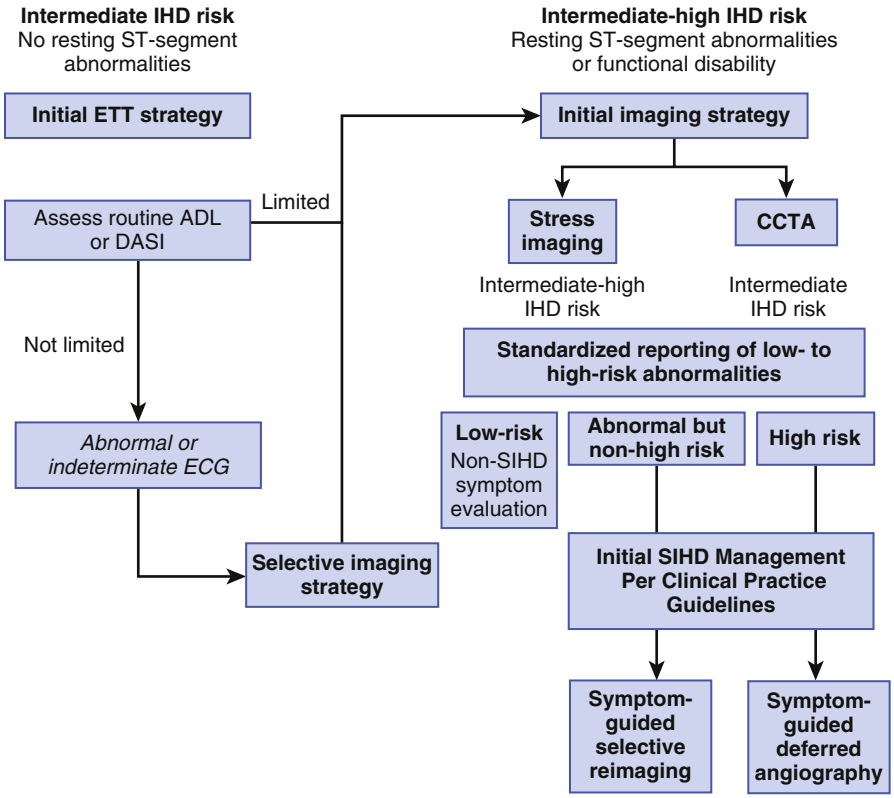

FIGURE 15.5 Diagnostic algorithm for women presenting with suspected ischemic heart disease. *ADL*, Activities of daily living; *CCTA*, coronary computed tomographic angiography; *DASI*, Duke Activity Status Index; *ETT*, exercise treadmill testing; *IHD*, ischemic heart disease; *SIHD*, stable ischemic heart disease. (From Mieres JH, Gulati M, Merz NB, et al. Role of noninvasive testing in the clinical evaluation of women with suspected ischemic heart disease: a consensus statement from the American Heart Association. *Circulation*. 2014;130:350–379.)

is independent of clinical, coronary anatomic, and LV function data. The principal criticism of the Duke score is the absence of consideration of clinical variables, especially age, or other exercise test variables such as HR.

SEPARATE SCORES FOR MEN AND WOMEN

These scores were developed and validated in the early 2000s (see "Classic References"). Separate scores for men and women incorporate three standard exercise test variables (ST-segment depression, peak HR, exercise angina score) and several other clinical variables (Fig. 15.6). These scores are not as simple as the Duke treadmill score but lend themselves to easy clinical application.

Cleveland Clinic Prognostic Score

This score was initially reported in 2007 (see "Classic References"). It incorporates most of the important prognostic exercise test variables, as well as other important clinical variables. The originally published nomogram is more difficult to apply in routine clinical settings, but it is available in a more user-friendly, free, online software application (Fig. 15.7).

Newer Scores and Observations

Several published scores and methods for patients with and without CAD emphasize non–ST-segment variables. None of these has been validated outside the derivation institution or compared to other scores (e.g., Duke treadmill) but nevertheless demonstrate the prognostic power of the non–ST-segment variables in a variety of populations.

The Fitness Risk Score was derived using more than 58,000 adults without established heart disease (about half women) to assess for all-cause mortality.[10] Patients were followed 10 years on average. The maximum predicted HR and functional capacity were the best exercise predictors. The score equation is:

$$\text{Maximum heart rate } (\%) + 12\ (\text{METs}) - 4\ (\text{Age}) + 43\ (\text{if female})$$

Score ranges of greater than 100, 0 to 100, −1 to −100, and less than −100 yielded mean survival at 10 years of 98%, 97%, 89%, and 62%, respectively.

Investigators in Finland proposed the SCORE-exe, which included functional capacity and HR responses to exercise and recovery.[27] In a population of 1531 patients with stable CAD taking beta blockers, these three variables had significant independent prognostic value over other clinical data on cardiovascular death and heart failure admissions. This score is not yet easily applied in the clinical setting.

Park and colleagues[28] followed 898 adults without cardiac disease prospectively for up to 27 years after undergoing treadmill exercise testing. Main outcome measures were silent and overt MI. They found that ST-segment change, inability to achieve target HR, abnormal HRR, and chronotropic incompetence were independent predictors of the outcomes. An integrated scoring model using these four parameters demonstrated a stepwise increase in risk as the number of abnormal parameters increased.

Arbit and associates[13] analyzed 11,218 patients with and without CAD not receiving beta blockers and demonstrated that reduced functional capacity (<7 METs), HRR less than 22 beats after 2 minutes, and chronotropic index less than 80 added significant incremental prognostic value to myocardial perfusion imaging for cardiac death and all-cause mortality. As the number of these three abnormal treadmill variables increased, the risk of mortality increased regardless of the scan interpretation. A patient with a normal scan but two or three variables that were abnormal had the same all-cause mortality risk as a patient with a severely abnormal scan but two or three variables that were normal. This study provides a simple method to incorporate non–ST-segment variables into the interpretation of both stand-alone exercise-ECGs and myocardial perfusion studies.

Post–Myocardial Infarction Evaluation

Since 2002, when the last full set of exercise testing guidelines was updated, treatment of MI and evaluation of post-MI patients have evolved greatly. In the original guidelines, exercise testing carried class I indications before hospital discharge (submaximal, 4 to 7 days), 14 to 21 days after discharge (symptom limited if not performed before discharge), and 3 to 6 weeks after discharge (symptom limited if predischarge submaximal exercise performed). These recommendations were based largely on the existing ACC/AHA guidelines for the management of acute MI. In this setting the exercise test was found to be safe, with a reported mortality rate of 0.03% and a nonfatal event rate of 0.09%.

Since 1997, the use of coronary angiography as part of the diagnostic evaluation and treatment of MI has taken priority. This evolution has limited the role of exercise testing in the stratification of post-MI patients. The most recent guidelines for both ST-segment elevation MI (STEMI)[29] and non-STEMI[30] state that the role of the simple exercise ECG is limited to patients who did not undergo coronary angiography following thrombolytic therapy, or patients who did not receive reperfusion therapy. In addition, these patients should have a LV ejection fraction greater than 40%, no other high-risk features, should be able to exercise, and should have interpretable ECGs. This subset of patients is likely to be a small percentage of the total postinfarction group. In addition, it is highly likely that many of these patients will undergo stress imaging rather than a simple exercise test. Nevertheless, when exercise testing is performed, the variables of prognostic importance are the same as in all other settings: functional capacity, HR, systolic BP, ventricular arrhythmias and ST segment deviation.

In the present clinical environment, realistic goals of exercise testing in the post-MI setting, whenever it is performed, should be threefold: to provide (1) a functional evaluation to guide the exercise rehabilitation prescription, (2) a basis for advice concerning return to work and other physical activities, and (3) an evaluation of present therapy.

TABLE 15.13 Multivariable Prognostic Scores

PROGNOSTIC SCORE	PROGNOSTIC INFORMATION	NUMBER OF PARTICIPANTS (N)	REFERENCE
Duke treadmill	Exercise time ST-segment deviation Angina score	613	Shaw LJ et al.
Cleveland Clinic	HRR Duke treadmill score	9,454	Lauer MS et al.
Fitness risk score	Maximal HR Functional capacity Age Gender	58,000	Ahmed HM et al.
SCOREexe	Functional capacity HR response	1,531	Kiviniemi AM et al.
Rancho Bernardo	ST depression Chronotropic incompetence HRR	898	Park J-I et al.
Arbit et al.	Exercise capacity HRR Chronotropic incompetence	11,218	Arbit B et al.

HR, Heart rate; *HRR*, heart rate recovery.
From Shaw LJ, Peterson ED, Shaw LK, et al. Use of a prognostic treadmill score in identifying diagnostic coronary disease subgroups. *Circulation*. 1998;98:1622–1630; Lauer MS, Pothier CE, Magid DJ, et al. An Externally validated model for predicting long-term survival after exercise treadmill testing in patients with suspected coronary artery disease and a normal electrocardiogram. *Ann Intern Med*. 2007;147:821–828; Ahmed HM, Al-Mallah MH, McEvoy JW, et al. Maximal exercise testing variables and 10-year survival: fitness risk score derivation from the FIT project. *Mayo Clin Proc*. 2015;90:346–355; Kiviniemi AM, et al. Exercise capacity and heart rate responses to exercise as predictors of short-term outcome among patients with stable coronary artery disease. *Am J Cardiol*. 2015;116:1495–1501; Park J-I, Shin SY, Park SK, et al. Usefulness of the integrated scoring model of treadmill tests to predict myocardial ischemia and silent myocardial ischemia in community-dwelling adults (from the Rancho Bernardo study). *Am J Cardiol*. 2015;115:1049–1055; Arbit B, Azarbal B, Hayes SW, et al. Prognostic contribution of exercise capacity, heart rate recovery, chronotropic incompetence, and myocardial perfusion single-photon emission computerized tomography in the prediction of cardiac death and all-cause mortality. *Am J Cardiol*. 2015;116:1678–1684.

VARIABLE	CHOOSE RESPONSE	SUM
Maximal heart rate	Less than 100 bpm = 30	
	100 to 129 bpm = 24	
	130 to 159 bpm = 18	
	160 to 189 bpm = 12	
	190 to 220 bpm = 6	
Exercise ST depression	1 to 2 mm = 15	
	Greater than 2 mm = 25	
Age	Greater than 55 yr = 20	
	40 to 55 yr = 12	
Angina history	Definite/typical = 5	
	Probable/atypical = 3	
	Noncardiac pain = 1	
Hypercholesterolemia?	Yes = 5	
Diabetes?	Yes = 5	
Exercise test: induced angina	Occurred = 3	
	Reason for stopping = 5	
	Total score:	

Exercise test score
MEN
Choose one per group
<40 = low probability
40-60 = intermediate probability
>60 = high probability

A

VARIABLE	CHOOSE RESPONSE	SUM
Maximal heart rate	Less than 100 bpm = 20	
	100 to 129 bpm = 16	
	130 to 159 bpm = 12	
	160 to 189 bpm = 8	
	190 to 220 bpm = 4	
Exercise ST depression	1 to 2 mm = 6	
	Greater than 2 mm = 10	
Age	Greater than 65 yr = 25	
	50 to 65 yr = 15	
Angina history	Definite/typical = 10	
	Probable/atypical = 6	
	Noncardiac pain = 2	
Smoking?	Yes = 10	
Diabetes?	Yes = 10	
Exercise test: induced angina	Occurred = 9	
	Reason for stopping = 15	
Estrogen status	Positive = –5, Negative = 5	
	Total score:	

Exercise test score
WOMEN
Choose one per group
<40 = low probability
40-60 = intermediate probability
>60 = high probability

B

FIGURE 15.6 Prognostic Exercise Test Scores for Men and Women. Exercise test scores for men **(A)** and women **(B)**; *bpm,* beats per minute. To determine risk group, total points for the appropriate choice for each clinical and exercise test variable. If there is no appropriate choice for a particular variable, score points as zero for that variable. *Exercise ST depression* is only horizontal or downsloping. *Diabetes* is insulin or noninsulin requiring. *Smoking* is any current or prior cigarette smoking. *Estrogen status* positive includes women who are premenopausal, receiving hormone replacement therapy, or with intact ovaries under age 50. Otherwise, women are estrogen status negative. (From Morise AP, Jalisi F. Evaluation of pretest and exercise test scores to assess all-cause mortality in unselected patients presenting for exercise testing with symptoms of suspected coronary artery disease. *J Am Coll Cardiol*. 2003;42:842–850.)

Predicting long-term survival (for suspected patients with a normal electrocardiogram)

Abnormal heart rate recovery: No | Yes

Age (Years): 30-93

Diabetic? No

Frequent ventricular ectopy during recovery: No | Yes

History of smoking? No | Yes

Hypertension? No | Yes

Male? No | Yes

Proportion of predicted METs achieved: 0.2-2.4

ST segment depression (mm): 0-8

Test-induced angina pectoris? No | Yes

Typical angina pectoris? No | Yes

Run calculator | Reset

FIGURE 15.7 Cleveland Clinic prognostic score. Predicts 3-, 5- and 10-year survival after exercise treadmill testing. The Cleveland Clinic Risk Calculator is available at https://riskcalc.org/. Entering this URL will bring you to the site listing many scores developed at the Cleveland Clinic. Choose "Heart Disease" and then "For Patients with Suspected Coronary Artery Disease and a Normal Electrocardiogram". Definition of terms used in this calculator follow. *Typical angina*: chest discomfort that is substernal, is brought on by physical or mental exertion, and is relieved within minutes by rest or nitroglycerin. *Smoking*: regular smoking now or within the past year. *Hypertension:* resting systolic BP ≥140 mm Hg, resting diastolic BP ≥90 mm Hg, or use of medications for treatment of hypertension. *Proportion of predicted* metabolic equivalents *(METs)* (metabolic equivalents) *achieved*: in men, predicted METs = [14.7 – (0.11 × age)]; in women, [14.7 – (0.13 × age)]. *ST depression:* only count horizontal or downsloping ST depression that is at least 1 mm; otherwise record as 0. *Exercise-induced angina:* any angina is included, whether or not it is test terminating. *Abnormal heart rate recovery:* calculated as HR at the end of graded exercise minus HR 1 min later; for upright cool-down, consider abnormal if ≤12 beats/min; for supine cool-down, consider abnormal if ≤18 beats/min. *Frequent ventricular ectopy in recovery:* includes at least seven premature ventricular beats/min, frequent ventricular couplets, any ventricular triplets, nonsustained or sustained ventricular tachycardia or torsade des pointes, or ventricular fibrillation occurring in the first 5 minutes of recovery.

Preoperative Evaluation in Noncardiac Surgery (see Chapter 23)

It is estimated that noncardiac surgery has a complication rate as high as 11%, and that more than 40% of these complications are due to cardiovascular issues.[31] Cardiovascular complications are the leading cause of perioperative death within 30 days of surgery, with a rate currently estimated at 1.7% in the United States,[32] that is similar worldwide.[31] Comprehensive consideration of the type of surgery that is to be performed along with an appropriate evaluation of each specific patient aims to yield a benefit-risk assessment that guides subsequent decisions and patient management. Although stress testing is widely used in the evaluation of patients with CVD, very few randomized trials have addressed the value of preoperative stress testing. A recent comprehensive systematic review and meta-analysis of preoperative testing prior to noncardiac surgery[33] found a general lack of quality studies available. Most studies did not have a comparator group and there was a high heterogeneity among the studies. These data strongly support the current American[34] and European[31] guidelines that find no role for indiscriminate and routine preoperative stress testing. Importantly, such testing should be guided by patient history with specific signs and symptoms that suggest high risk CVD in the context of the particular type of noncardiac surgery that is to be performed. Such an assessment is integral to guide subsequent decisions regarding treatments and interventions, if any, that might mitigate postoperative adverse events.

Assessment of Therapy

The exercise ECG can be applied to assess the efficacy of therapy, whether medication, revascularization, cardiac rehabilitation, ablation, or other. Serial exercise testing can be performed to assess HR and double product at the onset of ischemia (i.e., angina or ST-segment depression). These parameters are generally chosen because of their reproducibility. Peak $\dot{V}o_2$ is the most reproducible measure, but CPX is not performed routinely.

EXERCISE TESTING IN NONATHEROSCLEROTIC HEART DISEASE

The latest iteration of ACSM guidelines on exercise testing is dominated by diagnostic and prognostic assessments of atherosclerotic CAD.[3] Less prominent are applications that pertain to certain nonatherosclerotic conditions. In each case, exercise imaging, especially with echocardiography, provides important information for evaluation of these conditions. This section emphasizes and expands on the value of the exercise-ECG test.

Valvular Heart Disease

The role of exercise ECG testing in patients with valvular heart disease is best exemplified in the current valvular heart disease guidelines from AHA/ACC, which were updated in 2020 (see Chapters 72, 73, and 75 to 77).[35] Exercise testing also has a role in patients with valvular heart disease who want to participate in competitive athletic activity.[36] Frequently, exercise testing is combined with echocardiography to assess structural and physiologic responses. This is the preferred approach in evaluating patients with mitral stenosis and disparate clinical and resting echocardiographic data, such as severe stenosis without symptoms or symptoms with mild to moderate stenosis. In patients with chronic severe mitral or aortic regurgitation, the diagnostic role of exercise testing is limited to the evaluation of functional capacity in patients with equivocal symptoms. The only valve lesion in which the simple exercise ECG still has a significant role in management is aortic stenosis. This latter topic is discussed in greater detail elsewhere.[37]

Aortic Stenosis

It is universally agreed that exercise testing is absolutely contraindicated in patients with symptomatic severe valvular aortic stenosis.[35] However, for asymptomatic patients, exercise testing has found a role in two specific scenarios (see Chapter 72).

Severe Acquired Aortic Valve Stenosis

The first scenario is asymptomatic patients with severe acquired valvular aortic stenosis, defined as a peak Doppler velocity of 4 m/sec or greater, valve area less than 1 cm^2, or a mean valve gradient greater than 40 mm Hg with associated normal LV systolic function.[38] Patients with more moderate stenosis but suspected symptoms might also be considered. When peak aortic velocity exceeds 5.5 m/sec, exercise testing should not be done even in the absence of symptoms.[39] In addition, patients with severe aortic stenosis and high-gradient and normal LV function are to be distinguished from those with low-gradient stenosis and either normal or reduced LV systolic function; this latter important issue warrants further evaluation that includes stress—echocardiography and not simple exercise—ECG testing.

Customary practice is to defer aortic valve replacement until symptoms develop (see Chapter 72). However, some patients with asymptomatic severe aortic stenosis who do not undergo early aortic valve replacement are still at increased short- and longer-term risk. The purpose of exercise testing in this setting is to induce either symptoms or an abnormal BP response, which most studies define

as a lack of increase or ≤20 mm Hg increase in systolic BP (Class IIa, level of evidence B). The Class IIa indication provides a basis to recommend valve replacement in patients who do not report any of the expected symptoms of severe aortic stenosis. Exercise testing in this scenario should be performed only in those with no reported symptoms or with symptoms that are equivocal at worst, such that aortic valve surgery is not indicated on that basis. They should have no extracardiac factors that limit exercise and no contraindications to aortic valve replacement. Considering that replacement of the aortic valve can currently be performed surgically or percutaneously, absolute contraindications for replacement are evolving. Protocols less intense than the standard Bruce protocol should be used, especially in elderly or untrained individuals. A modified Bruce or other low-level protocol can be used for patients who might manifest an earlier-than-anticipated adverse response. Special emphasis should be placed on the minute-by-minute BP response, patient symptoms, and heart rhythm. Exercise should be terminated for limiting dyspnea and fatigue at a low workload, any angina or dizziness, any decrease in systolic BP, and complex ventricular ectopy. All these should be considered abnormal responses, placing the patient in a higher-risk group. Limiting dyspnea and fatigue must be interpreted carefully according to what is appropriate for age- and sex-based expectations. Isolated ST-segment depression (i.e., >2 mm of horizontal or downsloping depression) is very prevalent but is considered a nonspecific finding in severe aortic stenosis.[37] If possible, termination should include a 2-minute cool-down walk and avoidance of the supine position to obviate acute LV volume overload.

Moderate to Severe Congenital Valvular Aortic Stenosis

The second scenario consists of young or adolescent patients with congenital aortic valve stenosis that is moderate to severe, defined as a mean Doppler gradient greater than 30 mm Hg or a peak Doppler gradient greater than 50 mm Hg. Exercise testing in this specific scenario is done to provide advice for patients wanting to participate in athletic activities,[36] as well as to evaluate asymptomatic patients with severe stenosis to assess the BP response and exercise tolerance, as with acquired stenosis. The testing procedure is similar to that for acquired aortic stenosis.

Mitral Regurgitation

In asymptomatic patients with severe mitral regurgitation, exercise testing may be useful to elicit symptoms or demonstrate reduced exercise capacity, and may prompt reclassification of patients to a stage of disease that warrants structural intervention with repair, replacement or mitral clip.

Echocardiographic stress testing can provide information beyond exercise capacity and is discussed elsewhere (see Chapter 76). Alternatively, a 6-minute walk test can be used in frail or elderly patients with severe mitral regurgitation to better reflect impairments in the ability to perform activities of daily living.[40]

Hypertrophic Cardiomyopathy

Exercise testing can play an important role in the evaluation of patients with HCM (see Chapter 54). In the 2020 ACC/AHA guidelines on HCM,[41] the exercise test carries a class I recommendation (level of evidence B) for assessing dynamic outflow obstruction using exercise echocardiography and for assessing patients with nonobstructive HCM for possible cardiac transplantation using CPX. In addition, class IIa indications (level of evidence B) are provided for determination of functional capacity and for risk stratification (i.e., rhythm and BP). Several reported series have demonstrated that such testing in patients with HCM is safe with a low and acceptable incidence of fatal and nonfatal complications.

Exercise testing in patients with HCM has clinical value in three clinical situations[38]: (1) defining the presence of exercise-induced outflow tract obstruction with Doppler echocardiography in patients with no gradient at rest; (2) identifying patients with coexistent CAD; (3) detecting patients with the high-risk indicator of an abnormal BP response.

The first two questions require exercise testing with imaging since in HCM, the exercise ECG is nonspecific for the evaluation of ischemia, and Doppler echocardiography is required to assess resting and exercise induced dynamic LV outflow tract gradients. These are discussed in detail elsewhere.[38,41]

An abnormal BP response during upright treadmill exercise is a risk factor for SCD in patients with HCM (see Chapter 54). It is of greater predictive value in patients younger than 50 years. An abnormal BP response is defined as either an initial increase in systolic pressure with a subsequent fall greater than 20 mm Hg, or a continuous fall from the start of exercise greater than 20 mm Hg. The NPV for SCD is reported to be in the mid-90% range, whereas the PPV is low. Therefore, further stratification as outlined in the guidelines[41] is required beyond the abnormal BP response. It is considered reasonable to reassess the BP response after therapy to reduce the outflow tract obstruction, but no data exist on this issue.

Adult Congenital Heart Disease

The 2018 AHA/ACC Guideline for the Management of Adults with Congenital Heart Disease[42] outlines the role of the exercise test for the evaluation of patients with selected congenital defects (see Chapter 82). The guidelines provide a class IIa recommendation for CPX for baseline evaluation and serial follow-up for response to treatment. In patients unable to perform CPX, a 6-minute walk test is recommended (class IIa) as it can provide objective information regarding prognosis beyond history alone. The use of exercise testing in several specific types of adult congenital heart disease is discussed.

A 2015 scientific statement from ACC/AHA addresses the selective use of exercise testing in individuals with congenital heart disease who want to participate in competitive athletics. The specific conditions where the exercise-ECG has a role include repaired and unrepaired aortic coarctation, repaired tetralogy of Fallot, surgically and congenitally corrected transposition of the great arteries, and coronary artery anomalies. Details regarding sport-specific intensity levels and recommendations are provided.[43]

CARDIAC RHYTHM DISTURBANCES

Exercise testing can be used in the evaluation of suspected cardiac arrhythmias, premature ventricular complexes (PVCs), or nonsustained VT.[1,20] Table 15.14 summarizes indications for exercise testing in the evaluation of arrhythmias. In addition, concerning the eligibility recommendations for competitive athletes with cardiac arrhythmias, an ACC/AHA statement covers the role of exercise testing in the settings of sinus bradycardia, heart block, isolated ventricular ectopic beats, nonsustained VT, and sustained monomorphic VT.[44]

Atrial Fibrillation

The AF guidelines state that exercise testing should be performed for three specific scenarios (see Chapter 66).[45] The first indication is when myocardial ischemia is suspected and initiation of type IC antiarrhythmic drug therapy is being considered. The second indication involves assessing the adequacy of HR control across a full spectrum of activity in patients with persistent or permanent AF (class Ic). No standard method for assessment of HR control has been established to guide management in patients with AF. Criteria for HR control vary with patient age but usually involve achieving ventricular rates between 90 and 115 beats/min during moderate exercise. Lastly, exercise testing may be used to induce possible exercise-induced AF.

Ventricular Preexcitation

Exercise testing carries a class Ib recommendation in either symptomatic or asymptomatic patients with preexcitation.[46] Identifying accessory pathways that are at risk of developing rapid conduction and life-threatening ventricular arrhythmias in response to AF is an important consideration. The abrupt loss of preexcitation during exercise testing identifies a low-risk patient in this respect. Care should be taken to ensure that the delta wave is truly absent. It is noteworthy that preexcitation with conduction abnormalities is a well-known cause of false positive ST segment changes.

Ventricular Arrhythmias

The 2017 AHA/ACC/Heart Rhythm Society Guideline for the Management of Patients with Ventricular Arrhythmias and the Prevention of

TABLE 15.14 Guideline Recommendations for Exercise-Electrocardiogram Testing in Heart Rhythm Disorders

Class I
Exercise testing is useful to assess for exercise-induced ventricular arrhythmias in patients with ventricular arrhythmia symptoms associated with exertion, suspected ischemic heart disease, or catecholaminergic polymorphic ventricular tachycardia *(Level of evidence: B-NR).*
In *asymptomatic* patients with preexcitation, the findings of abrupt loss of conduction over a manifest pathway during exercise testing in sinus rhythm is useful to identify patients at low risk of rapid conduction over the pathway *(Level of evidence B-NR).*
In *symptomatic* patients with preexcitation, the findings of abrupt loss of conduction over the pathway during exercise testing in sinus rhythm is useful for identifying patients at low risk of developing rapid conduction over the pathway *(Level of evidence B-NR).*
Class IIa
In patients with suspected long QT syndrome, exercise testing can be useful for establishing a diagnosis and monitoring the response to therapy *(Level of evidence B-NR).*
Exercise testing can be useful for evaluating response to medical or ablation therapy in patients with known exercise-induced ventricular arrhythmias *(Level of evidence: B)*
In patients with suspected chronotropic incompetence, exercise electrocardiographic testing is reasonable to ascertain the diagnosis and provide information on prognosis *(Level of evidence B-NR).*
In patients with exercise-related symptoms suspicious for bradycardia or conduction disorders, or in patients with 2:1 atrioventricular block of unknown level, exercise electrocardiographic testing is reasonable (*Level of evidence C-LD*)
In patients with exertional symptoms (e.g., chest pain, shortness of breath) who have first-degree or second-degree Mobitz type I atrioventricular block at rest, an exercise treadmill test is reasonable to determine whether they may benefit from permanent pacing (*Level of evidence C-LD*)
Atrial Fibrillation
The following are included as indications for exercise testing in atrial fibrillation, but are not given a recommendation class or level of evidence: • If adequacy of rate control is in question. • To reproduce exercise-induced atrial fibrillation. • To exclude ischemia before treatment of selected patients with a class IC antiarrhythmic drug.

From Al-Khatib SM, et al. 2017 ACC/AHA/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Circulation*. 2018;138:e210–e271; January CT, Samuel Wann L, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation. *Circulation*. 2014;130:e199–e267; Kusumoto FM, Mark H. Schoenfeld MH, et al. ACC/AHA/HRS guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay. *Circulation*. 2019;140: e382–e482; Page RL, Joglar JA, Caldwell, MA, et al. 2015 ACC/AHA/HRS guideline for the management of adult patients with supraventricular tachycardia. *Circulation*. 2016;133; e506–e574; Tracy CM, Hirsch AT, Misra S, et al. 2012 ACCF/AHA/HRS focused update of the 2008 guidelines for device -based therapy of cardiac rhythm abnormalities. *Circulation*. 2012;126:1784–1800.

Sudden Cardiac Death recommend that exercise testing be performed for known or suspected exercise-induced ventricular arrhythmias in order to provoke and diagnose the arrhythmia and determine response to the tachycardia.[20] Exercise-induced ventricular arrhythmias can be associated with CAD. Therefore, detection of ischemia with or without associated ventricular arrhythmias defines a role for the exercise test.

With respect to patients with known or suspected exercise-induced ventricular arrhythmias, it should be understood that exercise testing in this high-risk cohort is not a low-risk endeavor, and in many cases the physician should be in the room for the test. It is reasonable in these cases to have intravenous access in place.

Catecholaminergic Polymorphic Ventricular Tachycardia

This arrhythmia occurs in genetically predisposed individuals when they are subjected to intense emotional or physical stress.[38] Standard cardiac testing, including the ECG at rest, usually produces normal results. The arrhythmia is almost always inducible by a maximal exercise test and is frequently not inducible with programmed electrical stimulation. Catecholaminergic polymorphic VT generally appears in HRs above 120 to 130 beats/min and begins with polymorphic ventricular premature beats progressing to nonsustained VT and eventually to bidirectional or polymorphic VT. The purpose of the exercise test, therefore, is to achieve a diagnosis and determine the patient's response to treatment, namely, beta blockade.[20]

Long-QT Syndrome

When LQTS is suspected and the rest QTc is borderline, exercise testing can be performed safely given that arrhythmias do not usually develop in patients with LQTS during exercise (see Chapter 63). In addition, changes in the QT interval with exercise can be useful in identifying and stratifying patients with LQTS.[20] Further prolongation of (or failure to shorten) an already prolonged QT interval with exercise is typical of LQT1. LQT2 has normal shortening, whereas LQT3 has supranormal shortening of the QT interval with exercise. Beta blockade normalizes these responses. These responses can be useful in predicting and directing genetic testing in patients with LQTS.

Arrhythmogenic Right Ventricular Cardiomyopathy

Even though arrhythmias and SCD can occur during exercise in patients with arrhythmogenic right ventricular cardiomyopathy, exercise testing has no significant role in the management of these patients. Serious ventricular arrhythmias that do occur during exercise usually take the form of monomorphic VT with an LBBB pattern.[47]

ASSESSMENT OF THERAPY

Assessing the response to medical, ablative, or surgical therapy for exercise-induced ventricular arrhythmias is a class IIa, level of evidence B indication. Unlike anti-ischemic therapy, the endpoint is the presence or absence of significant ventricular arrhythmias with reasonable levels of exercise, depending on patient-specific factors.[48]

ASSESSMENT OF PACEMAKER FUNCTION

Even though earlier guidelines endorse exercise testing with rate-adaptive pacemakers to fine-tune or maximize the physiologic response, the 2012 guidelines regarding device-based treatment of cardiac arrhythmias do not even mention the use of exercise testing with implanted pacemakers.[48] This discrepancy raises a practical question. Despite the original endorsement of exercise testing in patients with rate-adaptive pacemakers, do electrophysiologists actually use exercise testing in clinical decision making for rate-adaptive pacemakers? Exercise testing could play a role with rate-adaptive pacemakers when exercise intolerance is not completely relieved by factory settings or empiric adjustments. This would be especially true in patients involved in significant physical activities or athletic participation.[38]

ADDITIONAL USES FOR EXERCISE TESTING

Chest Pain Units

Chest pain units are designed to assist in the triage and management of low-risk patients with chest pain among the millions of patients evaluated in emergency departments annually. Low-risk patients have stable hemodynamic signs, no arrhythmias, normal or near-normal findings on the ECG, and negative cardiac injury biomarkers and are appropriate for observation in a chest pain unit. Such units are designed to provide an integrated approach to further risk stratification by short-term observation, repeated ECGs, and serial cardiac injury biomarkers. In patients without further chest pain and no objective evidence of ischemia, an exercise test can be performed after 8 to 12 hours of observation. Such testing is often performed with a symptom-limited treadmill protocol. Several studies encompassing more than 3000 such patients have demonstrated that a negative test has a high NPV for subsequent cardiac events (Table 15.15). No adverse events during exercise testing have been reported. Those with a positive test are admitted for further evaluation, whereas those with a negative test can be discharged safely with outpatient follow-up. This strategy has been shown to be cost-effective compared with usual care in which such patients are admitted to the hospital.[49] Patients who are unable to exercise

TABLE 15.15 Chest Pain Unit: Patient Selection, Testing Procedure, and End Points

Patient Selection Criteria
Able to exercise
ECG: Normal or minor ST-T changes
Hemodynamically stable, no arrhythmia
Negative cardiac injury markers
Procedure
Bruce or modified Bruce protocol
End points
Symptom-limited
Ischemia (≥0.10 mV of horizontal ST depression or elevation)
Decreased blood pressure (≥10 mm Hg systolic) during exercise test
Result
Positive: ≥0.10 mV of horizontal ST-segment depression
Negative: No exercise-induced abnormalities at 85% MPHR
Nondiagnostic: <85% MPHR with no ECG evidence of ischemia

ECG, Electrocardiogram; *MPHR*, maximum age-predicted HR.
From Amsterdam EA, Lettino M, Ahrens I, et al. Testing of low-risk patients presenting to the emergency department with chest pain: a scientific statement from the American Heart Association. *Circulation*. 2010;122:1756.

or who have baseline electrocardiographic abnormalities can undergo stress imaging tests or computed tomographic angiography. The usefulness of such tests is discussed in detail elsewhere (see Chapters 16, 18, and 20).

The advent of high-sensitivity troponin testing may re-define the role of stress testing in the emergency department or chest pain unit. A recent expert panel concludes that management algorithms that include high-sensitivity troponin testing aim to mitigate over-testing, emergency department and chest pain unit overcrowding, and the low yield of true-positive testing. In this new paradigm, stress testing plays a more limited and specific role.[50]

Physical Activity and Exercise Prescription

Data derived from the exercise test can yield valuable objective information to assist in providing physical activity recommendations for patients with CVD, specifically regarding domestic, occupational, recreational, and athletic activities (see Chapter 33). The 2011 Compendium of Physical Activities: a Second Update of Codes and MET Values (see "Classic References") and its associated web link (http://links.lww.com/MSS/A82) provide 821 codes that reflect 21 major headings, numerous specific activities and their detailed descriptions, and associated MET values that can be used to identify the energy cost associated with a given activity. By using the exercise test to measure peak exercise capacity in METs and evaluate the HR, BP, and symptomatic responses to peak and submaximal MET levels, the clinician can combine this information with that derived from the compendium to counsel patients on their ability to perform a broad spectrum of activities and tasks. Ample data for the cardiac rehabilitation literature has shown that exercise in the range of 70% to 85% of the maximal measured HR is exceedingly safe.[51] It is important to realize, however, that the exercise test does not yield information regarding the patient's ability to perform sustained tasks for long periods or take into account the environmental conditions (e.g., temperature, humidity, altitude, wind) where the activity is performed. Therefore, data from the exercise test and the compendium can serve only as a guide to prudent activity counseling. Patients must be made aware of these other factors and instructed to use subjective symptoms scales (e.g., Borg Scale of Perceived Exertion) and HR to further tailor their activity performance.

Exercise training programs are designed to maintain or improve fitness and include the prescriptive components of intensity, duration, frequency, and modality. Details regarding the exercise prescription for patients with CVD are provided elsewhere.[1,3,51] For patients with CVD, the *intensity* of dynamic aerobic exercise is usually determined from the results of a pretraining exercise test by using either of two methods: 40% to 80% of peak exercise capacity using the *HR reserve* method ([peak HR – resting HR] × [percent intensity] + [resting HR]), and in patients who have performed a CPX, the HR at 40% to 80% of the measured peak $\dot{V}o_2$. A simpler approach is to have individuals exercise at 70% to 85% of their maximal measured HR. Intensity may be modified further by using the subjective perceived exertion scale at a rating of 11 to 16 on a scale of 6 to 20. In patients with an ischemic response during exercise, the intensity should be prescribed at a HR that is at least 10 beats below the symptomatic ischemic threshold (i.e., the HR at which ischemic ST depressions and typical angina begin to occur). The goal *duration* of exercise at the prescribed intensity is generally 20 to 60 minutes per session at a *frequency* of 3 to 5 days per week. Training *modalities* should ideally incorporate exercises that include rhythmic, large muscle group activities of both the upper and the lower extremities with varying types of exercise equipment such as treadmills, cycle ergometers and elliptical trainers. A symptom limited ECG stress test can also screen for the safety of resistance training in cardiac patients as the maximal HR × BP product attained at the stress test is rarely exceeded during clinical (non-body building) strength training (see "Classic References").

Emerging data on aerobic interval training (AIT) offer promise for patients with CVD. AIT involves alternating 3- to 4-minute periods of exercise at very high intensity (90% to 95% of peak HR) with exercise at moderate intensity (60% to 70% of peak HR). When such training is performed for approximately 40 minutes, three times per week, studies demonstrate greater improvements in peak $\dot{V}o_2$, endothelial function, and metabolic parameters than with standard continuous, moderate-intensity exercise.[52] The cardiovascular risks of AIT appear to be low in a supervised cardiac rehabilitation setting. Although more studies are needed, AIT can be considered in select patients as an alternative training modality for those with CVD enrolled in cardiac rehabilitation program.

DISABILITY ASSESSMENT

The U.S. Social Security Administration defines disability as "the inability to engage in any substantial gainful activity by reason of any medically determinable physical or mental impairment(s) which can be expected to result in death or which has lasted or can be expected to last for a continuous period of not less than 12 months."[53] In several cardiovascular conditions, disability is not based solely on the diagnosis but also on the functional limitations imposed by the condition. Thus, exercise testing plays an integral role in the determination of disability for several cardiovascular conditions, including chronic heart failure, ischemic heart disease, congenital heart disease, PAD, and valvular heart disease. The Institute of Medicine (IOM) convened a panel of experts to provide recommendations for updating the Social Security listings for cardiovascular conditions. Although each of the previous conditions have specific criteria to define the condition, functional disability in almost all of them is defined by the inability to attain a directly measured peak $\dot{V}o_2$ of 15 mL/kg/min using gas exchange (or 5 estimated METs) on a symptom-limited treadmill or stationary cycle test. Table 15.16 outlines details regarding exercise test criteria for specific cardiovascular conditions as recommended by IOM.

Evaluation of Peripheral Artery Disease

Exercise testing can be performed in patients with PAD to establish further the diagnosis by noninvasive techniques, particularly in patients with calf pain and borderline ankle-brachial indices (ABIs: 0.91 to 1.0), and objectively evaluate functional limitations imposed by PAD and the subsequent response to therapies (see Chapter 43). Assessment of the time to initial claudication symptoms *(claudication onset time)* and the *peak exercise time* to maximum tolerated calf pain should be assessed by using gradual graded exercise treadmill stages, such as the Gardner protocol (Table 15.17). For functional assessment, the 6-minute walk test (see Table 15.8) can also be used; during this test, both time and distance are measured to onset and to peak calf pain.

The post-exercise ABI can provide additional diagnostic information and is done by measuring the ABI in both ankles at rest and again immediately after exercise (see Chapter 43). During leg exercise, systolic BP normally increases in the arms but decreases in the

TABLE 15.16 Exercise Test Criteria for Disability Determination in Specific Cardiovascular Conditions

CARDIOVASCULAR CONDITION	SOCIAL SECURITY CRITERIA	IOM RECOMMENDATIONS
Chronic heart failure	Inability to attain five METs due to symptoms of dyspnea, fatigue, palpitations, or chest discomfort; frequent or complex ventricular ectopy; >10 mm Hg decrease in systolic blood pressure during graded exercise; signs due to inadequate cerebral perfusion.	Exercise testing in chronic heart failure is safe; CPX testing requires less subjective endpoint interpretation, using criteria of measured peak VO_2 <15 mL/kg/min with RER >1.1; or <5 estimated METs on standard treadmill test without gas exchange; frequent exercise-induced ventricular ectopy alone should not be listed as a criterion.
Ischemic heart disease	Exercise tolerance testing that demonstrates ischemia, or ≥10 mmHg fall in systolic blood pressure at ≤5 METs	Additional specific criteria when stress imaging tests are used.
Peripheral arterial disease	≥ 50% decrease in systolic blood pressure at the ankle from resting levels that requires ≥10 minutes to recover.	
Congenital heart disease (Adults)	Intermittent right to left shunting leading to cyanosis and arterial PO_2 of ≤ 60 Torr at ≤5 METs	Intermittent right to left shunting with pulse oximetry ≤85% at ≤5 METs; Exercise capacity with peak measured VO_2 <15 mL/kg/min or <5 estimated METs
Pulmonary hypertension	No previous criteria	Exercise capacity <5 METs
Valvular heart disease	No previous criteria	Exercise capacity <5 METs

IOM, Institute of Medicine; *METs*, Metabolic equivalents; *RER*, respiratory exchange ratio; *Vo_2*, oxygen uptake.
Information from the Institute of Medicine of the National Academies. *Cardiovascular Disability. Updating the Social Security Listings*. Washington, DC: National Academies Press; 2010.

TABLE 15.17 Gardner Testing Protocol for Patients with Peripheral Artery Disease

STAGE*	SPEED/GRADE	METS
1	2 mph/0%	2.5
2	2 mph/2%	3.1
3	2 mph/4%	3.6
4	2 mph/6%	4.2
5	2 mph/8%	4.7
6	2 mph/10%	5.3
7	2 mph/12%	5.8
8	2 mph/14%	6.4
9	2 mph/16%	6.9
10	2 mph/18%	7.5

METs, Metabolic equivalents.
*Each stage is 2 minutes in duration.
From Gardner AW, Skinner JS, Cantwell BW, et al. Progressive vs single-stage treadmill tests for evaluation of claudication. *Med Sci Sports Exerc.* 1991;23:402–408.

TABLE 15.18 American College of Cardiology/American Heart Association Guidelines for Exercise Testing in Peripheral Artery Disease

Class I

- Patients with ABI 0.91–0.99 may possibly have PAD, and should undergo exercise ABI if the clinical suspicion of PAD is significant.
- Patients with exertional non-joint-related leg symptoms and normal or borderline resting ABI (>0.90 and ≤1.4) should undergo exercise treadmill ABI testing to evaluate for PAD.

Class IIa

- In patients with PAD and an abnormal resting ABI (≤0.90). Exercise treadmill ABI testing can be useful to objectively assess symptoms, measure change in exercise ABI in response to exercise training or revascularization, and assess functional status.
- Exercise testing can help to individualize exercise prescriptions in patients with PAD before initiation of a formal program of structured exercise training.
- Administration of a 6-minute walk test in a corridor is a reasonable alternative to treadmill ABI testing for assessment of functional status.

ABI, Ankle-brachial index; *PAD*, peripheral artery disease.
From Gerhard-Herman MD, Gornik HL, Barrett C, et al. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2017;69(11):e71–e126.

ankles because of the peripheral vasodilation that occurs in exercising leg muscles. This leads to a mild decrease in the ABI in healthy patients that returns to normal within 1 to 2 minutes of recovery. In patients with PAD, ankle pressure decreases even more, thereby leading to a further decrease in the ABI and also a prolonged recovery time. Several diagnostic criteria have been proposed and include greater than a 5% drop in post-exercise ABI from resting levels, post-exercise ABI lower than 0.9, greater than a 30 mm Hg drop in systolic BP at the ankle, and recovery time to baseline ABI longer than 3 minutes.[54] Details regarding the use of exercise testing are also discussed in the ACC/AHA guidelines for the management of patients with PAD (Table 15.18).[55]

Patients with Diabetes

CAD remains the most common cause of morbidity and mortality in patients with diabetes mellitus (see Chapter 31). In recent years, strategies for the treatment of CAD in patients with diabetes have undergone much evolution such that regardless of symptoms or documented CAD, diabetic patients are treated with preventive therapies. In this context, the ability to specifically identify diabetic patients with disease who will benefit from more aggressive and, perhaps, invasive therapies remains a challenge. Exercise electrocardiographic testing has similar diagnostic sensitivity (approximately 60%) and specificity (80%) for diabetic patients with angina as for nondiabetic patients. Considerable prognostic power of the exercise ECG test lies beyond the ST-segment response. Poor exercise capacity and slow HRR in diabetic patients are markers of an adverse outcome. The value of the Duke prognostic score in patients with diabetes has not been well studied, and unlike the Morise score and the Cleveland Clinic Foundation risk score (see "Classic References"), it did not specifically address the presence of diabetes in the original cohort study. Therefore, at present, the Morise and Cleveland Clinic scores are more appropriate to apply in patients with diabetes who have normal resting ECG findings and undergo exercise electrocardiography.

At present, evidence is inadequate for recommending routine screening of asymptomatic diabetic patients with an exercise ECG.[56] The American Diabetes Association standards of medical care conclude that in asymptomatic patients, routine screening for CAD is not recommended, even before initiation of an exercise training program, because it does not improve outcomes as long as risk factors for CVD

are treated.[57] They recommend that diabetic persons who might be considered for advanced or invasive cardiac testing include those with (1) typical or atypical cardiac symptoms and (2) an abnormal resting ECG. Exercise ECG testing without or with imaging may be used initially. Pharmacologic stress echocardiography or nuclear imaging should be considered in diabetic persons in whom resting ECG abnormalities preclude exercise stress testing (e.g., LBBB or ST-T abnormalities) or in those who are not able to exercise.

SUMMARY

ECG exercise testing is a mature diagnostic testing modality with an extensive literature. It is exceedingly important as an initial diagnostic testing strategy to evaluate individuals with symptoms suggestive of coronary ischemia. It also carries invaluable prognostic information for patients in numerous clinical situations including ostensibly healthy individuals, individuals with stable CAD, individuals with chronic heart failure (aided by CPX), and individuals with valvular and other non-atherosclerotic heart diseases. Indeed, the duration of exercise performed on a standardized exercise protocol may be the simplest and best prognostic indicator in all of clinical cardiology.

ACKNOWLEDGMENT

The authors wish to acknowledge the previous contributions of Dr. Anthony Morise, which have laid the foundation for this chapter.

CLASSIC REFERENCES

Ainsworth BE, Haskell WL, Herrmann SD, et al. 2011 compendium of physical activities. *Med Sci Sports Exerc*. 2011;43:1575–1581.

Cole CR, Blackstone EH, Pashkow FJ, et al. Heart-rate recovery immediately after exercise as a predictor of mortality. *N Engl J Med*. 1999;341:1351–1357.

Gibbons RJ, Balady GJ, Timothy Bricker J, et al. ACC/AHA 2002 guideline update for exercise testing: summary article. *Circulation*. 2002;106:1883–1892.

Lauer MS, Pothier CE, Magid DJ, et al. An externally validated model for predicting long-term survival after exercise treadmill testing in patients with suspected coronary artery disease and a normal electrocardiogram. *Ann Intern Med*. 2007;147:821.

Mark DB, Hlatky MA, Harrell Jr FE, et al. Exercise treadmill score for predicting prognosis in coronary artery disease. *Ann Intern Med*. 1987;106:793–800.

Morise AP, Jalisi F. Evaluation of pretest and exercise test scores to assess all-cause mortality in unselected patients presenting for exercise testing with symptoms of suspected coronary artery disease. *J Am Coll Cardiol*. 2003;42:842–850.

Myers J, Arena R, Franklin B, et al. Recommendations for clinical exercise laboratories. *Circulation*. 2009;119:3144–3161.

Rodgers GP, Ayanian JZ, Balady G, et al. American College of Cardiology/American Heart Association clinical competence statement on stress testing. *Circulation*. 2000;102:1726–1738.

Shaw LJ, Peterson ED, Shaw LK, et al. Use of a prognostic treadmill score in identifying diagnostic coronary disease subgroups. *Circulation*. 1998;98:1622–1630.

Williams MA, Haskell WL, Ades PA, et al. Resistance exercise in individuals with and without cardiovascular disease: 2007 update: a scientific statement from the American heart association council on clinical cardiology and council on nutrition, physical activity, and metabolism. *Circulation*. 2007;116:572–584.

REFERENCES

Exercise Physiology and Technical Components of Exercise Testing

1. Fletcher GF, Ades PA, Kligfield P, et al. Exercise standards for testing and training. *Circulation*. 2013;128:873–934.
2. Pescatello LS, American College of Sports Medicine. *ACSM's Guidelines for Exercise Testing and Prescription*. 9th ed. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins Health; 2014.
3. American College of Sports Medicine, Riebe D, Ehrman JK, Liguori G, Magal M. *ACSM's Guidelines for Exercise Testing and Prescription*. 10th ed. Philadelphia: Wolters Kluwer; 2018.
4. Holland AE, Spruit MA, Troosters T, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. *Eur Respir J*. 2014;44:1428–1446.
5. Guazzi M, Arena R, Halle M, et al. 2016 focused update: clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. *Circulation*. 2016;133:e694–e711.
6. Myers J, Forman DE, Balady GJ, et al. Supervision of exercise testing by nonphysicians. *Circulation*. 2014;130:1014–1027.
7. Franklin BA, Thompson PD, Al-Zaiti SS, et al. Exercise-related acute cardiovascular events and potential deleterious adaptations following long-term exercise training: placing the risks into perspective-an update: a scientific statement from the American Heart Association. *Circulation*. 2020;141:e705–e736.
8. Skalski J, Allison TG, Miller TD. The safety of cardiopulmonary exercise testing in a population with high-risk cardiovascular diseases. *Circulation*. 2012;126:2465–2472.

Exercise Testing in Coronary Artery Disease: Diagnosis

9. Christman MP, Bittencourt MS, Hulten E, et al. Yield of downstream tests after exercise treadmill testing: a prospective cohort study. *J Am Coll Cardiol*. 2014;63:1264–1274.
10. Ahmed HM, Al-Mallah MH, McEvoy JW, et al. Maximal exercise testing variables and 10-year survival: fitness risk score derivation from the FIT Project. *Mayo Clin Proc*. 2015;90:346–355.
11. Marzlin KM, Webner C. Chronotropic incompetence. *AACN Adv Crit Care*. 2019;30:294–300.
12. Sydo N, Sydo T, Gonzalez Carta KA, et al. Prognostic performance of heart rate recovery on an exercise test in a primary prevention population. *J Am Heart Assoc*. 2018;7:e008143.
13. Arbit B, Azarbal B, Hayes SW, et al. Prognostic contribution of exercise capacity, heart rate recovery, chronotropic incompetence, and myocardial perfusion single-photon emission computerized tomography in the prediction of cardiac death and all-cause mortality. *Am J Cardiol*. 2015;116:1678–1684.
14. Schultz MG, La Gerche A, Sharman JE. Blood pressure response to exercise and cardiovascular disease. *Curr Hypertens Rep*. 2017;19:89.
15. O'Neal WT, Qureshi WT, Blaha MJ, et al. Relation of risk of atrial fibrillation with systolic blood pressure response during exercise stress testing (from the Henry Ford Exercise Testing Project). *Am J Cardiol*. 2015;116:1858–1862.
16. Chow R, Fordyce CB, Gao M, et al. The significance of early post-exercise ST segment normalization. *J Electrocardiol*. 2015;48:803–808.
17. Ghaffari S, Asadzadeh R, Tajlil A, et al. Predictive value of exercise stress test-induced ST-segment changes in leads V1 and avR in determining angiographic coronary involvement. *Ann Noninvasive Electrocardiol*. 2017;22:e12370.
18. Stein R, Ho M, Oliveira CM, et al. Exercise-induced left bundle branch block: prevalence and prognosis. *Arq Bras Cardiol*. 2011;97:26–32.
19. Stein R, Nguyen P, Abella J, et al. Prevalence and prognostic significance of exercise-induced right bundle branch block. *Am J Cardiol*. 2010;105:677–680.
20. Al-Khatib SM, Stevenson WG, Ackerman MJ, et al. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *Circulation*. 2018;138:e210–e271.
21. Baskaran L, Danad I, Gransar H, et al. A comparison of the updated Diamond-Forrester, CAD Consortium, and CONFIRM history-based risk scores for predicting obstructive coronary artery disease in patients with stable chest pain: the SCOT-HEART Coronary CTA Cohort. *JACC Cardiovasc Imaging*. 2019;12:1392–1400.
22. Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation*. 2012;126:e354–e471.
23. Genders TS, Steyerberg EW, Hunink MG, et al. Prediction model to estimate presence of coronary artery disease: retrospective pooled analysis of existing cohorts. *BMJ*. 2012;344:e3485.
24. Bittencourt MS, Hulten E, Polonsky TS, et al. European Society of cardiology-recommended coronary artery disease consortium pretest probability scores more accurately predict obstructive coronary disease and cardiovascular events than the Diamond and Forrester score: the Partners Registry. *Circulation*. 2016;134:201–211.
25. Kohli P, Gulati M. Exercise stress testing in women. *Circulation*. 2010;122:2570–2580.
26. Mieres JH, Gulati M, Bairey Merz N, et al. Role of noninvasive testing in the clinical evaluation of women with suspected ischemic heart disease. *Circulation*. 2014;130:350–379.

Exercise Testing in Coronary Artery Disease: Prognosis

27. Kiviniemi AM, Lepojärvi S, Kenttä TV, et al. Exercise capacity and heart rate responses to exercise as predictors of short-term outcome among patients with stable coronary artery disease. *Am J Cardiol*. 2015;116:1495–1501.
28. Park J-I, Shin S-Y, Park SK, Barrett-Connor E. Usefulness of the integrated scoring model of treadmill tests to predict myocardial ischemia and silent myocardial ischemia in community-dwelling adults (from the Rancho Bernardo study). *Am J Cardiol*. 2015;115:1049–1055.
29. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of cardiology foundation/American heart association task force on practice guidelines. *Circulation*. 2013;127:e362–425.
30. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;64:e139–e228.
31. Kristensen SD, Knuuti J, Saraste A, et al. 2014 ESC/ESA guidelines on non-cardiac surgery: cardiovascular assessment and management: the Joint Task Force on non-cardiac surgery: cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA). *Eur Heart J*. 2014;35:2383–2431.
32. Smilowitz NR, Gupta N, Ramakrishna H, et al. Perioperative major adverse cardiovascular and cerebrovascular events associated with noncardiac surgery. *JAMA Cardiol*. 2017;2:181–187.
33. Kalesan B, Nicewarner H, Intwala S, et al. Pre-operative stress testing in the evaluation of patients undergoing non-cardiac surgery: a systematic review and meta-analysis. *PloS One*. 2019;14:e0219145.
34. Fleisher LA, Fleischmann KE, Auerbach AD, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;64:e77–e137.

Exercise Testing in Nonatherosclerotic Heart Disease

35. Otto CM, Nishimura RA, Bonow RO, et al. 2020 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2021. https://doi.org/10.1016/j.jacc.2020.11.018.
36. Bonow RO, Nishimura RA, Thompson PD, Udelson JE. Eligibility and disqualification recommendations for competitive athletes with cardiovascular abnormalities: task Force 5: valvular Heart Disease. *J Am Coll Cardiol*. 2015;66:2385–2392.
37. Redfors B, Pibarot P, Gillam LD, et al. Stress testing in asymptomatic aortic stenosis. *Circulation*. 2017;135:1956–1976.
38. Morise AP. Exercise testing in nonatherosclerotic heart disease. *Circulation*. 2011;123:216–225.
39. Magne J, Lancellotti P, Piérard LA. Exercise testing in asymptomatic severe aortic stenosis. *JACC Cardiovasc Imaging*. 2014;7:188–199.
40. Bonow RO, O'Gara PT, Adams DH, et al. 2020 focused update of the 2017 ACC expert consensus decision pathway on the management of mitral regurgitation: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol*. 2020;75:2236–2270.
41. Ommen SR, Mital S, Burke MA, et al. 2020 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: a report of the American College of cardiology foundation/American heart association task force on practice guidelines. *J Am Coll Cardiol*. 2020;76:e159–e240.
42. Stout KK, Daniels CJ, Aboulhosn JA, et al. 2018 AHA/ACC guideline for the management of adults with congenital heart disease: a report of the American College of cardiology/American heart association task force on clinical practice guidelines. *Circulation*. 2019;139:e698–e800.
43. Van Hare GF, Ackerman MJ, Evangelista JK, et al. Eligibility and disqualification recommendations for competitive athletes with cardiovascular abnormalities: task Force 4: congenital Heart Disease. *J Am Coll Cardiol*. 2015;66:2372–2384.

44. Zipes DP, Link MS, Ackerman MJ, et al. Eligibility and disqualification recommendations for competitive athletes with cardiovascular abnormalities: task Force 9: arrhythmias and conduction defects. *J Am Coll Cardiol*. 2015;66:2412–2423.
45. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of cardiology/American heart association task force on practice guidelines and the heart rhythm Society. *J Am Coll Cardiol*. 2014;64:e1–e76.
46. Page RL, Joglar JA, Caldwell MA, et al. 2015 ACC/AHA/HRS guideline for the management of adult patients with supraventricular tachycardia: a report of the American College of cardiology/American heart association task force on clinical practice guidelines and the heart rhythm Society. *J Am Coll Cardiol*. 2016;67:e27–e115.
47. Massin MM. The role of exercise testing in pediatric cardiology. *Arch Cardiovasc Dis*. 2014;107:319–327.
48. Tracy CM, Epstein AE, Darbar D, et al. 2012 ACCF/AHA/HRS Focused Update of the 2008 guidelines for device-based therapy of cardiac rhythm abnormalities. *Circulation*. 2012;126:1784–1800.

Additional Uses for Exercise Testing

49. Amsterdam EA, Kirk JD, Bluemke DA, et al. Testing of low-risk patients presenting to the emergency department with chest pain: a scientific statement from the American Heart Association. *Circulation*. 2010;122:1756–1776.
50. Januzzi Jr JL, Mahler SA, Christenson RH, et al. Recommendations for institutions transitioning to high-sensitivity troponin testing: JACC Scientific Expert Panel. *J Am Coll Cardiol*. 2019;73:1059–1077.
51. American Association of Cardiovascular & Pulmonary Rehabilitation. *Guidelines for Cardiac Rehabilitation Programs*. 6th ed. Champaign, IL: Human Kinetics; 2021.
52. Quindry JC, Franklin BA, Chapman M, et al. Benefits and risks of high-intensity interval training in patients with coronary artery disease. *Am J Cardiol*. 2019;123:1370–1377.
53. Institute of Medicine (US) Committee on Social Security Cardiovascular Disability Criteria. *Cardiovascular Disability: Updating the Social Security Listings*. Washington, D.C: National Academies Press; 2010.
54. Aboyans V, Criqui MH, Abraham P, et al. Measurement and interpretation of the ankle-brachial index. *Circulation*. 2012;126:2890–2909.
55. Gerhard-Herman MD, Gornik HL, Barrett C, et al. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2017;135:e726–e779.
56. Jonas DE, Reddy S, Middleton JC, et al. Screening for cardiovascular disease risk with resting or exercise electrocardiography: evidence report and systematic review for the US Preventive Services Task Force. *J Am Med Assoc*. 2018;319:2315–2328.
57. American Diabetes Association. Cardiovascular disease and risk management: standards of medical care in diabetes-2020. *Diabetes Care*. 2020;43:S111–S134.