

## Exercise Standards for Testing and Training: A Scientific Statement From the American Heart Association

Gerald F. Fletcher, Philip A. Ades, Paul Kligfield, Ross Arena, Gary J. Balady, Vera A. Bittner, Lola A. Coke, Jerome L. Fleg, Daniel E. Forman, Thomas C. Gerber, Martha Gulati, Kushal Madan, Jonathan Rhodes, Paul D. Thompson and Mark A. Williams  
on behalf of the American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee of the Council on Clinical Cardiology, Council on Nutrition, Physical Activity and Metabolism, Council on Cardiovascular and Stroke Nursing, and Council on Epidemiology and Prevention

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## Exercise Standards for Testing and Training A Scientific Statement From the American Heart Association

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Paul D. Thompson, MD; Mark A. Williams, PhD; on behalf of the American Heart Association  
Exercise, Cardiac Rehabilitation, and Prevention Committee of the Council on Clinical Cardiology,  
Council on Nutrition, Physical Activity and Metabolism, Council on Cardiovascular and Stroke  
Nursing, and Council on Epidemiology and Prevention

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The 2001 version of the exercise standards statement<sup>1</sup> has served effectively to reflect the basic fundamentals of ECG-monitored exercise testing and training of both healthy subjects and patients with cardiovascular disease (CVD) and other disease states. These exercise standards are intended for use by physicians, nurses, exercise physiologists and specialists, technologists, and other healthcare professionals involved in exercise testing and training of these populations. Because of an abundance of new research in recent years, a revision of these exercise standards is appropriate. The revision deals with basic fundamentals of testing and training, with no attempt to duplicate or replace current clinical practice guidelines issued by the American Heart Association (AHA), the American College of Cardiology Foundation (ACCF), and other professional societies.

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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It is acknowledged that the published evidence for some recommendations made herein is limited, but the depth of knowledge and experience of the writing group is believed to provide justification for certain consensus recommendations based on expert opinion.

With regard to a literature search for this revision, no specific strategy or formal data quality assessment was used. Each of the 15 members of the writing group has specific expertise in  $\geq 1$  sections of the document. Accordingly, references were selected by the group on the basis of personal experience or readily available publications and databases. The cited references represent a consensus of the writing group.

## Exercise Testing

### Purposes of Exercise Testing

Exercise testing has been used for the provocation and identification of myocardial ischemia for  $>6$  decades,<sup>2</sup> and during this time additional purposes for testing have evolved. Exercise testing now is used widely for the following:

- Detection of coronary artery disease (CAD) in patients with chest pain (chest discomfort) syndromes or potential symptom equivalents
- Evaluation of the anatomic and functional severity of CAD
- Prediction of cardiovascular events and all-cause death
- Evaluation of physical capacity and effort tolerance
- Evaluation of exercise-related symptoms
- Assessment of chronotropic competence, arrhythmias, and response to implanted device therapy
- Assessment of the response to medical interventions

Understanding the purpose of the individual exercise test allows the test supervisor to determine appropriate methodology and to select test end points that maximize test safety and obtain needed diagnostic and prognostic information. During the past several decades, exercise testing has been focused increasingly on assessment of cardiovascular risk, not simply detection of coronary obstruction.<sup>3</sup> Ultimately, improved clinical outcome is a major goal of exercise testing.

### Physiology of Exercise Testing

Aerobic exercise, progressively increasing to maximal tolerance, is a common physiological stress that can elicit cardiovascular or pulmonary abnormalities not present at rest, while aiding in the determination of the adequacy of cardiac function. However, in addition to exercise, the cardiovascular response to physiological stress is also commonly evaluated through the use of pharmacological stress agents. Thus, whereas “stress testing” traditionally has referred to “exercise,” this term no longer remains precise. The following section will focus specifically on exercise as a means to provoke cardiovascular and pulmonary stress.

### Types of Exercise

Exercise involves muscle activity that has both mechanical (dynamic, static) and metabolic (aerobic, anaerobic) properties. *Dynamic (isotonic)* exercise, which causes movement of the limb, is also further classified as either *concentric* (shortening

of the muscle fibers, which is the most common type of muscle action) or *eccentric* (lengthening of the muscle fibers, such as might occur when a weight is lowered against gravity). *Static (isometric)* exercise results in no movement of the limb. The metabolic classification refers primarily to the availability of oxygen for the contraction process and includes *aerobic* (oxygen available) or *anaerobic* (without oxygen) processes. Most exercise involves both dynamic and static contractions as well as aerobic and anaerobic metabolism, and depending on the contribution of each, the physiological responses can be significantly different. Current clinical exercise testing procedures manifest a predominant dynamic–aerobic (endurance) component.

### Cardiovascular Responses to Exercise in Normal Subjects

As exercise is initiated and as its intensity increases, there is increasing oxygen demand from the body in general, but primarily from the working muscles.<sup>4</sup> To meet these requirements, cardiac output is increased by an augmentation in stroke volume (mediated through the Frank-Starling mechanism) and heart rate (HR), as well as an increasing peripheral arteriovenous oxygen difference. However, at moderate- to high-intensity exercise, the continued rise in cardiac output is primarily attributable to an increase in HR, as stroke volume typically reaches a plateau at 50% to 60% of maximal oxygen uptake ( $\dot{V}O_{2\max}$ ) except in elite athletes. Thus, maximal cardiac output during exercise is the product of augmentation of both stroke volume and HR.  $\dot{V}O_{2\max}$  is equal to the product of maximum cardiac output and maximum arteriovenous oxygen difference, and even in the absence or minimization of change in cardiac output, an important increase in  $\dot{V}O_{2\max}$  during exercise can result from increased oxygen extraction. Maximum arteriovenous oxygen difference has a physiological limit of 15 to 17 mL  $O_2$  per 100 mL blood. As a consequence, if maximum effort is achieved,  $\dot{V}O_{2\max}$  can be used to estimate maximum cardiac output.

At fixed, mild-to-moderate submaximal workloads below anaerobic threshold (the point during progressive exercise beyond which muscles cannot derive all required energy from oxygen utilization), steady-state conditions usually are reached within 3 to 5 minutes after the onset of exercise, and subsequently, HR, cardiac output, blood pressure, and pulmonary ventilation are maintained at reasonably constant levels.<sup>5</sup> As the exercise intensity surpasses anaerobic threshold and progresses toward a maximum level, sympathetic discharge becomes maximal and parasympathetic stimulation is inhibited, resulting in vasoconstriction in most circulatory body systems, except in exercising muscle and in the cerebral and coronary circulations. As exercise progresses, skeletal muscle blood flow and oxygen extraction increase, the latter as much as 3-fold. Total calculated peripheral resistance decreases, while systolic blood pressure, mean arterial pressure, and pulse pressure usually increase. Diastolic blood pressure can remain unchanged or decrease to a small degree, each of which is considered a normal response. The pulmonary vascular bed can accommodate as much as a 6-fold increase in cardiac output without a significant increase in transpulmonary gradient. In normal subjects, this is not a limiting determinant of peak exercise capacity. Cardiac output can increase as much as 4- to 6-fold above basal levels during

strenuous exertion in the upright position, depending on genetic endowment and level of training.

### **HR Response**

The immediate response of the cardiovascular system to exercise is an increase in HR that is attributable to a decrease in vagal tone, followed by an increase in sympathetic outflow.<sup>5</sup> During dynamic exercise, HR in sinus rhythm increases linearly with workload and oxygen demand. In subjects not prescribed a  $\beta$ -blocking agent, the maximal HR achieved during exercise is influenced heavily by age and age-related neural influences; the expected value can be predicted from one of several available equations, some of which are derived separately for men and women.<sup>6-8</sup> For one of the commonly used equations (maximum predicted HR = 220 – age in years), a high degree of variability exists among subjects of identical age ( $\pm 12$  beats per minute [bpm]). Accordingly, the practice of using achievement of 85% of age-predicted maximal HR to define sufficient effort during exercise testing is limited and should not be used in isolation as a termination criterion.<sup>9</sup>

Dynamic exercise increases HR more than either isometric or resistance exercise. A normal increase in HR during exercise is  $\approx 10$  bpm per metabolic equivalent (MET). Moreover, the HR response is generally continuous with increasing workload. An accelerated HR response to standardized submaximal workloads is observed after prolonged bed rest, indicating that physical conditioning also plays a role in the HR response, which also can change in response to anemia, metabolic disorders, variable vascular volume or peripheral resistance, or ventricular dysfunction. These conditions themselves do not appear to affect maximal HR unless capacity for exercise intensity becomes limited. Conversely, a lower-than-expected incremental rise in HR during a progressive exercise test could be attributed to an enhanced level of fitness and left ventricular (LV) function. As will be discussed in detail, inadequate HR response to exercise can be a marker not only for sinus node dysfunction but also for prognostically important cardiac disease and has been defined as chronotropic incompetence. The use of a  $\beta$ -blocking drug lowers both the incremental rise in HR and maximal HR obtained during exercise, thus limiting the physiological interpretation of the cardiac response to exercise. Other factors that can influence HR include body position, type of dynamic exercise, certain physical conditions, state of health, blood volume, sinus node function, medications, and the environment.

The change in HR immediately after termination of the exercise test, termed HR recovery, has received an increasing amount of attention in recent years. The decline of HR after exercise generally exhibits a rapid fall during the first 30 seconds after exercise, followed by a slower return to the preexercise level.<sup>10</sup> The rapid decline in HR is likely the manifestation of vagal reactivation.<sup>11</sup> Abnormality of HR recovery has consistently demonstrated prognostic value.<sup>12-17</sup>

### **Arterial Blood Pressure Response**

Blood pressure is dependent on cardiac output and peripheral vascular resistance. Systolic blood pressure rises with increasing dynamic work as a result of increasing cardiac output, whereas diastolic pressure usually remains about the same or is moderately decreased because of vasodilatation of the vascular bed. On occasion, diastolic blood pressure sounds can

be heard down to 0 mmHg in some normal subjects. A normal systolic blood pressure response to progressive exercise is dependent on both sex (higher in males) and age (higher with advancing age).<sup>5</sup> The average rise in systolic blood pressure during a progressive exercise test is about 10 mmHg/MET.

After maximum exercise, systolic blood pressure usually declines because of the rapid decrease in cardiac output, normally reaching resting levels or lower within 6 minutes, and even remaining lower than preexercise levels for several hours.<sup>18</sup> When exercise is terminated abruptly, some healthy people have precipitous drops in systolic blood pressure because of venous pooling (particularly in the upright position) and a delayed immediate postexercise increase in systemic vascular resistance to match the reduction in cardiac output. This postexercise hemodynamic response highlights the importance of an active cool-down period when possible.

### **Myocardial Oxygen Uptake**

Myocardial oxygen uptake is determined primarily by intramyocardial wall stress (ie, the product of LV pressure and volume, divided by LV wall thickness), contractility, and HR.<sup>1,4</sup> Accurate measurement of myocardial oxygen uptake requires cardiac catheterization to obtain coronary arterial and venous oxygen content. However, myocardial oxygen uptake can be estimated during clinical exercise testing by the product of HR and systolic blood pressure (double product or rate–pressure product) and ranges from the 10th percentile value of 25 000 to a 90th percentile value of 40 000 at peak exercise. A linear relationship exists between myocardial oxygen uptake and coronary blood flow. During exercise, coronary blood flow increases as much as 5-fold above the resting value. A subject with obstructive CAD often cannot provide adequate coronary blood flow to the affected myocardial tissue to meet the metabolic demands of the myocardium during exercise; consequently, myocardial ischemia occurs. Myocardial ischemia usually occurs at the same rate–pressure product rather than at the same external workload (eg, exercise test stage).<sup>19</sup>

### **Oxygen Uptake and the Ventilatory Threshold**

$\dot{V}_{O_2\max}$  is the peak oxygen uptake achieved during the performance of dynamic exercise involving a large part of total muscle mass. It is considered the best measure of cardiovascular fitness and exercise capacity.<sup>5</sup> By strictest definition,  $\dot{V}_{O_2\max}$  cannot be exceeded, despite an increase in work output. Although demonstration of the  $\dot{V}_{O_2}$  plateau against work rate is a valid demonstration of  $\dot{V}_{O_2\max}$ , patients often cannot achieve the plateau because of leg fatigue; lack of necessary motivation; general discomfort; or the presence of heart disease, LV dysfunction, myocardial ischemia, and associated symptomatology. Hence, it is common to refer to  $\dot{V}_{O_2\max}$  as the peak  $\dot{V}_{O_2}$  attained during volitional incremental exercise. In clinical practice,  $\dot{V}_{O_2\max}$  is not usually measured during an exercise tolerance test but is estimated from the peak work intensity achieved.

In contrast, submaximal oxygen uptake is the general designation for any level of oxygen uptake between maximal and resting levels. Submaximal oxygen uptake is most frequently described in terms of a percentage of  $\dot{V}_{O_2\max}$  (eg, 60%, 70%, or 80% of  $\dot{V}_{O_2\max}$ ) in designating exercise workload or intensity. To meet the metabolic demand of dynamic exercise, oxygen uptake quickly increases, achieving steady state, as previously described, when exercise intensity is of light or moderate



intensity and is below the ventilatory threshold. The ventilatory threshold is another measure of relative work effort and represents the point at which ventilation abruptly increases in response to increasing carbon dioxide production ( $\dot{V}CO_2$ ) associated with increased work rate, despite increasing oxygen uptake. In most cases, the ventilatory threshold is highly reproducible, although it might not be achieved or readily identified in some patients, particularly those with very poor exercise capacity.<sup>4</sup>

It is convenient to express oxygen uptake in multiples of resting oxygen requirements—that is, METs, whereby a unit of sitting/resting oxygen uptake (1 MET) is defined as  $\approx 3.5$  mL  $O_2$  per kilogram of body weight per minute ( $mL\ kg^{-1}\ min^{-1}$ ). For example, an oxygen uptake expressed as a 7-MET level would equal  $24.5\ mL\ kg^{-1}\ min^{-1}$ .  $\dot{V}O_{2max}$  is influenced by age, sex, exercise habits, heredity, and cardiovascular clinical status.

$\dot{V}O_{2max}$  is equal to the product of maximum cardiac output and maximum arteriovenous oxygen difference.  $\dot{V}O_{2max}$  divided by the HR at peak exercise (a quantity defined as the oxygen pulse) is therefore equal to the forward stroke volume (ie, cardiac output divided by HR) at peak exercise times the arteriovenous oxygen difference at peak exercise. Because the arteriovenous oxygen difference at peak exercise reaches a physiological limit and usually varies little across a wide spectrum of cardiovascular function, most of the clinical variation in the oxygen pulse at peak exercise is therefore attributable to variation in the forward stroke volume at peak exercise. Valid inferences about a patient's forward stroke volume at peak exercise therefore can be made from determinations of the oxygen pulse at peak exercise. Normal values for the oxygen pulse (and stroke volume) at peak exercise are dependent on a patient's age, size, and sex. Predicted values can be calculated easily, however, by dividing the patient's predicted  $\dot{V}O_{2max}$  (in milliliters per minute) by the predicted peak HR.<sup>20</sup> The oxygen pulse also is influenced by hemoglobin levels and the arterial oxygen saturation. Proper interpretation of oxygen pulse data therefore should take into account abnormalities in these indices.

#### Age

Maximum values of  $\dot{V}O_{2max}$  occur between the ages of 15 and 30 years and decrease progressively with age. At age 60 years, mean  $\dot{V}O_{2max}$  in men is approximately two thirds of that at 20 years.<sup>1</sup> A longitudinal decline in peak  $\dot{V}O_{2max}$  was observed in each of 6 age decades in both sexes; however, the rate of decline accelerated from 3% to 6% per 10 years in individuals in their 20s and 30s to  $>20\%$  per 10 years in individuals in their 70s and beyond,<sup>21</sup> as seen in Figure 1.

#### Sex

Women demonstrate a lower  $\dot{V}O_{2max}$  than that of men.<sup>22</sup> This lower  $\dot{V}O_{2max}$  in women is attributed to their smaller muscle mass, lower hemoglobin and blood volume, and smaller stroke volume relative to men.<sup>1</sup> The rate of decline for each decade is larger in men than in women from the fourth decade onward.<sup>21</sup>

#### Exercise Habits

Physical activity has an important influence on  $\dot{V}O_{2max}$ . In moderately active young men,  $\dot{V}O_{2max}$  is  $\approx 12$  METs, whereas young men performing aerobic training such as distance running can have a  $\dot{V}O_{2max}$  as high as 18 to 24 METs ( $60$  to  $85\ mL\ kg^{-1}\ min^{-1}$ ).<sup>1</sup> A similar relationship was found in active versus sedentary women.<sup>22</sup>

#### Cardiovascular Clinical Status

$\dot{V}O_{2max}$  is affected by the degree of impairment caused by disease. In particular, preexisting LV dysfunction or the development of such with exercise-induced myocardial ischemia can greatly affect  $\dot{V}O_{2max}$ . In addition, the development of signs or symptoms associated with the need for exercise test termination, such as angina pectoris, hypertension, or cardiac dysrhythmia, can greatly impact  $\dot{V}O_{2max}$ . Thus, it is difficult to accurately predict  $\dot{V}O_{2max}$  from its relation to exercise habits and age alone because of considerable scatter because of underlying disease. However, achieved values for  $\dot{V}O_{2max}$  can be compared with average normal values by age and sex.<sup>1</sup>

### Exercise Testing Procedures

#### Absolute and Relative Contraindications to Exercise Testing

Absolute and relative contraindications to exercise testing balance the risk of the test with the potential benefit of the information derived from the test. Assessment of this balance requires knowledge of the purpose of the test for the individual subject or patient and what symptom or sign end points will be for the individual test.

#### Absolute Contraindications

- Acute myocardial infarction (MI), within 2 days
- Ongoing unstable angina
- Uncontrolled cardiac arrhythmia with hemodynamic compromise
- Active endocarditis
- Symptomatic severe aortic stenosis
- Decompensated heart failure
- Acute pulmonary embolism, pulmonary infarction, or deep vein thrombosis
- Acute myocarditis or pericarditis
- Acute aortic dissection
- Physical disability that precludes safe and adequate testing

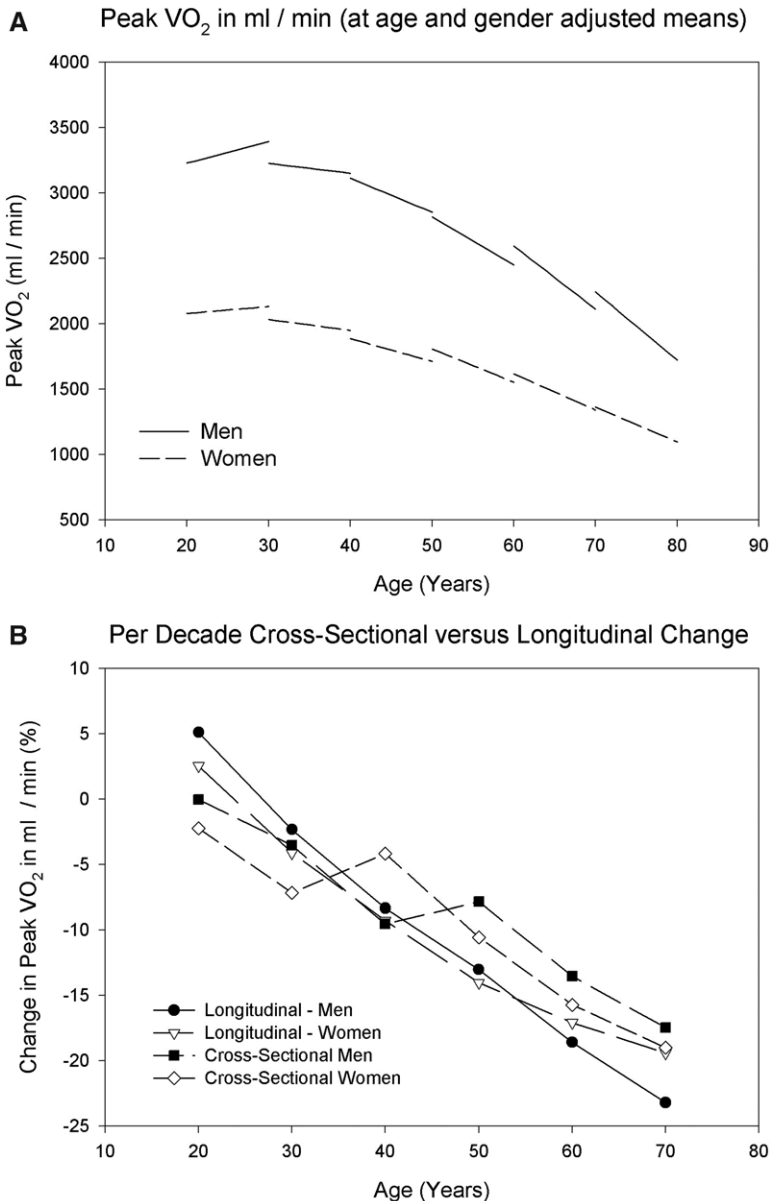
#### Relative Contraindications

- Known obstructive left main coronary artery stenosis
- Moderate to severe aortic stenosis with uncertain relation to symptoms
- Tachyarrhythmias with uncontrolled ventricular rates
- Acquired advanced or complete heart block
- Hypertrophic obstructive cardiomyopathy with severe resting gradient
- Recent stroke or transient ischemic attack
- Mental impairment with limited ability to cooperate
- Resting hypertension with systolic or diastolic blood pressures  $>200/110$  mm Hg
- Uncorrected medical conditions, such as significant anemia, important electrolyte imbalance, and hyperthyroidism

#### Subject Preparation

Preparations for exercise testing include the following:

- The purpose of the test should be clear in advance to maximize diagnostic value and to ensure safety. If the indication



**Figure 1.** Progressive and accelerating decline in peak  $\text{VO}_2$  according to age decades in clinically healthy men and in women. Reprinted from Fleg JL et al.<sup>21</sup> Copyright © 2005, the American Heart Association, Inc.

for the test is not clear, the referring provider should be contacted for further information.

- The subject or patient should not eat for 3 hours before the test. Routine medications may be taken with small amounts of water. Subjects should dress in comfortable clothing and wear comfortable walking shoes or sneakers.
- The subject or patient should receive a detailed explanation of the testing procedure and purpose of the test, including the nature of the progressive exercise, symptom and sign end points, and possible complications.
- When exercise testing is performed for the diagnosis of ischemia, routine medications may be held because some drugs (especially  $\beta$ -blockers) attenuate the HR and blood pressure responses to exercise. If ischemia does not occur, the diagnostic value of the test for detection of CAD is limited. No formal guidelines for tapering or holding medications exist, but 24 hours or more could be required for sustained-release preparations, and the patient should

be instructed to resume medication if rebound phenomena occur. Many exercise test evaluations occur while patients are taking usual medications, which should be recorded for correlation with test findings.

- A brief history and physical examination are required to rule out contraindications to testing and to detect important clinical signs, such as cardiac murmur, gallop sounds, pulmonary wheezing, or rales. Subjects with a history of worsening unstable angina or decompensated heart failure should not undergo exercise testing until their condition stabilizes. Physical examination should screen for valvular or congenital heart disease, and abnormal hemodynamic responses to exercise in these patients could require early termination of testing.

A resting supine standard 12-lead ECG should be obtained before exercise to compare to previously obtained standard ECGs to determine if changes have occurred over time. Subsequently, supine and standing (sitting if cycle ergometry is used) “torso” ECGs (with the limb electrodes on the trunk

of the body to minimize motion and muscle artifact during exercise) should be recorded because these could differ importantly from the preexercise standard ECG. The torso ECG is not equivalent to a standard ECG because the torso ECG can shift the frontal plane axis to the right, increasing voltage in the inferior leads.<sup>23,24</sup> This could cause a disappearance of Q waves in a patient with a documented previous Q-wave inferior MI or could produce lead placement-dependent artifactual Q waves in some normal subjects. Most of the change between supine limb-lead standard electrocardiographic recordings and upright torso electrocardiographic recordings is attributable to electrode position and not to the positional change.<sup>25</sup>

Standing control torso-lead ECGs should be recorded before testing to allow direct comparison with exercise tracings. If torso-lead tracings will be taken in the supine position during recovery, a supine torso-lead tracing also should be obtained in the control period. Blood pressures in the upright position should be recorded before beginning exercise. Hyperventilation at rest could produce nonspecific ST-segment changes in some otherwise normal subjects, and these also might occur during exercise as false-positive responses for the identification of ischemia.<sup>26–28</sup> Hyperventilation before testing has been suggested to decrease test specificity, and its routine use has been criticized in a recent guideline.<sup>29</sup> When electrocardiographic changes occur with hyperventilation, this should be acknowledged in the test interpretation.

### **Electrocardiographic Recording**

#### *Skin Preparation*

An important factor governing the recording quality of an exercise ECG is the interface between electrode and skin. Removal of the superficial oils and layer of skin by gentle abrasion significantly lowers resistance, thus improving the signal-to-noise ratio. The areas for electrode application are first shaved and then rubbed with alcohol-saturated gauze. After the skin dries, it is marked with a felt-tipped pen and rubbed with fine sandpaper or other rough material. With these procedures, skin resistance can be reduced to 5000  $\Omega$  or less.

#### *Electrodes and Cables*

Disposable electrodes used in exercise testing are generally silver–silver chloride combinations with adherent gel. Contact between electrodes and the skin generally improves with several minutes of application time and with the moisture that occurs with sweating during exercise, although excess sweating can result in loosening of the contact between electrode and skin. Wrapping the torso with a 6-inch elastic bandage or with a fitted torso net can reduce noise produced by electrode and cable movement, especially in obese patients. Electrode placement for signal stability in large-breasted women can be difficult, sometimes requiring tradeoff of variable location and motion artifact.

Hard-wired connecting cables between the electrodes and recorder should be light, flexible, and properly shielded. Most available commercial exercise cables are constructed to lessen motion artifact by digitizing the electrocardiographic waveform at the cable box proximal to the attachment to the electrocardiograph recorder itself. Cables generally have a life span of about 1 year and eventually must be replaced to reduce acquired electrical interference and discontinuity. It is

increasingly popular to use digital conversion boxes that wirelessly transmit to the recording electrocardiograph.

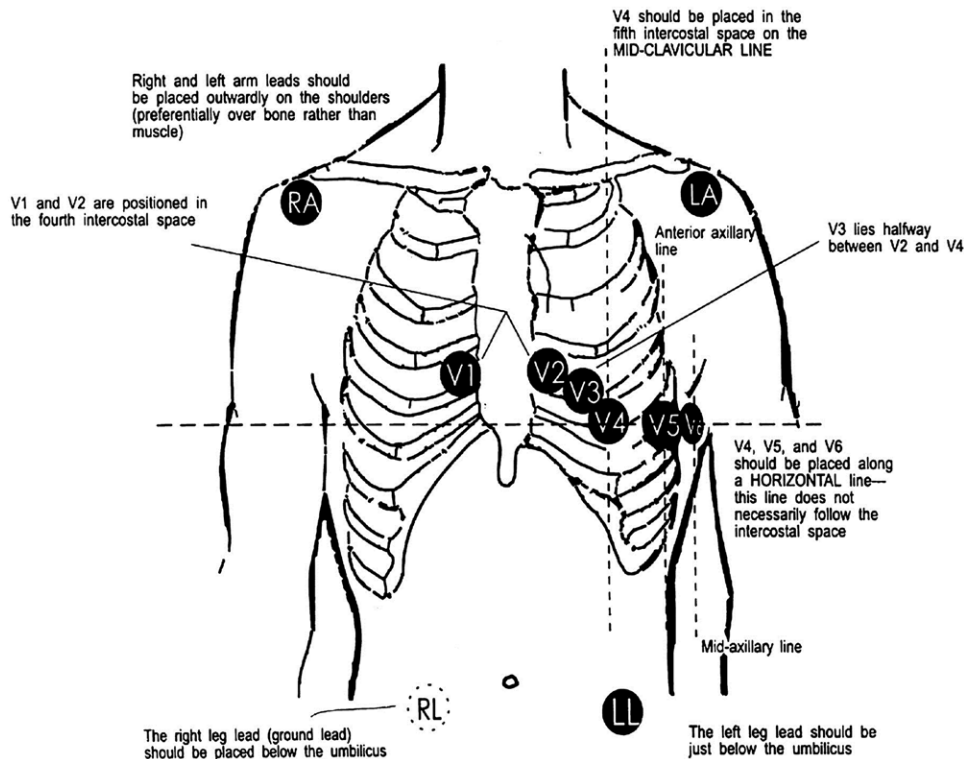
#### *Electrocardiographic Leads for Exercise Testing*

Because a high-quality standard 12-lead ECG with electrodes placed on the limbs cannot be obtained during exercise, electrode placement on the torso is standard for routine testing. Multiple leads improve test sensitivity.<sup>30</sup> As noted, varied electrode placement results in varied waveforms.<sup>23</sup> Although these do alter QRS and T-wave morphology, they are nonetheless valid for interpretation of heart rhythm and are generally similar to the standard ECG for detecting ST-segment deviation.<sup>24,31,32</sup> Torso electrodes generally are applied under the lateral clavicles (for the arm leads) and high under the ribcage (for the leg leads), as shown in Figure 2. Nonstandard electrode placement should be documented on the tracing.

**Bipolar CM<sub>5</sub>.** A useful bipolar chest lead, not present in the standard 12-lead ECG, can be constructed by using an electrode placed over the manubrium just below the sternal notch that is paired with precordial lead V<sub>5</sub> in its standard position midway between V<sub>4</sub> and V<sub>6</sub> in the anterior axillary line. The resulting precordial bipolar lead CM<sub>5</sub> has been found to have the highest sensitivity for the detection of exercise-induced subendocardial ischemia among commonly used single leads.<sup>33</sup> This results from the general axis of the lead along the LV cavity from base to apex and also from the high lead strength of the electrode pair in this position.

**Lead –aVR in Exercise Testing.** Lead aVR, when inverted, takes its place in the frontal plane halfway between standard bipolar leads I and II. Because this axis also aligns with the general axis of the left ventricle, –aVR (inverted aVR) is widely used in routine electrocardiography in other countries and also has been endorsed for routine use in resting electrocardiography by AHA/ACCF statements.<sup>34</sup> ST-segment deviation is opposite in aVR and –aVR, with ST depression attributable to subendocardial ischemia in –aVR showing up as ST elevation in standard-lead aVR.<sup>35</sup> For many years, aVR was generally ignored in both routine and exercise electrocardiography. Recognition of ST depression in aVR as a useful finding in some cases of ST-elevation infarction has prompted its reevaluation in general exercise testing. Several studies have highlighted its usefulness for the detection of demand ischemia during exercise and for the recognition of left main and proximal left anterior descending stenoses.<sup>36,37</sup> It is likely that much of this diagnostic value is attributable to the relationship of the derived lead to the axis of the left ventricle as a result of torso placement of the electrodes (which actually makes a torso-based –aVR somewhat similar to CM<sub>5</sub> in axis). It should be noted that the spatial diagnostic information contained in aVR cannot exceed that of the other routine electrocardiographic leads because it is mathematically dependent on (and calculated from) any 2 bipolar limb leads.<sup>34</sup> This notwithstanding, the clinical value of aVR (–aVR) appears promising.

**Electrocardiographic Mapping During Exercise.** Multiple electrodes in excess of the standard 10 can be used to derive body surface potential maps at rest and during exercise, which can provide additional insight into exercise-related ischemia.<sup>38–40</sup> Because of complexity, these are not routinely



**Figure 2.** Placement of the limb leads on the torso is necessary for reduction of noise in the ECG during exercise, whereas precordial lead placement is unchanged. Waveforms of activity-compatible torso-lead ECGs differ from those derived from standard 12-lead ECGs, but ST-segment shifts with torso electrodes are valid. The manubrial electrode can be paired with standard lead  $V_5$  to produce bipolar  $CM_5$ . From the figure, it can be seen that  $-aVR$  (inverted  $aVR$ ) using the torso electrode positions to produce the central terminal has spatial orientation that is similar in orientation to  $CM_5$ . See text for further details on these leads. LA indicates left arm; LL, left leg; RA, right arm; and RL, right leg. Reproduced with permission from Fletcher et al.<sup>1</sup> ©2001 American Heart Association, Inc.

used for clinical exercise test purposes. Details are beyond the scope of the present statement.

**Relative Sensitivity of Leads.** In general, more electrodes lead to greater test sensitivity.<sup>30</sup> The lateral precordial leads ( $V_4$  through  $V_6$ ) are capable of detecting 90% of all ST depression observed in multiple lead systems, and recent studies have emphasized the general individual sensitivity of  $CM_5$  and  $(-aVR)$ , both of which are in the general vector direction of the standard lateral precordial leads. Unlike ST elevation during acute MI, ST depression during demand-induced subendocardial ischemia during exercise does not localize the area of myocardium that is involved.

#### Computer-Assisted Electrocardiographs

Because electrocardiographic artifact during exercise is an interpretive problem, most digitized resting and exercise ECGs use averaged updated cardiac cycles to generate representative complexes for each lead.<sup>34</sup> These can involve incremental updating or averaging of multiple aligned cycles to reduce random noise and to reduce beat-to-beat variability caused by respiration and movement. Automated measurement of ST-segment shifts based on individual representative complexes has the potential to increase precision of the magnitude of repolarization deviation,<sup>41</sup> but this is true only when reliable points determining baseline, QRS onset, and QRS offset (for determining the J-point and ST-segment levels at any specified time after the J point) are selected accurately by the computer algorithm. At faster HRs, there invariably is merging of the end of the T wave with the P wave in patients in sinus rhythm, making the standard T-P baseline unusable during exercise for most patients. For this reason, the end of the PR segment is used as a compromise isoelectric baseline by automated algorithms. Errors in determination of the end

of the PR segment, as occur when the reliable point is actually on the descending limb of a P wave with a shortened PR interval during exercise, will confound the baseline used for measurement of ST-segment shift and will result in incorrect automated ST-segment measurement. Measurement error also will result from failure of automated detection of the end of the QRS complex. As is true with automated algorithms for the interpretation of resting ECGs, the computer should be an adjunct to, not a substitute for, human interpretation.

#### Exercise Equipment

Details on exercise testing equipment and exercise testing laboratories can be found in the AHA's "Guidelines for Clinical Exercise Testing Laboratories."<sup>42,43</sup> Treadmill and cycle ergometers are the most commonly used dynamic exercise testing devices. Figure 3 illustrates the relation of  $\dot{V}O_2$  and METs to stages in a variety of treadmill protocols and kilopond-meters-per-minute values for bicycle ergometry. Treadmill testing is generally favored in the United States, where bicycle riding is less prevalent than in Europe and elsewhere. Having both exercise modes available is advantageous, given that some individuals have difficulty with treadmill ambulation for reasons that include imbalance and orthopedic limitations, whereas other individuals develop earlier exercise fatigue using the bicycle.

#### Treadmill

The treadmill should have front rails, side rails, or both to aid in subject stability. However, subjects should be encouraged not to tightly grasp the front or side rails because this action supports body weight and thus reduces the workload at any given stage, leading to the potential for a significant overestimation of oxygen uptake. It can be helpful if subjects remove their hands from the rails, close their fists, and place one finger of each hand on the rails to maintain balance after they are accustomed to



FUNCTIONAL CLASS	CLINICAL STATUS	O <sub>2</sub> COST ml/kg/min	METS	BICYCLE ERGOMETER	TREADMILL PROTOCOLS				METS	
NORMAL AND I	HEALTHY, DEPENDENT ON AGE, ACTIVITY	SEDENTARY HEALTHY		1 WATT = 6.1 Kpm/min  FOR 70 KG BODY WEIGHT Kpm/min	BRUCE MODIFIED 3 min Stages MPH %GR		BRUCE 3 min Stages MPH %GR		NAUGHTON	
					6.0	22	6.0	22		
					5.5	20	5.5	20		
					5.0	18	5.0	18		
II		LIMITED							2 min Stages MPH %GR	
III		SYMPTOMATIC								
IV										

**Figure 3.** Relation of exercise workload ( $\dot{V}O_2$  and metabolic equivalents [METs]) to stages of the standard Bruce protocol and other treadmill protocols and to stationary bicycle ergometry. Completion of Stage 4 of the Bruce protocol (4.2 mph at a 16% grade) approximates 1500 kpm/min on the bicycle. Functional class refers to New York Heart Association class. kpm indicates kilopond-meters; MPH, miles per hour; and %GR, percent grade. Reproduced with permission from Fletcher et al.<sup>1</sup> ©2001 American Heart Association, Inc.

walking on the treadmill. The treadmill should have variable speed and grade capability and must be accurately calibrated. Most modern computer-driven treadmills can be programmed to adjust automatically to a wide range of stepped or ramp exercise protocols. Standard tables can be used to convert treadmill grade and speed into estimated MET levels.<sup>44,45</sup>

#### Cycle Ergometer

Electrically braked cycles vary the resistance to the pedaling speed (rate-independent ergometers), thereby permitting better power output control, because it is common for subjects who are fatigued or unable to cooperate to decrease their pedaling speed. The highest values of  $\dot{V}O_2$  and HR are obtained with pedaling speeds of 50 to 80 rpm. Cycle ergometers are calibrated in kiloponds or watts (W); 1 W is equivalent to  $\approx 6$  kilopond-meters per minute (kpm/min). Because exercise on a cycle ergometer is not weight bearing, kiloponds or watts can be converted to oxygen uptake in milliliters per minute. METs are obtained by dividing  $\dot{V}O_2$  in milliliters per minute by the product of body weight (in kilograms)  $\times 3.5$ .

The cycle ergometer is usually less expensive, occupies less space, and is less noisy than a treadmill. Upper body motion is usually reduced, making it easier to obtain blood pressure measurements and to record the ECG. Care must be taken to prevent isometric or resistance exercise of the arms while grasping the handlebars. However, a major limitation of cycle ergometer testing is discomfort and fatigue of the quadriceps muscles that can limit test tolerance. Leg fatigue in an inexperienced subject could cause early test termination before reaching a true  $\dot{V}O_{2\max}$ . Thus,  $\dot{V}O_{2\max}$  is 10% to 20% lower in cycle versus treadmill testing in those not accustomed to cycling.<sup>46</sup>

#### Exercise Protocols

Protocols for clinical exercise testing generally include an initial warm-up period (at low workload), followed by progressive graded exercise with increasing loads and an adequate time interval in each level, and a post-maximum effort recovery

period (again at low workload). Several different treadmill protocols are in general use and are seen in detail in Figure 3.<sup>44,45</sup>

The test protocol should be selected according to the purpose of testing and the individual patient.<sup>47</sup> Advantages of the standard Bruce protocol include its use in many published studies and its achievement of end-stage equilibrium. A disadvantage is the large interstage increments in workload between stages that can make estimation of  $\dot{V}O_{2\max}$  less accurate. Some subjects, especially those who are elderly, obese, or have gait difficulties, are forced to stop exercising prematurely because of musculoskeletal discomfort or an inability to tolerate the high workload increments. Initial zero or one-half stages (1.7 mph at 0% and 5% grades) can be used for subjects with compromised exercise capacities. Many protocols have been used in place of the Bruce.<sup>43</sup> The Cornell protocol reduces the large workload changes between stages of the standard Bruce protocol by reducing stage duration to 2 minutes while interpolating additional half stages.<sup>48</sup> The Naughton and Balke protocols also provide more modest increases in workload between stages and are useful choices for elderly, deconditioned patients. A complete set of protocols can be found in the American College of Sports Medicine guide for exercise prescription and testing.<sup>44</sup>

Ramp protocols start the subject at a relatively low treadmill speed, which is increased gradually until the patient has a good stride.<sup>49</sup> The ramp angle of incline is increased progressively at fixed intervals (ie, 10 to 60 seconds, or now even continuously) starting at 0% grade, with the increase in grade calculated on the patient's estimated functional capacity, such that the protocol will be completed in 6 to 12 minutes. In this type of protocol, the rate of work increases continuously, and complete steady states are not reached. Exercise protocols should be individualized according to the type of subject being tested. A 9-minute targeted ramp protocol that increases in small steps has many advantages, including more accurate estimates of MET level.<sup>50</sup>

For cycle ergometry, the initial power output is usually 10 or 25 W (150 kpm/min), usually followed by increases of 25

W every 2 or 3 minutes until end points are reached. If arm ergometry is substituted for cycle ergometry, a similar protocol may be used, except that initial power output and incremental increases are lower. Two-minute stages are most popular with arm ergometry.<sup>51,52</sup> However, most subjects who are unable to use their legs for treadmill or bicycle exercise generally undergo pharmacological stress testing with imaging.

The 6-minute walk test is a functional test that can be used to evaluate submaximal exercise capacity. This assessment has frequently been used in patients with chronic disease, such as heart failure, chronic obstructive pulmonary disease, and peripheral arterial occlusive disease.<sup>53–55</sup> Patients are instructed to walk down a 100-foot corridor at their own pace, attempting to walk as much distance as possible in 6 minutes. At the end of the 6-minute interval, the total distance walked is determined and the symptoms experienced by the patient recorded. Detailed guidelines describing the administration of the 6-minute walk test are available.<sup>56</sup> The intensity of effort associated with the 6-minute walk test is variable, ranging from submaximal to maximal, and accordingly it correlates only modestly with  $\dot{V}O_{2\max}$  ( $r \approx 0.50$ ).<sup>53,57</sup> Electrocardiographic monitoring is not routinely done with 6-minute walk testing, thus limiting its diagnostic value for ischemia or arrhythmia.

### Exercise Test Supervision

Exercise testing should be performed under the supervision of a qualified health professional who is appropriately trained to administer exercise tests.<sup>43</sup> Good clinical judgment should be foremost in deciding indications and contraindications for exercise testing.<sup>58</sup> Although absolute contraindications are clear, in selected cases with relative contraindications to high level exercise, even submaximal testing can provide valuable information about functional capacity and prognosis. Absolute and relative contraindications to exercise testing are subsequently discussed. In any procedure with a risk of complications, the test administrator should be certain that the subject understands the risks and benefits of the test, and written informed consent should be obtained. Good communication with the patient about testing is mandatory.

The physician should be responsible for ensuring that the exercise laboratory is properly equipped and that exercise testing personnel are appropriately trained. Exercise testing should be conducted only by well-trained personnel with sufficient knowledge of exercise physiology and ability to recognize important changes in rhythm and repolarization on the ECG.<sup>43</sup> The degree of subject supervision needed during a test can be determined by the clinical status of the subject being tested. This determination is made by the physician or physician's designated staff member, who asks pertinent questions about the subject's medical history, performs a brief physical examination, and reviews the standard 12-lead ECG performed immediately before testing. Supervision can be assigned to a properly trained nonphysician (ie, a nurse, physician assistant, or exercise physiologist or specialist) for testing apparently healthy younger people (<40 years of age) and those with stable chest pain syndromes. Recent recommendations permit additional flexibility with regard to supervision personnel.<sup>43</sup> Possibly with the exception of young, apparently healthy individuals (eg, exercise testing of athletes), a physician should be immediately

available during all exercise tests. For additional details about supervision and interpretation of exercise tests, reference is made to the document on clinical competence in stress testing from the ACCF, AHA, and American College of Physicians.<sup>59</sup>

Although exercise testing is considered a safe procedure,<sup>60</sup> acute MI and deaths have been reported during testing. The physician or senior medical (healthcare) professional conducting the test must be trained in advanced cardiopulmonary resuscitation. A defibrillator and appropriate medications also should be immediately available. Surveys suggest that 0 to 6 deaths or cardiac arrests per 10 000 tests and 2 to 10 MIs per 10 000 tests might be expected, but these estimates will vary markedly with the prevalence and severity of underlying heart disease in the tested population.<sup>60,61</sup> Risk is higher in patients being evaluated for malignant ventricular arrhythmias and in the unrevascularized post-MI patient, whereas serious complications are very rare in clinically normal subjects. Table 1 lists several classes of complications that can result from exercise tests.

### Perceived Exertion

The subjective rating of the intensity of exertion perceived by the person exercising is generally a sound indicator of relative fatigue. As an alternative to using HR alone to clinically determine intensity of exercise, the 6-to-20 Borg scale of perceived exertion<sup>62</sup> is useful (Table 2). Special verbal and written explanations about the rating of perceived exertion (RPE) are available for subjects. Although there is some variation among subjects in their actual rating of fatigue, they seem to rate consistently from test to test. Thus, the Borg scale can assist the clinician in judging the degree of fatigue reached from one test to another and in correlating the level of fatigue during testing with that experienced during daily activities. In general, a Borg scale rating >18 indicates the patient has performed maximal exercise, and values higher than 15 to 16 suggest that the ventilatory threshold has been exceeded.

### Angina Characteristics and Scale

Levels of anginal discomfort in those with known or suspected CAD are also excellent subjective end points. Whether typical angina occurs with exercise or is the reason for termination of the test is an important observation in evaluation of the exercise test, and it is an important factor in calculation of the Duke Treadmill Score.<sup>63</sup>

**Table 1. Complications Secondary to Exercise Testing**

Cardiac	Bradyarrhythmias
	Tachyarrhythmias
	Acute coronary syndromes
	Heart failure
	Hypotension, syncope, and shock
Noncardiac	Death (rare; frequency estimated at 1 per 10 000 tests, perhaps less)
	Musculoskeletal trauma
	Soft-tissue injury
Miscellaneous	Severe fatigue (malaise), sometimes persisting for days; dizziness; body aches; delayed feelings of illness

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**Table 2. Borg Scale for Rating Perceived Exertion**

20-Grade Scale	
6	
7	Very, very light
8	
9	Very light
10	
11	Fairly light
12	
13	Somewhat hard
14	
15	Hard
16	
17	Very hard
18	
19	Very, very hard
20	

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### Indications for Termination of Exercise Testing

The decision to terminate exercise is an important function of test supervision that is generally determined by the purpose of testing in individual subjects. Symptom-limited testing is desirable for general evaluation, but this recommendation could be modified in several situations.<sup>58</sup>

#### Absolute Indications

- ST-segment elevation (>1.0 mm) in leads without preexisting Q waves because of prior MI (other than aVR, aVL, and V1)
- Drop in systolic blood pressure >10 mmHg, despite an increase in workload, when accompanied by any other evidence of ischemia
- Moderate-to-severe angina
- Central nervous system symptoms (eg, ataxia, dizziness, near syncope)
- Signs of poor perfusion (cyanosis or pallor)
- Sustained ventricular tachycardia (VT) or other arrhythmia, including second- or third-degree atrioventricular (AV) block, that interferes with normal maintenance of cardiac output during exercise
- Technical difficulties in monitoring the ECG or systolic blood pressure
- The subject's request to stop

#### Relative Indications

- Marked ST displacement (horizontal or downsloping of >2 mm, measured 60 to 80 ms after the J point [the end of the QRS complex]) in a patient with suspected ischemia
- Drop in systolic blood pressure >10 mmHg (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 VT, including multifocal ectopy, ventricular triplets, supraventricular tachycardia, and bradyarrhythmias that have the potential to become more complex or to interfere with hemodynamic stability
- Exaggerated hypertensive response (systolic blood pressure >250 mmHg or diastolic blood pressure >115 mmHg)
- Development of bundle-branch block that cannot immediately be distinguished from VT

### The Postexercise Period

Some abnormal responses occur only in recovery.<sup>64</sup> A cool-down period of walking slowly in early recovery is commonly used, although this can delay or eliminate the appearance of ST-segment depression as compared with abrupt placement in the supine position, which increases cardiac work because of increased venous return.<sup>65</sup> Monitoring should continue for 6 to 8 minutes after exercise, or longer if the patient is symptomatic or if blood pressure, HR, and ST segments have not returned to near-baseline values. Even when no abnormalities occur at peak exercise, postexercise attention is necessary because an abnormal electrocardiographic response might occur only during the recovery period. Mechanical dysfunction and electrophysiological abnormalities in the ischemic ventricle after exercise can persist for minutes to hours. Monitoring of blood pressure should continue during recovery because abnormal responses could occur, particularly hypotension, and arrhythmias also might be present in the recovery period.

### Management of Pacemakers and Implantable Defibrillators

Exercise testing can be used to assess rate responsiveness of implanted pacemakers and occasionally reveals abnormalities of tracking function that can limit effort capacity. In patients with implanted defibrillators that are triggered by rapid rate alone, firing function should be temporarily disabled before maximum testing if the threshold HR might be reached during exercise. In the presence of a ventricular paced rhythm, the ECG cannot be evaluated for ischemia, and it should be noted that "pacemaker memory" could produce abnormal repolarization that can mimic ischemia when long-term pacing is discontinued to examine the underlying electrocardiographic waveform.<sup>66</sup>

## Clinical and Cardiopulmonary Responses During Exercise

### Clinical Responses

#### Symptoms

Assessment of perceived symptoms is an integral component of the exercise test. Symptom assessment typically includes separate quantification of dyspnea, angina, and perceived exertion. Scales for each of these symptoms are provided in the present statement and other documents.<sup>43</sup> Typical anginal symptoms induced by the exercise test are predictive of CAD and are even more predictive with associated ST-segment depression.<sup>67</sup> Exercise limited by dyspnea seems to portend a worse prognosis than does angina or leg fatigue.<sup>68,69</sup> It is important to obtain from the patient a careful description of all perceived symptoms during exercise and to document what the patient considers to be the primary limiting factor. An accurate



quantification of patient-reported symptoms also can be used to prescribe an appropriate intensity for exercise training.

#### *Physical Signs*

The subject's general appearance during the exercise test is also of value and should be carefully observed during the exercise test. Signs of poor perfusion, such as cyanosis or pallor, and increasing nervous system symptoms, such as ataxia, dizziness, and vertigo, serve as absolute test termination criteria.<sup>58</sup> Although the diagnostic value has not been confirmed, cardiac auscultation immediately after exercise has been proposed to assess cardiac function. "Gallop" sounds, a palpable precordial bulge, or the development of a mitral regurgitant murmur after exercise could suggest LV dysfunction resulting from exercise.<sup>70</sup>

#### *Exercise Capacity*

Aerobic exercise capacity is one of the single best predictors of risk for future adverse events in apparently healthy individuals, those at increased risk for CVD, and virtually all patient populations,<sup>16,71–73</sup> independent of other traditional risk factors.<sup>74</sup> In a recent meta-analysis,<sup>71</sup> it was reported that each 1-MET increase in aerobic capacity resulted in a 13% and 15% decrease in rates of all-cause death and cardiovascular events, respectively. Maximal work capacity achieved during an exercise test, which frequently is used to estimate aerobic capacity, is influenced by several factors, including patient's familiarization with the exercise test equipment, selection of an appropriate exercise protocol, patient's level of training, and environmental conditions at the time of testing.<sup>75</sup> In estimating exercise capacity, the amount of work performed in METs (or exercise stage achieved) is preferred to the number of minutes of exercise because protocols and conditions vary. Age- and sex-predicted peak MET levels have been described previously in the present document, and peak values achieved have prognostic significance.<sup>22,76–79</sup> Thus, aerobic capacity should be reported as both the actual value achieved and a percent-predicted value. To provide the most accurate estimation of exercise capacity, handrail use should be minimized when performing the test on a treadmill. Moreover, a conservative exercise test protocol, with smaller workload adjustments from one stage to the next, is preferable in patients with a diminished functional capacity.<sup>75</sup> All exercise testing procedures should be consistent when serial assessments are performed to assess therapeutic efficacy or disease progression. The use of ventilatory expired gas analysis (discussed in subsequent sections) greatly improves the reliability of key variables obtained from the exercise test.<sup>43</sup>

#### *Cardiopulmonary Exercise Testing*

Ventilatory expired gas analysis allows for the capture of minute ventilation ( $\dot{V}_E$ ),  $\dot{V}_{O_2}$ , and  $\dot{V}_{CO_2}$  through a face mask or mouthpiece. When combined with traditional testing procedures, this assessment is commonly referred to as cardiopulmonary exercise testing (CPX). CPX provides the most accurate noninvasive quantification of maximal aerobic capacity (ie,  $\dot{V}_{O_{2max}}$  or peak  $\dot{V}_{O_2}$ ) and subject effort (via the respiratory exchange ratio:  $\dot{V}_{CO_2}/\dot{V}_{O_2}$ ). Commercially available ventilatory expired gas systems are also commonly capable of performing pulmonary function tests. Finally, several variables obtained exclusively from CPX, such as the  $\dot{V}_E/\dot{V}_{CO_2}$  ratio or slope and the partial pressure of end-tidal  $CO_2$ , provide valuable diagnostic and prognostic information in certain

patient populations (eg, those with heart failure or pulmonary arterial hypertension). Thus, CPX provides the clinician with a highly accurate, reliable, and comprehensive assessment of all systems involved in the response to aerobic exercise (ie, cardiac, pulmonary, and skeletal muscle). Currently, CPX is common in clinical practice for patients with heart failure who are being considered for transplantation and for those with unexplained exertional dyspnea.<sup>58</sup> A detailed description of CPX can be found in a scientific statement by the AHA.<sup>19</sup>

#### **The ECG During Exercise**

##### *Electrocardiographic Findings During Exercise in Normal Subjects*

###### *P Wave*

During exercise, P-wave magnitude increases significantly in the frontal plane inferior leads. P-wave duration is generally unchanged or is minimally longer.<sup>80</sup>

###### *PR Segment*

The PR segment shortens and slopes downward in the inferior leads during exercise.<sup>81</sup> The decreasing slope has been attributed to atrial repolarization (the Ta wave) and can cause apparent ST-segment depression when the negative Ta wave persists into the early ventricular repolarization period.<sup>82,83</sup>

###### *QRS Complex*

High-frequency content of the QRS power spectrum increases with exercise in normal subjects, perhaps as a result of increased conduction velocity within the heart.<sup>84</sup> QRS duration in normal subjects generally decreases at higher exercise workloads.<sup>85</sup> Septal Q waves measured in lateral leads tend to increase in magnitude during exercise in normal subjects,<sup>86,87</sup> whereas R waves decrease and S waves tend to increase in inferior leads.<sup>88</sup> These separate findings can be incorporated into a QRS score for diagnostic purposes.<sup>89</sup>

###### *J-Point Deviation and Upsloping ST Depression*

The J junction, also known as the J point (representing the time-voltage coordinate of the end of the QRS complex and the beginning of the ST segment) can be depressed at maximum exercise and then gradually return to preexercise values in recovery. Upsloping ST depression at peak exercise might be seen in 10% to 20% of normal subjects,<sup>90,91</sup> and J-point depression is more common in older patients. The magnitude of ST depression should be measured 60 to 80 ms after the J point. In normal subjects with resting J-point elevation because of early repolarization, the ST level generally normalizes with exercise; this is a normal finding and should not be considered equivalent to ST depression in relation to the elevated baseline.

###### *T Wave*

A general decrease in T-wave amplitude is observed during early exercise, but it rises to control values at higher exercise workloads and rises further to above control values during early recovery.<sup>88</sup>

###### *U Wave*

No significant changes are noted with exercise; however, U waves can be difficult to identify at ventricular rates >120 bpm because of the close approximation of the T and P waves with the increased HR of exercise.



*QT-Interval Dynamics*

As a result of the interval–duration relationship, action potentials shorten as HR increases with exercise, and the resulting QT interval of the ECG is further affected by neurohumoral changes that accompany effort.<sup>92</sup> In most normal subjects, the absolute QT decreases from the onset of effort, although in some subjects (more commonly women) there can be a paradoxical absolute QT prolongation in the early minutes of the test.<sup>93</sup> When the measured QT interval is corrected for rate by the Bazett formula (corrected QT = measured QT/RR<sup>0.5</sup>), it is common for the corrected QT to rise early in exercise and then decrease as rates increase at higher exercise workloads.<sup>94</sup>

***Abnormal Electrocardiographic Changes During Exercise and Recovery in Ischemia****ST-Segment Deviation*

Changes in the level of the ST segment comprise the earliest abnormal finding in the history of exercise testing and have been the focus of standard test criteria for the diagnosis of myocardial ischemia for well over half a century. The ST level is measured relative to the end of the PR segment (the P–Q junction) because the T(U)–P segment during exercise is difficult or impossible to measure when HRs are fast. Three or more consecutive beats in the same lead with a stable baseline should be identified and the average magnitude and tangent direction of displacement at 60 to 80 ms after the J point determined, either manually or by use of computer-averaged complexes.<sup>95</sup> It is essential to visually verify automated measurements made by computer.

**ST-Segment Depression.** ST-segment depression is the traditional manifestation of exercise-induced myocardial ischemia.<sup>91,96</sup> ST-segment depression recorded on the body surface represents the magnitude and direction of electrical gradients generated by ischemic vectors across the endocardium and epicardium, as well as the location of the recording electrodes. Upsloping, horizontal, and downsloping types of ST-segment depression are illustrated in Figure 4. Demand ischemia during exercise is limited primarily to the endocardium, with reductions in phase 2 plateau amplitude and also less negative phase 4 resting membrane potentials contributing to ST depression on the surface ECG.<sup>3</sup> The standard criteria for test positivity include horizontal or downsloping ST depression  $\geq 1$  mm (0.1 mV) at 60 to 80 ms after the J point. When modest resting ST depression is present on the upright control ECG before exercise, only additional ST depression during exercise is measured for analysis. In the presence of resting ST-segment elevation at 60 to 80 ms after the J point because of early repolarization, only ST-segment changes below the P–Q baseline should be used for analysis.<sup>97</sup>

Markedly depressed upsloping ST-depression responses to exercise (2.0 mm at 80 ms after the J point) could identify underlying CAD and future adverse events in highly symptomatic patients with angina,<sup>98</sup> and increased area of the time integral of upsloping ST depression might be associated with increased risk of future coronary events in higher-risk men.<sup>99</sup> However, upsloping ST depression during exercise, whether rapid or slow in configuration, is not usefully predictive for the presence of myocardial ischemia in general populations.<sup>100</sup> Because upsloping ST-segment depression is comparably prevalent in less

highly selected patients with CAD and in normal subjects,<sup>90</sup> it is generally defined as an “equivocal” test response. Equivocal test responses are a major reason for the reduced sensitivity of the exercise ECG. However, if upsloping ST depression were considered a positive response, it would result in unacceptably low specificity of the test. Other recognized causes of false negative test responses include inadequate effort and anatomically mild disease; test sensitivity rises markedly with increasing severity of obstruction.<sup>90,96,101</sup> 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. The anatomic and functional severity of CAD also can be related to the time of appearance of ischemic ST-segment depression. The lower the workload and rate–pressure product at which it occurs, the worse is the prognosis and the more likely the presence of multivessel disease; the duration of ST depression in the recovery phase also can be related to the severity of CAD.<sup>91</sup>

***ST-Segment Elevation in Postinfarction Patients With Q Waves.***

Exercise-induced elevation can occur in an infarct area where prior Q waves are present. The development of  $>0.10$  mV of J-point elevation ( $>1.0$  mm at standard gain) at 60 ms after the J point is considered an abnormal response. In the presence of prior Q-wave MI, this could represent reversible ischemia in the peri-infarct area or ventricular dyskinesia or akinetic LV segmental wall motion.<sup>102,103</sup> Approximately 30% of subjects with anterior infarction and 15% of subjects with inferior infarction demonstrate exercise-induced ST-segment elevation in Q-wave leads. The changes could result in reciprocal ST-segment depression that simulates myocardial ischemia in other leads. However, ST-segment elevation and ST-segment depression in the same test also could indicate multivessel CAD. Myocardial imaging techniques can help distinguish the concomitant presence of a new myocardial ischemic zone from reciprocal changes induced by ST-segment elevation in Q-wave leads.

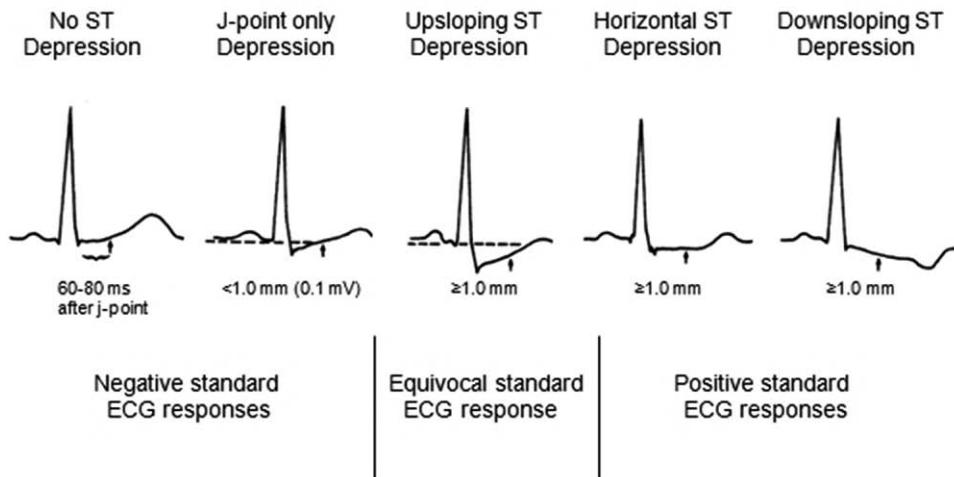
***ST-Segment Elevation in Subjects Without Prior Infarction.***

In subjects without previous infarction (absence of Q waves on the resting ECG), ST-segment elevation during exercise frequently localizes the site of severe transient combined endocardial and subepicardial ischemia resulting from significant subtotal proximal occlusive CAD.<sup>104</sup> It also can occur during spasm in otherwise nonobstructed or mildly obstructed coronary arteries,<sup>105</sup> but this is uncommon.<sup>106</sup> Exercise-induced ST-segment elevation is more commonly associated with anatomically severe fixed proximal obstruction than with coronary spasm in otherwise unobstructed arteries.

*ST-Segment Normalization*

Repolarization changes that are present at rest, including T-wave inversion and ST-segment depression, have been reported to normalize during clinical episodes of angina and during exercise in some subjects with ischemic heart disease. Normalization of the ST segment during exercise might be related to cancellation effects of oppositely directed forces from multiple areas of ischemia (ischemic counterpoise),<sup>107,108</sup> which could explain false negative test findings in some patients with multivessel CAD. It is usual for young subjects with early repolarization to have normalization of resting ST-segment elevation during exercise.

## ST SEGMENT DEPRESSION DURING EXERCISE



**Figure 4.** Definition of ST-segment depression changes during exercise. Positive standard test responses include horizontal or downsloping depression  $\geq 1.0$  mm (0.1 mV), whereas upsloping ST depression  $\geq 1.0$  mm is considered equivocal (a change that does not usefully separate normal from abnormal). All ST depression  $< 1.0$  mm additional from baseline is defined as negative. The waveforms depicted are modified from Tavel<sup>610</sup> with permission of the publisher, copyright © 2001, American College of Chest Physicians, but the classification and definitions represent the consensus of the writing group.

**HR Adjustment of ST-Segment Depression.** Peak HR and the change in HR during exercise are lower in patients with ischemic disease than in normal subjects.<sup>101</sup> At the same time, increasing HR during graded exercise is what influences progressive ST-segment depression because it is a major determinant of myocardial oxygen demand.<sup>109</sup> As a consequence, it is physiologically rational to adjust observed ST-segment depression for the change in HR associated with its production to derive indices of the presence and extent of obstructive CAD. HR adjustment of ST-segment depression can improve the sensitivity of the exercise test with preservation of test specificity, primarily from improved classification of patients with equivocal test responses attributable to upsloping ST segments.<sup>90,110</sup> Differences in test performance among studies with these methods could result from population differences and from technical differences in methodology. The methods are not accurate in the early phase after Q-wave infarction in patients with resting abnormalities of repolarization, but they do seem to increase the sensitivity of the exercise ECG in general populations.<sup>111</sup> Further prospective evaluation of their values and limitations for specific purposes of testing is required.

**The ST/HR Slope and the ST/HR Index.** Calculation of maximal ST-segment (ST)/HR slope in microvolts per beat per minute is performed by linear regression analysis relating the measured amount of ST-segment depression in individual leads to the HR at the end of each stage of exercise, starting at end exercise. An ST/HR slope  $> 2.4$   $\mu\text{V}/\text{bpm}$  is considered abnormal, and values  $> 6$   $\mu\text{V}/\text{bpm}$  are suggestive of anatomically extensive disease, including 3-vessel or left main CAD.<sup>111</sup> The practical use of this measurement requires an exercise protocol with gradual increments in HR, such as the Cornell Protocol, because large increments in rate between stages of the Bruce Protocol limit the ability to calculate statistically valid ST/HR slopes by regression.<sup>48</sup> A modification of the ST/HR slope method is the simple ST/HR index calculation, which represents the average changes of ST-segment depression with HR throughout the course of the exercise test and requires no regression calculation. The ST/HR index measurements during ischemia are lower than the ST/HR slope measurements

because ST change is averaged over the entire HR change of exercise, with an ST/HR index of  $> 1.6$   $\mu\text{V}/\text{bpm}$  defined as abnormal.<sup>90,111</sup> Because it is calculated from only upright control and peak exercise data, the ST/HR index can be derived from tests that are not gently graded. The ST/HR index has been shown in retrospective application to improve prediction of coronary events in asymptomatic higher-risk men<sup>112</sup> and also in asymptomatic lower-risk men and women.<sup>113</sup> These methods require further prospective evaluation.

**Recovery Phase ST/HR Loops and Hysteresis.** As the HR slows during early recovery from peak exercise, the recovery phase behavior of the depressed ST segment as it returns to normal differs in normal subjects and patients with ischemia. ST/HR loops and hysteresis provide alternative criteria for test positivity and negativity. After 1 minute of recovery, ST depression attributable to ischemia is generally greater than it was at the same HR during exercise, whereas in normal subjects it is less.<sup>114</sup> Extension of this principle to encompass measurement of the recovery phase area above or below the ST depression occurring with exercise forms the basis of ST/HR hysteresis, where the term hysteresis is used to indicate asymmetry of measured responses with respect to another variable occurring during exercise and recovery, such as time from peak effort, or in this case to matched HR during exercise and recovery. ST/HR hysteresis appears to provide higher diagnostic and prognostic test accuracy than that found for simultaneously measured standard ST-segment depression criteria and for the ST/HR indices.<sup>115–117</sup>

### Beyond the ST Segment

Because the surface ECG reflects uncanceled summation of individual action potentials in the heart, and because demand-induced ischemia affects action potentials beyond alterations in plateau phase and resting membrane potential, it is reasonable to expect changes in the exercise ECG that extend beyond the ST segment, either alone or as modified for HR behavior.<sup>116,118</sup> Several changes in the ECG during exercise-induced ischemia have been proposed as markers for obstructive CAD. Even though these findings are not used in routine test interpretation, they are described briefly in the

next sections. It is emphasized that prospective evaluation of these criteria in larger, multicenter populations is required for clarification of their value and limitations.<sup>3</sup> Combinations of criteria have the potential to improve test accuracy,<sup>119</sup> but comprehensive prospective evaluation of the value and limitations of combinations of standard and alternative criteria in relevant populations is needed if further progress is to be made in exercise ECG.

**P-Wave Abnormalities.** Among patients with chest pain evaluated by myocardial perfusion imaging, exercise-related P-wave duration and terminal P-wave amplitude in  $V_1$  have been reported to be greater in patients with reversible ischemia than in patients with normal scans,<sup>120–122</sup> a finding that might be attributed to left atrial pressure overload during ischemia. An increase in P-wave duration by signal-averaging has also been associated with ischemia.<sup>80</sup>

**R-Wave Amplitude Changes.** The average response in normal subjects is an increase in R-wave amplitude during submaximal exercise, with a decrease at maximum exercise. An increase in R wave at peak exercise has been associated with myocardial ischemia,<sup>123,124</sup> perhaps as a correlate of LV ischemic dilatation. Exercise-induced changes in R-wave amplitude have not consistently improved diagnostic accuracy of the exercise ECG, despite use of several lead systems, clinical subsets of subjects, and different criteria for an abnormal response.<sup>125</sup>

**QRS Duration.** Careful measurement of QRS duration during the course of exercise has suggested that absence of QRS shortening at peak exercise can be a marker for underlying CAD, particularly in women and in some situations with otherwise false-positive ST-segment responses.<sup>85,126–129</sup> Further exploration of these observations with global measurements of QRS duration obtained by digitized simultaneous lead acquisition of “global” QRS determinations is warranted.

**High-Frequency QRS Fragmentation.** Reduction of root mean square and peak amplitudes of signal-averaged high-frequency QRS complexes and occurrence of reduced high-frequency amplitude zones have been found to have useful test performance characteristics for the detection of CAD.<sup>130,131</sup> These techniques require special filtering methodology.

**QRS Score.** An index based on exercise-induced changes in amplitudes of Q, R, and S waves was introduced as the Athens QRS score<sup>89</sup> and has been related to the extent of CAD and to the anatomic extent of myocardial ischemia.<sup>118,132</sup> The QRS score has been separately shown to complement ST-segment depression criteria for the detection of CAD.<sup>133</sup>

**T-Wave Changes.** An increase in precordial T-wave amplitude has been associated with the localized onset of apical asynergy during dobutamine stress electrocardiography.<sup>134</sup> The morphology of the T wave is influenced by body position, respiration, hyperventilation, drug therapy, and myocardial ischemia/necrosis. In patient populations with a low CAD prevalence, normalization of inverted T waves with exercise is a nondiagnostic finding. In patients with CAD, findings have varied. Exercise-induced normalization of inverted T waves after non-Q-wave

infarction has been associated with reversible ischemia during dobutamine stress echocardiography<sup>135</sup> but also has been associated with perfusion of the ischemic area and late recovery of ventricular function after anterior infarction.<sup>136</sup>

**U-Wave Changes.** Exercise-induced U-wave inversion in subjects with a normal resting ECG can be a marker of myocardial ischemia in up to one quarter of patients with single-vessel left anterior descending disease.<sup>137</sup> Sympathetic stimulation by both exercise treadmill testing and by isoproterenol infusion, but not atrial pacing, was found to prolong the QT interval, with U-wave enlargement in subjects with some types of congenital long-QT syndrome.<sup>138</sup>

**QT Interval and QT Hysteresis.** Absence of QT interval shortening at peak exercise (as generally rate-corrected by the Bazett formula) has been proposed as a marker for inducible ischemia. However, differences in peak HR between patients with and without ischemia and problems with inaccuracy of the Bazett correction at the faster rates that occur during exercise have limited the applicability of peak-exercise QT interval alone as an electrocardiographic criterion for ischemia.<sup>94</sup> The QT interval–HR relationship or QT/RR relationship during early stages of exercise can be defined by linear regression<sup>93</sup>; however, greater value for diagnosis of CAD appears to result from examination of QT–RR interval hysteresis during exercise and recovery, for which patients with ischemia have greater decrease in recovery QT intervals than during exercise itself, both relative to cycle length rather than time.<sup>139</sup>

**Disorders of Impulse Formation.** Disorders of impulse formation include supraventricular and ventricular arrhythmias. Exercise can induce cardiac arrhythmias under several conditions, including diuretic and digitalis therapy.<sup>140–142</sup> Recent ingestion of alcohol or caffeine can exacerbate arrhythmias. Because exercise increases myocardial oxygen demand, in the presence of CAD, exercise-induced myocardial ischemia could predispose the subject to ectopic activity. It seems that ischemia with ST depression is not as arrhythmogenic as ischemia with ST elevation. Exercise-induced arrhythmias are generated by enhanced sympathetic tone, increased myocardial oxygen demand, or both. The period immediately after exercise is particularly dangerous because of the high catecholamine levels that are associated with generalized vasodilation. Peripheral arterial dilation induced by exercise and reduced cardiac output, resulting from diminished venous return secondary to sudden termination of muscular activity, can lead to a reduction in coronary perfusion in early recovery while the HR is still elevated. The increased sympathetic tone in the myocardium can stimulate ectopic Purkinje pacemaker activity by accelerating phase 4 of the action potential, which provokes spontaneous discharge and leads to increased automaticity.

Exercise can suppress cardiac arrhythmias that are present at rest. This phenomenon has been attributed to the overdrive suppression of the ectopic impulse formation by sinus tachycardia that is caused by exercise-induced vagal withdrawal and increased sympathetic stimulation. Exercise-induced sinus tachycardia might inhibit automaticity of an ectopic focus because it “overrides” automaticity of the Purkinje tissue.



**Supraventricular Arrhythmias.** Sinus arrhythmias with periods of sinus bradycardia and wandering atrial pacemaker are relatively common during early exercise and the immediate recovery phase. Atrial ectopic contractions and atrial “group” beats can occur in either normal or diseased hearts. Exercise-induced transient atrial fibrillation and flutter occur in <1% of individuals who undergo exercise testing.<sup>143</sup> These arrhythmias can be induced by exercise in healthy individuals or in subjects with rheumatic heart disease, hyperthyroidism, Wolff-Parkinson-White (WPW) syndrome, or cardiomyopathy, and they can be problematic if the ventricular response is rapid. Paroxysmal AV junctional tachycardia is observed during exercise only rarely. Exercise-induced supraventricular arrhythmias alone are not usually related to CAD but are more often related to older age, pulmonary disease, recent alcohol ingestion, or excessive caffeine intake.

**Ventricular Arrhythmias.** Ectopic ventricular beats are the most frequent cardiac arrhythmia during exercise. Their prevalence is related directly to age and cardiac abnormalities. In general, ectopic ventricular beats are of concern in subjects with a family history of sudden death or a personal history of cardiomyopathy, valvular heart disease, or severe myocardial ischemia. VT can be nonsustained or sustained, and exercise-related types include catecholamine-triggered polymorphic VT and right ventricular outflow tract VT associated with arrhythmogenic right ventricular dysplasia. The diagnostic and prognostic values of patterns of ventricular ectopy during and after exercise have been variable. Recent studies have suggested that frequent or complex repetitive ventricular activity during exercise, and particularly ventricular ectopy in the recovery period after exercise, can be independent predictive markers for death.<sup>144,145</sup>

**Disorders of Impulse Conduction.** Disorders of impulse conduction include abnormalities of normal impulse initiation and conduction through the heart.

**Bundle-Branch and Fascicular Blocks.** Intracardiac conduction blocks can exist before exercise, develop during exercise, or disappear during exercise. Rate-dependent intraventricular blocks that develop during exercise often precede the appearance of chronic blocks that develop later at rest.<sup>146</sup> Both left and right bundle-branch blocks have been reported to occur during exercise.<sup>146–148</sup> Diagnosis of myocardial ischemia from the exercise ECG is usually impossible when left bundle-branch block is present. There can be a marked degree of exercise-induced ST-segment depression in addition to that found at rest in normal subjects with left bundle-branch block, and there is no clear difference in ST-segment response to exercise between those with and those without myocardial ischemia. Left bundle-branch block that develops during exercise might or might not be associated with CAD,<sup>146,147</sup> but it does predict higher risk of death and major cardiac events.<sup>149</sup> The disappearance during exercise of intraventricular blocks that are present at rest is rare.<sup>150</sup>

Preexisting right bundle-branch block<sup>148,151–154</sup> does not invalidate interpretation of the exercise ECG, except in the anterior precordial leads ( $V_1$ ,  $V_2$ , and  $V_3$ ), where ST depression is frequently present at baseline and increases with exercise even in the absence of coronary obstruction. Because ST depression

limited to these precordial leads alone is rare in myocardial ischemia, the usual diagnostic criteria can be applied in the remaining inferolateral leads. The development of right bundle-branch block during exercise is less common than the development of left bundle-branch block in populations with a high prevalence of underlying heart disease, but whereas left bundle-branch block occurs commonly in patients with nonischemic cardiomyopathies, right bundle-branch block has been associated with underlying CAD as the origin of disease, particularly with obstructive disease affecting the left anterior descending artery.<sup>155</sup> The strength of this association has been questioned by a recent study,<sup>156</sup> and rate-dependency of the right bundle in less selected populations could limit predictive value.

**AV Conduction.** Shortening of the PR interval (by as much as 0.10 or 0.11 seconds) during exercise as the sinus rate increases is normal, probably because of increased sympathetic tone and vagal withdrawal. This usually occurs in young, healthy individuals.<sup>81</sup>

**FIRST-DEGREE AV BLOCK.** First-degree AV block occurs occasionally at the end of exercise or during the recovery phase, particularly in the presence of occult AV node disease. Medications or conditions that can produce prolonged AV conduction time (eg, digitalis,  $\beta$ -blockers, some calcium channel blockers, inflammatory disorders of the heart) predispose the individual to lengthening of the PR interval.

**SECOND-DEGREE AV BLOCK.** The occurrence of Wenckebach-type (Mobitz type I) AV block during exercise is rare because vagal tone is reduced during exercise, whereas sympathetic neurohumoral tone increases. The clinical significance of exercise-induced Mobitz type II AV block generally is related to CAD or to aortic valve stenosis and could herald the development of permanent block, but type II block also can be a rate-related phenomenon that appears as the sinus rate is accelerated beyond a critical level.<sup>157,158</sup> When second-degree AV block develops during exercise, the test should be terminated.

**THIRD-DEGREE (COMPLETE) AV BLOCK.** Acquired advanced or complete AV block at rest is a relative contraindication to exercise testing because increasing sympathetic drive without effective rate increase can result in complex ventricular arrhythmias. Exercise testing can be conducted in subjects with congenital complete AV block if there are no coexisting significant congenital anomalies that reduce test safety. The development of complete block during exercise testing is uncommon, but it can be related to transient ischemia.<sup>159</sup> Development of advanced or complete AV block should prompt termination of the test.

**Exercise and Preexcitation Syndromes.** Exercise can provoke, abolish, or have no effect on ventricular preexcitation in individuals with known WPW syndrome.<sup>160</sup> When exercise does not interfere with preexisting preexcitation, significant ST depression can be observed during exercise testing. In the presence of WPW syndrome, the ST depression cannot be said to be attributable to ischemia but instead could be a false-positive occurrence if the delta wave persists at peak exercise. Although exercise has been considered a predisposing factor to initiate tachyarrhythmia in WPW syndrome, prevalence of tachyarrhythmias during or after exercise is low in WPW subjects, and



disappearance of the delta wave during exercise can identify patients at lower risk for sudden death.<sup>161,162</sup>

### ***Diagnostic Value of the Exercise ECG for Identification of CAD and for Assessment of Its Severity***

A meta-analysis of 147 studies of the test performance of the exercise ECG for the detection of CAD revealed a mean test sensitivity of 68% and a mean test specificity of 77%, with sensitivities ranging from 23% to 100% and specificities ranging from 17% to 100%.<sup>96</sup> Reasons for these extraordinary ranges of values include marked differences in the characteristics of the populations studied, differences in definition of the presence and severity of disease, and differences in many additional factors that govern the diagnostic performance of a test, as described in the sections that follow.

### ***Sensitivity, Specificity, and Receiver Operating Characteristic Curves***

Sensitivity and specificity define how effectively a test separates subjects with disease from healthy individuals (ie, how well a test diagnoses disease). Sensitivity is the percentage of those individuals with a disease who will have abnormal tests. Sensitivity is influenced by disease severity, effort level, and anti-ischemic drugs. Specificity is the percentage of those without the disease who will have normal test results, and it can be affected by drugs such as digoxin, by baseline electrocardiographic patterns, and by LV hypertrophy. Sensitivity and specificity are inversely related; when sensitivity is the highest, specificity is lowest, and vice versa. All tests have a range of inversely related sensitivities and specificities that can be selected by specifying a discriminant or diagnostic cut point.<sup>163</sup> Receiver operating characteristic curve analysis is used for evaluating the accuracy of a statistical model when cut points are used to classify patients as diseased or nondiseased. As a graphical tool, a receiver operating characteristic plot displays the test sensitivity on the y-axis against 1 minus the test specificity on the x-axis for varying values of the diagnostic cut point. The area under the curve provides a summary measure that averages the diagnostic accuracy across the range of test values. It equals 1.0 for perfect accuracy and 0.5 when the curve corresponds to random chance. Thus, the closer the area is to 1.0, the more accurate the test.<sup>163</sup> From a meta-analysis of multiple studies, the standard exercise test cut point of 0.1 mV (1 mm) of horizontal or downsloping ST-segment depression has been selected as the discriminating cut point and has a sensitivity of 68% and specificity of 77%.<sup>58</sup> The sensitivity and specificity of stress testing are limited by the general use of angiographic CAD as the diagnostic “gold standard,” and hence most data are derived from studies in which patients underwent both exercise testing and cardiac catheterization. Because patients selected for coronary arteriography are more likely to have obstructive CAD, these data are subject to a workup bias that inflates the estimated sensitivity and deflates the specificity. The diagnostic accuracy of a test also will be influenced by criteria that are used to determine whether an adequate level of stress has been achieved. This often is defined as having attained 85% of maximum predicted HR, where maximum predicted HR is estimated as 220 minus age in years. There are shortcomings to using this calculation for diagnostic purposes, and it should not be used as a sole reason to terminate the test.<sup>9</sup>

### ***Factors Affecting Test Sensitivity***

The choice of a discriminant value is further complicated by the fact that some exercise test responses do not have established values that separate normal subjects from those with disease. 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 a higher sensitivity. For instance, the exercise test has a higher sensitivity in individuals with triple-vessel disease than in those with double-vessel disease, which in turn is higher than those with single-vessel disease.<sup>90,91</sup> Accordingly, test sensitivity in any study population will vary with the extent of disease, even though all patients will have a diagnosis of CAD.

### ***Factors Affecting Test Specificity***

Workup bias, as described previously, reduces exercise test specificity by including patients with previously positive tests but no disease at catheterization in the “normal” population under study.<sup>164</sup> A test also can have a lower specificity if it is used in individuals who are more likely to have false-positive results (eg, those with an abnormal resting ECG, including bundle-branch block, resting ST-T-wave abnormalities, or LV hypertrophy).

### ***Positive and Negative Predictive Values***

Predictive values help define the diagnostic value of a test. The predictive value of a test is greatly influenced by the prevalence of disease in the group (or individual) 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 disease before testing and the probability that the test provided a true result.” Thus, a test has a higher positive predictive value and lower negative predictive value when used in a high-prevalence population; conversely, a higher negative predictive value and lower positive predictive value occur in a lower-prevalence population. 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.

### ***Pretest and Posttest Probability of Disease***

Understanding interactions among sensitivity, specificity, and predictive values can help to optimize the use of diagnostic exercise testing. Several clinical variables affect the likelihood of atherosclerotic CAD before the patient undergoes the exercise test. These include age, sex, symptoms, and the presence and extent of traditional risk factors (eg, hypertension, hyperlipidemia, diabetes mellitus). On the basis of individual likelihood of disease and the performance characteristics of the outcome on exercise ECG, the posttest likelihood of obstructive CAD can be estimated for a given individual.

### ***Assessment of Anatomic and Functional Extent of CAD***

Exercise-induced ST-segment depression does not provide a reliable assessment of the specific coronary vessel(s) involved. However, ST-segment elevation in leads without Q waves, though an uncommon response, usually reflects transmural ischemia that can be localized by the leads involved: Leads V<sub>2</sub> through V<sub>4</sub> reflect left anterior descending artery disease; lateral leads reflect left circumflex and diagonal vessel disease; and leads II, III, and aVF

reflect right CAD (in a right dominant circulation).<sup>58</sup> As noted previously, 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, however, to realize that prognostically important CAD can be present without significant luminal obstructive lesions, particularly in the presence of endothelial dysfunction and unstable but nonobstructive plaque.<sup>165</sup> Hence, 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 in the later section on prognosis.<sup>3</sup>

### Stress Imaging Modalities and Exercise Testing

The addition of various imaging modalities to exercise can provide greater diagnostic accuracy than exercise electrocardiographic testing alone. Imaging provides information on the location and amount of ischemic myocardium and on LV function. Exercise or pharmacological stress imaging studies are useful particularly when the resting ECG has baseline abnormalities (eg, left bundle-branch block or resting ST depression >1 mm) that limit the accurate interpretation of the exercise ECG or when the results of the exercise ECG are equivocal or indeterminate.

#### The Ischemic Cascade

The limitation of coronary flow reserve by hemodynamically “significant” stenoses leads to a mismatch between myocardial oxygen supply and demand during stress. The acute metabolic consequences of this mismatch include decreased production of adenosine triphosphate and increased production of lactate, and they result in alterations of the electrical properties and mechanical function of the myocardium. These alterations occur in rapid succession in a characteristic sequence termed *ischemic cascade* and include, in typical order, reduced LV compliance, regional wall motion abnormalities attributable to decreased myocardial contractility, increased LV end-diastolic pressure, and ST-segment changes exceeding the usual threshold of 0.1 mV.<sup>166</sup> The clinical symptom of angina pectoris often occurs last, if at all.

Pharmacological stress imaging identifies the relative lack of increase in perfusion in myocardial territories supplied by a stenotic coronary artery relative to perfusion in territories where coronary flow augments normally, as opposed to the metabolic or functional consequences of the mismatch between oxygen supply and demand resulting from exercise-induced ischemia.

#### Pharmacological Stress Testing and Agents

In patients unable to exercise for reasons such as deconditioning, peripheral vascular disease, orthopedic disabilities, neurological disease, or other concomitant illnesses, several pharmacological agents can be used to induce mismatch of myocardial oxygen demand and supply in lieu of physical exercise or to unmask locally limited capacity for coronary vasodilatation. Medications used for pharmacological stress testing include dobutamine, selective A2a adenosine receptor agonists, and adenosine.

##### Dobutamine

Adrenergic agents such as dobutamine increase myocardial oxygen demand by increasing myocardial contractility, HR, and blood pressure. Dobutamine is infused intravenously at

doses that increase every 3 minutes until a maximal dose is reached or an end point has been achieved. ECG, HR, and blood pressure are monitored during each stage.

The primary end point with dobutamine testing is a target HR of 85% of the age-predicted maximal value, in the absence of higher-grade arrhythmia, angina, intolerable side effects, and significant increase or decrease in blood pressure. Intravenous atropine may be given if an adequate HR is not achieved with dobutamine infusion alone. Complications of dobutamine infusion include nausea, headache, tremor, anxiety, angina and atypical chest pain, atrial and ventricular arrhythmias, and hypertension or hypotension. MI (<0.02%) and death (<0.002%) as complications are very rare.<sup>167</sup> Side effects or complications can be treated by intravenous injection of adrenergic  $\beta$ -receptor-blocking agents such as metoprolol or esmolol.

##### Selective A2a Adenosine Receptor Agonists and Adenosine

Vasodilators such as adenosine, dipyridamole, and regadenoson cause coronary vasodilation in normal epicardial arteries.<sup>168,169</sup> Because of autoregulation, coronary arteries with metabolically significant stenoses already recruit vasodilator reserve at rest to maintain coronary flow; therefore, they cannot increase coronary flow as much as coronary arteries without stenoses when vasodilators are given. The relative lack of increased perfusion during vasodilation can be visualized with nuclear myocardial perfusion agents. Vasodilator stress agents are not commonly used for stress echocardiography in the United States, where dobutamine may serve as an alternative to exercise.

Nuclear perfusion imaging with vasodilator agents is useful particularly for the diagnosis of CAD in patients with left bundle-branch block on resting ECG,<sup>168</sup> because artifactual perfusion defects can occur in patients with normal coronary arteries and left bundle-branch block with exercise or dobutamine stress. Side effects of vasodilator agents include flushing, chest pain, headache, nausea, dyspnea, and AV block, which can be reversed with aminophylline.<sup>168</sup> Because of the short half-life of adenosine, side effects usually resolve very shortly after termination of the infusion. Adenosine and dipyridamole should not be used in patients with second- or third-degree block who do not have permanent pacemakers in place or in patients with severe asthma or chronic obstructive lung disease.<sup>168</sup> Because caffeine can block the effects of adenosine and the A2a receptor agonists, patients should refrain from consuming caffeine for 24 hours before the test.

#### Nuclear Myocardial Perfusion Imaging

Stress myocardial perfusion imaging can be performed as single-photon emission computed tomography (SPECT)<sup>168</sup> or positron emission tomography (PET).<sup>170</sup> SPECT is currently more widely available and technically less challenging than PET, and the diagnostic and prognostic value of SPECT is better established. SPECT uses commercially available tracers such as technetium (Tc)-99m sestamibi, Tc-99m-tetrofosmin, and, less commonly, thallium-201. PET uses myocardial perfusion imaging agents with very short half-lives, of which rubidium (Rb)-82 can be produced with a generator, whereas N-13 ammonia requires a local cyclotron. Compared with SPECT, PET typically has higher spatial and temporal resolution, has a lower effective radiation dose, allows quantitative measurement of myocardial perfusion, and can be performed faster.

However, recent developments in imaging protocols (stress only), gamma camera technologies (solid-state cadmium zinc telluride detectors), and raw data processing algorithms (iterative reconstruction) have reduced the effective radiation dose and duration of SPECT imaging considerably. Nonetheless, cumulative radiation is a factor in serial perfusion imaging.

SPECT and N-13 ammonia PET can be performed with exercise and pharmacological stress, whereas R-82 PET imaging can be performed only with pharmacological stress because of the extremely short tracer half-life. The radioisotope is injected, and scanning is performed at rest and, depending on the approach, immediately after exercise or 1 to 2 minutes before the end of the stress agent infusion. Myocardial perfusion images at rest and during stress are displayed as tomographic slices in 3 different views to visualize all myocardial segments without overlap.<sup>168</sup> Perfusion defects that are present during exercise but not at rest indicate myocardial ischemia. Perfusion defects that are present during exercise and persist at rest suggest previous MI.

The sensitivity of exercise SPECT, vasodilator SPECT, and PET approaches to nuclear myocardial perfusion imaging for detecting coronary artery stenoses  $\geq 50\%$  range from 87% to 90%, with corresponding specificities of 73% to 89%.<sup>168,171</sup>

### **Echocardiography**

With exercise stress, echocardiographic images in several views are obtained with electrocardiographic gating (ie, synchronized to the QRS complex) at rest and while the patient performs stationary cycling or immediately after treadmill exercise.<sup>172</sup> Images must be obtained within 1 to 2 minutes (preferably <1 minute) after exercise because inducible regional wall motion abnormalities resolve rapidly after stress. With pharmacological stress, images are obtained at baseline, with low-dose and peak dobutamine infusion, and during recovery. Echocardiography by itself has no known risks, and serial testing has no known cumulative effects.

The images obtained during different phases of the stress test are compared side by side. Myocardial contractility normally increases with exercise, whereas ischemia causes hypokinesis, akinesis, or dyskinesis of the affected segments. An exercise or stress echocardiogram is considered positive if regional wall motion abnormalities develop with exercise in previously normal segments or become more severe in already abnormal segments.

The sensitivities of various approaches to stress echocardiography for detecting coronary artery stenoses  $\geq 50\%$  have ranged from 68% to 98% in different populations, with corresponding specificities of 44% to 100%.<sup>173,174</sup> The diagnostic accuracy of exercise and stress echocardiography is reduced in patients with limited acoustic windows and poor image quality (as can result from obesity or obstructive lung disease).

### **Cardiac Magnetic Resonance Imaging and Computed Tomography**

Technological advances in magnetic resonance imaging and computed tomography have resulted in increasing use of these modalities for cardiac imaging. Standard exercise equipment is typically not magnetic resonance imaging safe, but cardiac magnetic resonance with use of vasodilator stress to assess myocardial perfusion<sup>175,176</sup> or with use of dobutamine stress to assess regional myocardial function<sup>177</sup> is performed routinely in many experienced centers. Recent developments have

allowed cardiac magnetic resonance imaging to be used with exercise treadmill testing.<sup>178</sup>

The linear relationship between iodine concentration in tissue and image intensity makes computed tomography theoretically ideally suited for quantitative myocardial perfusion measurements, but technical limitations, including radiation dose to patients, have limited its development. An increasing number of clinical reports on vasodilator stress myocardial perfusion imaging with computed tomography are being published at the time of this writing.<sup>179,180</sup>

### **Guidelines and Appropriate Use Criteria**

Indications for these tests include establishing a diagnosis of CAD in symptomatic patients with chest pain, determining myocardial viability before revascularization, assessing prognosis after MI or in patients with chronic angina, and evaluating cardiac risk before noncardiac surgery. Details about exercise and stress testing with cardiac imaging modalities can be found in the comprehensive, evidence-based guidelines for exercise testing,<sup>58</sup> radionuclide imaging,<sup>168</sup> and echocardiography<sup>174</sup> that the ACCF and the AHA have published for many years. The sources cited in the present document are the most recent and final updates of these procedure-based guidelines. The ACCF and AHA now include these procedural guidelines in the ongoing updates of disease-based guidelines, such as those for stable ischemic heart disease, acute coronary syndromes, heart failure, and other conditions.

The ACCF, along with the AHA and other specialty and subspecialty societies, has developed "appropriate use criteria" for diagnostic tests and procedures that are used in the care of patients with known or suspected CVD. Appropriate use criteria can be periodically updated. These documents reflect an ongoing effort by the ACCF to critically and systematically create, review, and categorize clinical situations in which such procedures may be used. Although it is recognized that levels of evidence supporting test appropriateness will vary, practical consensus is required where conclusive evidence is lacking. It is anticipated that appropriate use criteria will have an impact on physician decision making, test performance, and reimbursement policy and will guide future research. Appropriate use criteria for stress cardiac nuclear imaging and stress echocardiography are outlined in detail elsewhere.<sup>181,182</sup>

## **Prognosis and Diagnosis**

### **Prognostic Value of the Exercise ECG**

In addition to its role in the diagnosis of CAD, exercise electrocardiographic testing provides a standardized method to gauge prognosis regardless of whether CAD is present. In fact, although reliance on exercise testing for CAD diagnosis increasingly is challenged by alternative diagnostic strategies (eg, imaging modalities, serologic markers), application of exercise electrocardiographic testing to assess prognosis is increasing<sup>3,183</sup> and often serves as a complementary perspective for management decisions.<sup>3,184</sup>

### **Prognostic Value of Exercise Capacity**

Exercise capacity, or the amount of work achieved before exhaustion, is the most powerful predictor of survival. Multiple studies have specifically demonstrated the utility of exercise



capacity testing to gauge prognosis.<sup>71,74,185</sup> The longer and more intensely a patient can exercise during an exercise test, the less likely he or she will die soon from CAD or other causes.

Nonetheless, several procedural issues must be addressed in the assessment of maximal exercise capacity. Many regard CPX as a superior means to assess exercise performance because gas exchange measurements provide detailed information on maximal oxygen consumption, ventilatory responses, and level of effort.<sup>19</sup> However, CPX testing requires specialized equipment to measure concentrations and volumes of expired gases. In contrast, standard treadmill or cycle exercise testing is widely available and relatively inexpensive. An abundant body of literature demonstrates that exercise duration on a standard protocol is a powerful predictor of prognosis in patients with known or suspected CVD. Nevertheless, there are considerations that help optimize the value of standard exercise testing to assess exercise capacity and prognosis. The widely used Bruce protocol was developed as an efficient diagnostic test for middle-aged men; however, it might not be the optimal protocol to assess exercise capacity in heterogeneous populations, particularly in elderly, obese, and deconditioned individuals. In these populations, the large increments in aerobic requirements between successive stages often result in premature termination of exercise with the Bruce protocol because of physical limitations instead of physiological exhaustion, thereby diminishing the prognostic implications of low exercise performance. As noted previously in the present document, a wide range of alternative exercise testing protocols involving smaller increments in energy requirements between stages are available that could be better suited to measure exercise capacity in elderly and deconditioned individuals.

A related limitation of routine prognostic assessment based on exercise capacity is that many stress testing laboratories use exercise primarily as a stimulus for diagnostic imaging—that is, patients are encouraged to exercise principally to reach 85% of the maximally predicted HR, a threshold assumed sufficient for sensitive diagnosis of CAD. With imaging as the priority, the goal for each patient to exercise to exhaustion is often not emphasized. In addition, the assumption that 85% of the maximum HR provides a sufficient threshold of cardiac work to diagnose ischemia has been challenged.<sup>186</sup> Both diagnostic and prognostic evaluations might be better served by testing protocols tailored to each patient's "true" maximum exercise capacity. Furthermore, exercise capacity often is reported merely in terms of duration, which fails to incorporate exercise intensity and implicitly detracts from the value of the stress test as a prognostic tool. Quantifying exercise as estimated METs provides a superior format with which to report exercise capacity and facilitates physiologically meaningful comparison of different protocols or modes in which identical exercise times can have significantly different prognostic implications.

Another limitation to quantification of exercise capacity as a prognostic marker relates to the challenge of comparing each individual's capacities to age- and sex-matched standards. Whereas absolute METs achieved by a 40-year-old man might be greater than those achieved by a 70-year-old woman, he still might fall into a relatively lower stratum of performance relative to others of his age and sex. Whereas it had once been typical to identify high risk (poor prognosis) only on the basis

of cut points of <5 METs in women and <7 METs in men, it is more logical and accurate to assess each individual relative to age- and sex-based standards. Still, even this stratification is only an approximation because differences in height, weight, and mode of exercise all modify exercise potential and ideally should be incorporated into stratifications of age and sex standards.<sup>3,79,187</sup> Others have demonstrated the differences between formulas that have been developed to approximate "normal standards of oxygen utilization" against which peak  $\dot{V}O_2$  measured during CPX can be compared<sup>188</sup>; these so-called "normal" values vary considerably between well-validated formulas depending on which patient traits were included or omitted for each calculated value of  $\dot{V}O_2$ .

#### *Abnormal Chronotropic Response to Exercise*

Chronotropic incompetence is the inability of the HR to increase commensurate with increased activity or demand. An intact HR response is vital for matching cardiac output to metabolic demands during exertion. Investigations in population-based and clinical cohorts demonstrated that an impaired chronotropic response is predictive of cardiac events and all-cause death.<sup>189,190</sup> Despite such specific theoretical value, definition of chronotropic response often remains relatively ambiguous. The simplest approach is to report change in HR with exercise relative to peak HR. Because peak HR decreases with age, age-predicted maximal HR is often determined as 220 minus age in years. An inability to achieve  $\geq 85\%$  of age-predicted maximum HR has been considered chronotropic incompetence. However, baseline functional capacity and resting HR also have bearing on chronotropic responses. Therefore, an alternative method to determine chronotropic incompetence entails assessment of the proportion of HR reserve used at peak exercise, defined by the difference between age-predicted maximal HR and resting HR. The difference is divided by the observed HR reserve to determine the proportion of HR reserve used. This value is often referred to as the chronotropic index or the proportion of HR reserve used during exercise. A proportional HR reserve of <80% has been used to define significant chronotropic incompetence.<sup>189</sup>

A recent comprehensive review of chronotropic response to exercise addresses additional complexities of these assessments and recommends individualized clinical evaluation.<sup>191</sup> Revised formulas for more precise determination of age-predicted maximal HR in healthy adults ( $208 - 0.7 \times \text{age}$ ), in women ( $206 - 0.88 \times \text{age}$ ),<sup>8</sup> and in patients with CAD ( $164 - 0.72 \times \text{age}$ ) have been proposed.<sup>6,192</sup> Whereas  $\beta$ -blockers might be considered an important confounder in prognostic assessment of chronotropic competence, useful predictive value in patients taking  $\beta$ -blockers was found for a partition of  $\leq 62\%$  of age-predicted maximal HR reserve.<sup>193</sup>

#### *Abnormal HR Recovery*

Although universally accepted criteria have not been established, a decline in HR from peak exercise of  $\leq 12$  beats 1 minute after cessation of the exercise test, while in the upright position, is most frequently used to define an abnormal HR recovery response.<sup>16</sup> When patients are immediately placed in the supine position at the completion of exercise, as can occur with echocardiographic imaging, HR recovery tends to be greater in the first minute because of augmented venous



return. Numerous investigations have demonstrated that a decreased HR recovery is a strong adverse prognostic marker in both apparently healthy and patient populations, irrespective of differences in patient populations, medications, or baseline functional capacity.<sup>12–17,194</sup>

Nonetheless, the magnitude of HR recovery is strongly dependent on the type of recovery protocol used, and inconsistencies in the literature have led to some uncertainty about this index. Some HR recovery protocols entail active cool-down. Initial reports of HR recovery were based on patients who underwent an upright cool-down protocol with a slow walk for 2 minutes immediately after exercise. With this protocol, HR recovery value of  $\leq 12$  beats was identified as a best cut point,<sup>195</sup> with a 4-fold increase in mortality hazard ratio. In contrast, some protocols involve stationary standing, sitting, or lying supine after exercise. When different protocols are used, HR recovery cut points have tended to be higher,<sup>196</sup> but the implications of attenuated HR deceleration were similar.

#### *Blood Pressure Abnormalities During Exercise and Recovery*

A decline in systolic blood pressure below resting value and an initial increase during early exercise followed by a decrease  $\geq 10$  mmHg are 2 common definitions of exercise-induced hypotension<sup>197</sup> that serve as potential indications to terminate exercise, especially in the presence of evident ischemia or other known heart disease.<sup>58</sup> Pathophysiological mechanisms for exercise-induced hypotension include aortic outflow obstruction, severe LV dysfunction, and myocardial ischemia. Exercise-induced hypotension consistently has been shown to be a marker of increased risk for adverse events.<sup>197</sup> Occasionally, subjects without clinically significant heart disease will exhibit exercise-induced hypotension related to dehydration, inappropriate titration of antihypertensive therapy, or prolonged strenuous exercise.

An exaggerated systolic blood pressure response to exercise has been defined as a maximal value of  $\geq 210$  mmHg for men and  $\geq 190$  mmHg for women.<sup>197</sup> A rise in diastolic blood pressure during exercise of  $>10$  mmHg above the resting value or an absolute value of 90 mmHg also is considered abnormal and could predict increased likelihood of CAD.<sup>198</sup> Recommended relative indications for exercise test termination are a systolic or diastolic blood pressure of  $>250$  and  $>115$  mmHg, respectively.<sup>58</sup> An exaggerated systolic blood pressure response to exercise could indicate an increased risk for future hypertension, LV hypertrophy, and cardiovascular events.<sup>197</sup> A failure of systolic blood pressure to fall or a rise in the short-term recovery period, relative to the maximal exercise value, has been shown to be predictive of an increased risk of death.<sup>199</sup>

#### *Arrhythmias During Exercise and Recovery*

The literature on ventricular ectopy during exercise or in recovery has been inconsistent. Some reports indicate that ventricular ectopy during exercise testing heralds increased risk of death,<sup>145</sup> whereas others do not. Other studies indicate increased risk of death in those demonstrating increased ventricular ectopy in recovery.<sup>200</sup> One report focuses more specifically on origin of the ventricular ectopy, indicating that ectopy with a right bundle-branch block morphology, often associated with significant LV dysfunction, was more likely to

predict death than ectopy originating from the right ventricular outflow tract or other relatively benign variants.<sup>201</sup>

#### *Prognostic Value of Exercise Imaging*

The literature focused on prognostic value of exercise electrocardiographic testing is evolving in parallel with a separate literature focused on prognostic value of imaging variables during exercise and pharmacological stress testing. Advantages of imaging include the opportunity to characterize ejection fraction, extent and distribution of ischemia, presence of coronary calcification, and, in some cases, even the intrinsic structure of stenoses, all of which are powerful risk predictors for both death and cardiovascular events. These indices are generally recommended to complement but not replace standard exercise prognostic electrocardiographic testing.<sup>181</sup> Exercise capacity remains an important predictor of outcomes even when SPECT imaging is available, and relatively little additional prognostic insight is gained by adding SPECT imaging findings in those with  $\geq 10$  METs of exercise capacity.<sup>202</sup> In another study, when treadmill test capacity exceeded 9 minutes, myocardial perfusion findings added little to the already favorable determination of risk.<sup>203</sup>

In contrast, imaging<sup>204</sup> adds value in patients who cannot exercise with sufficient intensity to determine risk by exercise alone. Adults who are older, deconditioned, female, or overweight are among those for whom imaging improves prognostic assessment.<sup>205</sup> It remains relatively difficult to determine when pharmacological stress should be substituted for exercise stress to determine prognosis in situations in which exercise performance might be low.<sup>206–209</sup> It would seem physiologically and diagnostically confounding to convert exercise to pharmacological stress when angina or potential angina equivalent occurs as a limiting symptom in patients with subthreshold HR.

#### *Prognostic Exercise Test Scores*

The Duke Treadmill Score was introduced in 1991 as a set of treadmill exercise findings that predict individual risk for death on the basis of a weighted combination of exercise duration, ST-segment depression, and the presence and nature of angina during testing.<sup>210</sup> The score is calculated by subtracting 5 times the ST depression (in millimeters) and 4 times the angina score (no angina = 0, nonlimiting angina = 1, and test-limiting angina = 2) from minutes of exercise duration on the standard Bruce protocol. The component of the Duke Treadmill Score that has been consistently validated for independent prognostic utility is exercise capacity; independent prognostic utility of angina and even of exercise-induced ST-segment changes is less certain.<sup>196,211</sup>

The concept of the exercise testing score has evolved through identification, generally by logistic regression, of a broader spectrum of clinical and exercise testing variables that can be used as a multivariate score to predict risk. First developed as a score to improve the sensitivity of the exercise test for the diagnosis of CAD in men<sup>212</sup> and later also in women,<sup>213</sup> the Morise score was subsequently applied to the prediction of death,<sup>214,215</sup> demonstrating greater risk discrimination than the Duke score in the same population. The concept of the multivariate score has continued to evolve by combining exercise capacity with HR dynamics<sup>13,196</sup> and also by combining

exercise capacity, HR dynamics, ventricular ectopy, and other clinical variables in a nomogram developed by multivariable Cox proportional-hazards modeling.<sup>216</sup>

On the basis of the same prognostic principles, other scores based on initial risk determined from Framingham assessment using exercise capacity and HR dynamics have been developed.<sup>217,218</sup> In these studies, initial prognostic risk stratification was enhanced significantly by the combination of additional clinical and exercise variables.

### Additional Uses of Exercise Testing

#### *Exercise Prescription*

Although the indications for exercise testing are varied, the assessment of exercise response and determination of functional capacity are particularly useful in the development of the exercise plan or prescription. Furthermore, in recording the exercise response to various levels of intensity, the exercise test can also serve to identify inappropriate or abnormal signs or symptoms, which are useful in the evaluation of safety of exercise programming. These findings determine the limitations or contraindications to higher exercise intensities or types of exercise programming, although this applies primarily to patients with structural heart disease rather than to the healthy population. The exercise test provides for the appropriate training intensity prescription by setting targets for HR reserve (40%–80% of peak),  $\dot{V}O_2$  reserve (40%–80% of peak), percent of peak exercise HR achieved (65%–80%), and RPE (11–16 on a 6-to-20 Borg scale).<sup>45,219</sup>

#### *Assessment of Therapeutic Response*

##### *Response to Exercise Training*

The response to exercise training can be evaluated with the exercise test in determining potential changes in peak  $\dot{V}O_2$  (functional capacity), cardiovascular and perceptual responses to submaximal exercise, and in patients with heart disease symptomatology.<sup>4</sup> Ideally, expected improvement in these indices would include increased peak  $\dot{V}O_2$  and reduced HR, systolic blood pressure, and RPE at standardized submaximal exercise intensities. In addition, training results in increased exercise time and workload to provocation of symptoms previously identified during submaximal exercise, such as angina pectoris, exaggerated dyspnea, or undue fatigue. Measurable improvements, or lack thereof, provide the basis for updates in the exercise prescription and determination of subsequent strategies for patient care.

##### *Response to Medication*

Management of medication prescribed to control exercise-related symptoms or various inappropriate cardiorespiratory responses also can be evaluated with exercise testing. Determination of abnormal signs or symptoms such as angina pectoris, hypertension, cardiac arrhythmias, and the associated various levels of exercise intensity in which these occur, can be evaluated. Ideally, expected improvement in such indices during exercise would include elimination of abnormal signs/symptoms, prolongation of time to occurrence of signs/symptoms, or increased submaximal exercise intensity associated with these signs/symptoms, as examples.

#### *Functional Classification of Disability*

Exercise testing is used to determine the degree of disability in subjects with various forms of heart and vascular disease, including ischemic heart disease, heart failure, cardiomyopathy, arrhythmias, congenital heart disease, and peripheral artery disease (PAD).<sup>75</sup> Failure to achieve a 5-MET capacity when aerobic capacity is estimated from workload and failure to reach 15.0 mL kg<sup>-1</sup> min<sup>-1</sup> when aerobic capacity is measured directly by CPX have been used as criteria for disability by the Social Security Administration.

#### *Evaluation of Perioperative Risk for Noncardiac Surgery*

In most ambulatory patients, exercise testing with electrocardiographic monitoring provides both an estimate of functional capacity and the detection of myocardial ischemia through changes in the ECG and hemodynamic response. Details on the use of stress testing in the assessment of perioperative cardiovascular risk during noncardiac surgery are presented in the “ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery.”<sup>220</sup> In patients with important abnormalities on the resting ECG (eg, left bundle-branch block, LV hypertrophy with “strain” pattern, or digitalis effect), exercise cardiac imaging should be considered. However, pharmacological stress imaging techniques are preferred in patients who are unable to perform adequate exercise, particularly for patients being evaluated for peripheral vascular surgery who are limited by claudication.

### Interpretation of the Exercise Test in Specific Populations and Settings

#### *Asymptomatic Subjects*

Routine screening for ischemia of asymptomatic individuals at low risk for CAD with exercise tests is not recommended, and detailed guidelines for exercise testing in asymptomatic people are presented in the ACCF/AHA guidelines for exercise testing<sup>58</sup> and also in more recent guidelines and statements.<sup>221,222</sup> Although there is evidence that the development of an ischemic electrocardiographic response at low workloads of testing among asymptomatic men is associated with a higher relative risk of future events such as angina pectoris, MI, and sudden death, the absolute risk of cardiac events in these populations remains low.<sup>223</sup> As a consequence, the predictive value of any test in low-risk populations must be low. It is also acknowledged that prospective, multicenter studies to demonstrate that interventions based on exercise electrocardiographic findings alone can favorably alter clinical outcomes in asymptomatic subjects are wanting.

Even so, several exercise electrocardiographic findings have been related to future risk and have potential importance for risk management.<sup>16</sup> In a study that used the Ellestad protocol in asymptomatic men and women with known CAD,<sup>224</sup> electrocardiographic ischemic changes and an exercise duration  $\leq 5$  minutes correlated with subsequent events in men  $>40$  years of age, but it was concluded that the exercise ECG had limited value in women and in men  $\leq 40$  years of age. A study in 6100 asymptomatic men who were free of clinically detectable CVD revealed that the occurrence of frequent premature ventricular depolarizations during exercise testing was associated with a long-term (25-year) increase in the risk of

death from cardiovascular causes; no significant increase in shorter-term risk was reported.<sup>225</sup> In apparently healthy volunteers from the Baltimore Longitudinal Study of Aging, an ischemic ST-segment response to exercise was associated with  $\approx 3$ -fold higher risk of future CAD than that associated with a normal response. However, the positive predictive value was only about 25%. A concomitant abnormal exercise thallium scintigraphic response identified a subset of older individuals with a 48% risk of an event over a mean 4.6-year follow-up.<sup>226</sup> Exercise-induced frequent or repetitive premature ventricular beats did not have significant prognostic value in this population.<sup>227</sup> In retrospective analysis of asymptomatic low-risk men and women in a large Framingham offspring cohort, abnormal HR-adjusted ST-segment findings, but not standard ST-depression criteria alone, identified increased 4-year risk of coronary heart disease events.<sup>113</sup>

With regard to subjects who are asymptomatic but have risk factors for CAD, exercise testing could have greater predictive value. In the Seattle Heart Watch Study,<sup>223</sup> men with  $\geq 1$  risk factor (positive family history, smoking, hypertension [blood pressure  $>140/90$  mm Hg], and hypercholesterolemia [total cholesterol  $>240$  mg/dL]) and 2 abnormalities on exercise testing (chest pain, exercise  $<6$  minutes, ST depression  $>1.0$  mm, or  $<90\%$  predicted HR) had a 30-fold increase in 5-year cardiac risk. Exercise testing was of no predictive value in the group with no risk factors. In the Lipid Research Clinics Coronary Primary Prevention Trial,<sup>228</sup> hypercholesterolemic men with  $>1$  mm of ST depression on exercise testing had a 5.7-times greater risk of death from CAD than those with a negative test. Interestingly, a positive test was not significantly associated with nonfatal MI. In the Multiple Risk Factor Intervention Trial,<sup>99,229</sup> retrospective analyses using the ST/HR index found a nearly 4-fold increase in the 7-year rate of death from CAD among men with an abnormal test response<sup>112</sup> and suggested that the exercise ECG might serve to identify high-risk men who do benefit from interventions targeting risk factor reduction.<sup>230</sup> Therefore, in asymptomatic men  $>40$  years of age with  $\geq 1$  risk factor, exercise testing could provide useful information as a guide to aggressive risk factor intervention.<sup>231</sup> Recent data suggest that this might be extended to women as well.<sup>71,73,232,233</sup> However, prospective evaluation of outcomes is needed to validate these suggestions.

### **Before Participation in Vigorous Exercise**

Vigorous physical exertion, usually defined as exercise requiring an oxygen uptake  $\geq 6$  METs or  $21 \text{ mL kg}^{-1} \text{ min}^{-1}$ ,<sup>234</sup> is associated with an increased risk of acute MI<sup>235,236</sup> and sudden cardiac death<sup>237,238</sup> compared with less vigorous and sedentary activity. However, individual risk of adverse events is reduced in conditioned subjects, and thus routine exercise is strongly encouraged for people with and without established heart disease. Whether exercise testing should be performed in asymptomatic adult subjects before beginning vigorous exercise has been controversial—even more so for routine screening of young people before engaging in athletics.

Exercise testing before beginning an exercise program has been addressed in adults by a prior AHA guideline<sup>58</sup> and recommendation,<sup>239</sup> as well as by the prior version of the present document.<sup>1</sup> These documents specify that routine screening

of asymptomatic low-risk younger individuals is not recommended,<sup>58</sup> but they do recommend exercise testing before starting a vigorous exercise program in asymptomatic people with diabetes mellitus,<sup>58</sup> in men and women  $>45$  and  $55$  years of age, respectively,<sup>58,239</sup> and in those with “major coronary risk factors.” These standards are in accord with recommendations based on the following considerations.

Exercise testing should not provide an impediment to routine exercise in normal people with a low likelihood of risk for exercise-related morbidity or mortality. Most acute cardiac events are attributable to plaque rupture of minor stenoses that are not likely themselves to be obstructive and therefore would not be directly identified by exercise testing. Although extensive obstruction makes unstable plaque more likely and might be more readily identified by exercise testing, it is not highly prevalent in asymptomatic people at low risk for CAD. Prediction of exercise-related MI and sudden death by exercise testing is therefore limited by the same factors that reduce exercise test diagnostic performance in asymptomatic adults: positive predictive value is very low and false-positive tests are highly prevalent when event rates are low, and test specificity is imperfect. On the basis of these considerations, the present standards do not recommend routine exercise testing for prediction of infarction or sudden death during exercise in asymptomatic low-risk younger subjects. However, there are reasons for exercise testing before starting a vigorous exercise program in selected asymptomatic subjects that are not related to risk prediction for acute infarction or sudden death. A positive exercise test might be useful in intensifying risk factor management, particularly when functional test findings such as chronotropic incompetence, reduced HR recovery, limited effort capacity, or blood pressure abnormalities suggest increased risk of all-cause death. Furthermore, asymptomatic patients at higher risk for obstructive CAD could benefit from the reassurance provided by a normal test, which might facilitate prescription of and compliance with more vigorous exercise. Exercise-related arrhythmias, abnormal blood pressure responses, or ischemic electrocardiographic changes in otherwise asymptomatic patients at higher risk can provide insight into limited effort capacity. Exercise testing is recommended before vigorous exercise or competitive athletics in individuals with chest pain or with dyspnea on exertion, with or without known CAD, to evaluate whether vigorous exercise is appropriate for such an individual, to establish training limits, and to develop an exercise prescription. Exercise stress testing also can be recommended before vigorous exercise in high-risk asymptomatic individuals who are classified as CAD equivalents by the National Cholesterol Education Program.<sup>240</sup> This includes those with diabetes mellitus, symptomatic carotid disease, peripheral vascular disease, and a calculated Framingham 10-year risk (<http://www.mdcalc.com/framingham-cardiac-risk-score>) of  $\geq 20\%$ .

### **Exercise Electrocardiographic Testing in Women**

Exercise testing has similar diagnostic and prognostic value in women as it does for men.<sup>241</sup> Although ST-segment depression with exercise stress testing often has been thought to be less accurate in women, the sensitivity and specificity of standard ST-segment depression criteria for significant CAD in women



have been estimated to be 61% and 70%, respectively.<sup>242</sup> These are lower but similar in magnitude to what was found in a meta-analysis of predominately male participants, in whom sensitivity and specificity were 68% and 77%, respectively,<sup>96</sup> and might be explained at least in part by lower electrocardiographic amplitudes in women than in men. Exercise capacity is a powerful diagnostic and prognostic marker.<sup>75,211,243–246</sup> In a study of 135 women who underwent stress testing and subsequent angiography, exercise capacity was among the best stress testing variables for predicting the presence of CAD, and it improved the sensitivity and specificity of exercise testing when added to ST-segment depression.<sup>246</sup> In another study of both men and women, the achievement of  $\geq 10$  METs was associated with a lower prevalence of ischemia as evaluated by SPECT imaging than was the achievement of  $< 7$  METs (0.4% versus 7.1%,  $P < 0.001$ ).<sup>247</sup> Those who achieved  $> 10$  METs and had no ST-segment depression with exercise had no significant ischemia detected.

The prognostic value of exercise capacity has been shown in both asymptomatic women<sup>73,233</sup> and symptomatic women.<sup>248–250</sup> In a retrospective review in women referred for stress testing, for every MET increase in exercise capacity, there was a 25% reduction in the rate of all-cause death.<sup>248</sup> In a cohort of 5721 asymptomatic women, exercise capacity was an independent predictor of death as well, where for each additional MET achieved, there was a 17% reduction in the rate of all-cause death.<sup>73</sup> From this cohort of women, age-predicted exercise capacity was lower for women than for men.<sup>22</sup> In addition, inability to achieve 85% of age-predicted exercise capacity was associated with at least twice the risk of all-cause death and cardiac death in asymptomatic women from which the age-predicted levels were derived and also in a symptomatic cohort of women when compared with women who achieved  $\geq 85\%$  of their age-predicted fitness level.<sup>22</sup> A recent study has suggested particular prognostic value of chronotropic incompetence for subsequent MI in women.<sup>251</sup>

The use of the Duke Treadmill Score for the diagnosis and prognosis of CAD in women with an intermediate probability of CAD has been well established, as women were included in the initial description of this risk scoring system.<sup>63</sup> In a series of 976 symptomatic women referred for exercise testing and angiography, the presence of CAD correlated with the Duke Treadmill Score risk: a low-, moderate-, and high-risk Duke Treadmill Score was associated with CAD ( $> 75\%$  luminal narrowing) in 19.1%, 34.9%, and 89.2% of women, respectively.<sup>252</sup> The frequency of 3-vessel disease or left main CAD was 3.5%, 12.4%, and 46%, respectively. In terms of prognosis, the Duke Treadmill Score has been shown to be an excellent tool in symptomatic women.<sup>63,210,252</sup> A low Duke Treadmill Score is associated with an annual mortality rate of 0.25%, in contrast to an annual mortality rate of 5% in those with a high Duke Treadmill Score.<sup>210</sup> Overall, survival for women appears to be better than that for men at all levels of the Duke Treadmill Score.<sup>63,252</sup> In the WOMEN (What is the Optimal Method for ischemia Evaluation in Women?) study, exercise treadmill testing and exercise myocardial perfusion imaging had similar 2-year posttest predictive outcomes in women with interpretable ECGs and good effort capacity. These investigators concluded that because the exercise treadmill

test provided significant diagnostic cost savings, it should be considered the initial diagnostic strategy in symptomatic women with suspected CAD.<sup>253</sup>

Cardiac syndrome X has been defined as the presence of chest pain and electrocardiographic changes with exercise but no evidence of coronary disease on an angiography.<sup>254,255</sup> This is seen more frequently in women than in men. Although overall prognosis in these women is better than in those with obstructive coronary disease, syndrome X is nonetheless associated with an increased rate of cardiovascular mortality, including sudden cardiac death, MI, and heart failure.<sup>256–259</sup> It is possible that stress tests that are deemed false-positives because of subsequent normal coronary angiography actually represent a population of women with cardiac syndrome X. Further studies are needed to evaluate women with a false-positive exercise ECG but persistent chest pain to pursue the diagnosis of cardiac syndrome X.

### *The Pediatric Population*

The acquisition of exercise test data in pediatric patients requires special considerations and accommodations. Appropriate-sized or adjustable equipment (eg, cycle ergometers, blood pressure cuffs, mouthpieces) are needed. It is also sometimes necessary to modify protocols. Low ramp rates are needed for small children performing cycle ergometry. The speed required for the higher levels of the Bruce protocol could be too rapid for small patients. In contrast, for many relatively healthy adolescent subjects, the lower stages of the Bruce protocol might seem tedious and are unlikely to yield any useful clinical information.<sup>260</sup>

Interpretation of exercise test data in pediatric subjects also can be challenging. Peak  $\dot{V}O_2$  and related variables vary with age, size, and (especially after puberty) sex. Proper interpretation of data therefore generally relies on prediction equations, generated from a population of normal subjects, which take these factors into account. In pediatrics, the most widely used prediction equations are the height-based equations (which rely on height rather than weight to avoid the potential confounding effects of adiposity/obesity).<sup>261</sup> The limitations of these prediction equations must, however, be considered. They tend to generate unrealistically low values for small children, especially boys. Hence, for subjects  $< 130$  cm tall, it is probably best to calculate the predicted peak  $\dot{V}O_2$  on the basis of data indicating that the peak  $\dot{V}O_2$  of an average prepubescent boy is  $42 \text{ mL kg}^{-1} \text{ min}^{-1}$  and that of an average prepubescent girl is  $38 \text{ mL kg}^{-1} \text{ min}^{-1}$ .<sup>262</sup> The patient's ideal weight-for-height should be used in these calculations. For patients with an unusually tall and thin body habitus (body mass index [BMI]  $< 18 \text{ kg/m}^2$ ), the height-based prediction equations generate unphysiologically high values, and the weight-based prediction equations should be used.<sup>20</sup> Whichever equations are chosen by a laboratory, the validity of the predictions for the population served by the laboratory should be established by testing several normal subjects and confirming that the predicted values agree well with the results of these tests.<sup>56</sup>

The goals of exercise testing in children also differ significantly from the adult population. Although myocardial ischemia is rare in the pediatric setting, confounding baseline electrocardiographic abnormalities (eg, conduction

abnormalities and ST abnormalities) and exercise-induced ST changes unrelated to myocardial ischemia are common among pediatric cardiology patients. Even in conditions where there is a potential for impaired coronary perfusion (eg, congenital coronary artery anomalies, heart transplant recipients, and in Kawasaki disease and other forms of acquired CAD), baseline abnormalities and other factors compromise the sensitivity and specificity of exercise testing with electrocardiographic monitoring. For patients with known or suspected CAD, stress echocardiography or myocardial perfusion imaging could enhance the diagnostic accuracy of the test.<sup>263–265</sup>

Chest pain, however, is quite common in the pediatric years and is rarely attributable to myocardial ischemia. If, on the basis of history or physical examination, an ischemic origin is suspected, an imaging study of the coronary arteries should be the first diagnostic study. Because of its poor diagnostic accuracy for myocardial ischemia in children, exercise electrocardiographic testing has a limited role in this setting.<sup>266</sup> Pediatric chest pain is more commonly related to exercise-induced asthma. An exercise test with pre- and postexercise spirometry might be a worthwhile study if this condition is suspected.

For patients with congenital heart defects, the primary purpose of an exercise test is usually to assess the patient's exercise capacity and cardiopulmonary response to exercise. Measurements at peak exercise are particularly helpful in this regard. However, for peak exercise data to be reliable and reproducible, it is important to ascertain that the patient expends a maximal or near-maximal effort. Exercise laboratory personnel should therefore be familiar with effective techniques for motivating children to expend adequate efforts. During CPX testing, patients should be encouraged to continue exercising until the respiratory exchange ratio exceeds 1.09. In prepubescent children, anaerobic metabolic pathways might not be expressed to the extent seen in older individuals, and a respiratory exchange ratio of 1.05 could be sufficient.<sup>267</sup> Reliance on the peak HR as a marker of effort expenditure often is not possible, as many patients with congenital heart disease have chronotropic defects and cannot achieve normal peak HRs.<sup>268</sup>

Exercise test data also can be helpful in the management of pediatric patients with arrhythmias. In general, exacerbation or precipitation of arrhythmias during exercise is associated with an increased risk for serious adverse events. In patients with structurally normal hearts, the suppression of ectopy during exercise is associated with a benign prognosis.<sup>269</sup> In patients with structural abnormalities, however, the absence or suppression of ectopy during exercise has little prognostic significance.<sup>270</sup>

### **The Older Adult**

The optimal use of exercise testing in the older adult (defined as people  $\geq 65$  years of age and people with clinically significant conditions or physical limitations that affect movement, physical fitness, or physical activity) requires that age-associated changes in the response to aerobic exercise and age differences in the prevalence and severity of CAD and comorbid conditions be considered.<sup>271–274</sup>

The physiological response to aerobic exercise undergoes important changes with aging, even in the absence of CVD, including age-related reductions in  $\dot{V}O_{2\max}$  that are

associated with the age-related decline in maximal HR.<sup>3</sup> As a consequence, older adults are often required to exert a higher percentage of their maximal capacity at specific submaximal exercise loads than that exerted by younger people.<sup>271</sup>

Systolic blood pressure continues to increase throughout adult life related to progressive arterial stiffening,<sup>275</sup> whereas diastolic pressure plateaus in the sixth decade of life and decreases thereafter. The systolic blood pressure response to both maximal and submaximal aerobic exercise also is increased with age.<sup>276</sup> This age-associated rise in exercise systolic blood pressure is more pronounced in women than men, paralleling the steeper age-associated increase in resting systolic blood pressure in women.<sup>277,278</sup> Finally, aging is accompanied by a less complete emptying of the left ventricle during strenuous aerobic exercise, as reflected by a blunted increase in LV ejection fraction attributable to LV stiffness and decreased compliance.<sup>279–282</sup> Because the augmentation of plasma catecholamines during exercise seems to be preserved or increased in older adults,<sup>283,284</sup> a unifying explanation for the age-associated reduction in HR and ejection fraction responses to maximal aerobic exercise is a decrease in  $\beta$ -adrenergic responsiveness.

Numerous noncardiac conditions that frequently occur in older adults can limit their ability to undergo aerobic exercise testing. Some disorders, such as PAD and chronic obstructive lung disease, frequently coexist with CAD because of shared risk factors. Degenerative arthritis of weight-bearing joints is the most prevalent chronic disorder in older adults. Additionally, mental health issues and cognitive impairment<sup>285</sup> can also affect the ability to perform exercise testing in the older adult. Moreover, unfamiliarity with vigorous exercise and fear of exercise testing equipment can intimidate older patients, resulting in submaximal test results. When added to the effects of comorbid ailments, the end result could be a symptom-limited test of only a few minutes.

To understand how age might affect the diagnostic utility of exercise testing, it is essential to recognize how aging affects the characteristics of CAD. Large autopsy studies have demonstrated that the prevalence of CAD, as defined by a diameter stenosis  $>50\%$  in one or more coronary arteries, increases dramatically with age.<sup>286–288</sup> In addition, coronary angiographic data from the Coronary Artery Surgery Study, the Duke data bank, and other series have documented an age-associated increase in CAD severity.<sup>289</sup> Because more severe CAD is more readily detected by exercise or pharmacological stress testing than milder disease, an age-associated increase in the sensitivity of exercise testing for the prediction of CAD might be expected. Such a finding has been documented for the exercise ECG, with an increase in sensitivity from 56% in patients  $<40$  years of age to 84% in those  $>60$  years of age. However, the specificity of the exercise ECG declined from 84% in patients  $<40$  years of age to 70% in those  $>60$  years of age.<sup>290</sup>

The most common modalities used to perform maximal aerobic exercise testing are the motorized treadmill and the electronically or mechanically braked cycle ergometer. The treadmill is preferred in older subjects who do not have significant balance or gait disturbances. Although cycle ergometry can be used for older patients with gait or balance disorders and impaired vision, in many instances local muscle fatigue will lead to premature test termination.<sup>45</sup>

Regardless of whether treadmill or cycle ergometry is used, a protocol with modest, equal increments in work rates should be used to achieve an exercise duration of 8 to 12 minutes. This is often difficult to achieve in the older adult. The use of smaller, more frequent increments in work rate is preferable to larger, less frequent increases, both physiologically and psychologically. Protocols using a constant treadmill speed with small changes of grade, such as the Naughton or Balke protocols, provide more data points with less need for gait changes than the simultaneous increases of speed and elevation every 3 minutes during the more commonly used Bruce protocol. Similarly, cycle ergometric exercise tests should start at a low resistance and progress in modest increments. For either treadmill or cycle ergometry, some laboratories use a ramp protocol with small, almost imperceptible increments of work rate every minute or less. Regardless of the exercise modality or specific protocol, adequate time should be allowed to familiarize the older patient with the testing equipment and to provide a 1- to 2-minute warm-up period. These pretest maneuvers will help alleviate the anxiety of the older patient and reduce the risk of musculoskeletal injury and falls.<sup>45,75</sup>

Despite the greater prevalence and severity of CAD with age, exercise testing remains as safe a procedure in the elderly as in younger populations with proper techniques and monitoring. National surveys of exercise laboratories have documented very low overall risks of MI or cardiac death, and age has not been identified as a risk factor for these events. However, age-associated increases in isolated ectopic beats and nonsustained supraventricular and ventricular arrhythmias, even in clinically asymptomatic subjects,<sup>227,291</sup> have been observed. The supervising clinician should be aware that myocardial ischemia or MI in the older adult can present as marked dyspnea, extreme fatigue, or chest pressure, rather than as typical chest discomfort or pain.

Exercise testing is well established as a useful tool for assessing the progress of patients with stable CAD and those who have had MI. Available data in the older adult, although more limited, suggest similar prognostic value in this age group. As in the general post-MI population, inability to perform treadmill exercise after MI confers a high risk for future death. In 111 infarct survivors >64 years of age, one group observed a 1-year mortality rate of 37% in the 63 patients not eligible for exercise testing, versus only 4% in those able to exercise. In the latter group, 1-year mortality rate was best predicted by the magnitude of systolic blood pressure rise during exercise; the mortality rate was 15% in patients with an increase <30 mmHg versus 1.8% in those with an increase >30 mmHg.<sup>292</sup> The prognostic importance of systolic blood pressure response to exercise was confirmed in 188 post-MI patients >70 years of age.<sup>293</sup> In this latter study, peak cycle work rate <60 W, exercise duration <5 minutes, and increase in rate–pressure product <12 500 also predicted increased cardiovascular death. In contrast, ST-segment depression and ventricular arrhythmia predicted recurrent MI and need for coronary revascularization but not death.

In older patients with stable CAD, exercise testing also has diagnostic and prognostic utility.<sup>211,294</sup> In 419 CAD patients >65 years of age, one study revealed that severe ST-segment depression induced by cycle ergometry predicted triple-vessel

disease.<sup>295</sup> Ischemic ST-segment depression predicted an increased risk of cardiac death in another study of older patients with stable CAD.<sup>296</sup> Although not recommended for routine use in apparently healthy older adults, exercise testing has also demonstrated prognostic significance in such a population.<sup>297</sup>

Although information about the utility of exercise testing among individuals >75 years of age is limited, available data suggest similar value to that in younger elders, a possible exception being concentration of risk by the Duke treadmill score.<sup>205</sup> In 5314 male veterans 65 to 92 years of age undergoing clinically indicated exercise testing, each 1-MET greater exercise capacity was associated with a 12% lower risk of death over 8 years of median follow-up. In the subset of 2754 men >70 years of age (mean 75.3 years), a similar trend was seen; men achieving 5 to 6 METs had a 45% lower mortality rate than those attaining <4 METs.<sup>298</sup> Exercise echocardiography in 2159 patients >70 years (mean 75 years) with known or suspected CAD showed that the change in LV wall motion score (based on a 4-point dyskinesis ranking in each of 16 segments) from rest to peak exercise was a potent independent predictor of both death and major cardiac events.<sup>206,299</sup> This confirmed data in a series of 335 octogenarians in whom LV wall motion score stratified patients into low- and high-risk groups with annualized event rates of 1.2% and 5.8% per year, respectively,<sup>300</sup> and an earlier study of patients whose mean age was 72 years.<sup>301</sup> Exercise radionuclide imaging has also shown prognostic utility in this age group.<sup>302</sup> The use of exercise testing for risk stratification, exercise prescription, and assessment of therapeutic intervention in this “older old” population will continue to increase with changing demographics.

### **Hypertension**

Hypertension per se is not an indication for exercise testing, but it is very often present in individuals who are referred for testing. The test should be postponed if resting systolic blood pressure exceeds 200 mmHg or if diastolic exceeds 115 mmHg. Antihypertensive medications generally should not be withheld before testing. Hypertensive individuals often have an exaggerated pressure response to exercise even if resting levels are controlled. A systolic pressure >250 mmHg or a diastolic pressure >115 mmHg during exercise is an indication for test termination, although there is little clinical evidence that this actually leads to cerebrovascular events during testing. Several studies have related impaired diastolic function to reduced aerobic capacity in people with hypertension and normal systolic LV function.<sup>303,304</sup> Among 6578 asymptomatic participants in the Lipid Research Clinics Prevalence Study, a pressure >180/90 mmHg during stage 2 of the Bruce exercise protocol was associated with a greater risk of cardiovascular death in normotensive individuals but not in those with hypertension.<sup>305</sup> Maximal exercise blood pressure was not predictive in normotensive or hypertensive individuals after adjustment for resting pressure. Reduced exercise capacity is a strong predictor of adverse cardiovascular outcomes in otherwise healthy people with hypertension,<sup>306</sup> as is true in normotensive individuals.

### **Obesity**

Exercise testing is useful in the clinical evaluation of obese patients with known or suspected CAD. However, obtaining an accurate assessment of peak cardiopulmonary responses



during exercise often poses a challenge in this patient population. For many obese patients, particularly the morbidly obese, this is related to gait instability, low functional capacity, coexisting orthopedic impairments, and uneven body weight distribution. In one study, 25 obese women (mean BMI of 40 kg/m<sup>2</sup>) were assigned to various ramp and Bruce or modified Bruce protocols on the basis of a pretest activity questionnaire. Despite a longer time to reach fatigue when the ramp protocols were used, mean peak  $\dot{V}O_2$  was not significantly different between tests. In another study, obese subjects with CAD were assigned to 2 severe energy-deficient study groups (one with exercise and the other by diet) plus a control group. All had exercise testing with  $\dot{V}O_2$  studies 6 times in a 2-year period with the Weber-Janicki protocol.<sup>307</sup> There were no differences between groups with the testing methodology, and all completed each test with satisfactory end points. In conclusion, these 2 studies and clinical experience reveal that obese subjects can have exercise tests effectively performed with a variety of protocols. Low-impact walking protocols, starting at low work rates with small increments between stages, are preferred in this patient population.

### **Diabetes Mellitus**

Because diabetes mellitus is a potent risk factor for CAD, exercise testing can be useful both in screening for CAD in asymptomatic individuals who have diabetes mellitus and in assessing prognosis. Asymptomatic individuals who have diabetes mellitus generally show reduced aerobic capacity relative to nondiabetic age-matched peers, as well as a reduced chronotropic response, likely because of autonomic dysfunction.<sup>308</sup> Among 1341 patients with diabetes mellitus referred for exercise testing, 36% had an impaired chronotropic response, defined by achievement of <80% of predicted HR reserve. Such individuals were at increased risk for total mortality, MI, and coronary revascularization procedures, independent of conventional risk factors.<sup>309</sup> Although a blunted chronotropic response to treadmill exercise is observed in patients who have diabetes mellitus and without evident cardiac autonomic neuropathy, this chronotropic impairment is greater among those with neuropathy.<sup>310</sup> Reduced HR recovery has also been associated with adverse cardiovascular outcomes and all-cause death in diabetic populations.<sup>311</sup> Multiple studies have reported an inverse relationship between exercise capacity and mortality rate in individuals who have diabetes mellitus as in individuals who do not have diabetes mellitus. In a study of 2867 male veterans with diabetes mellitus referred for exercise testing, each 1-MET lower exercise capacity was associated with an 18% higher risk of death over a mean follow-up of 7.8 years, independent of conventional risk factors.<sup>312</sup> Although screening of asymptomatic patients who have diabetes mellitus with exercise ECG or pharmacological myocardial perfusion imaging could identify substantial numbers of individuals with inducible myocardial ischemia, the recent Detection of Ischemia in Asymptomatic Diabetics (DIAD) and Do You Need to Assess Myocardial Ischemia in Type-2 diabetes (DYNAMIT) trials showed no significant benefit of such screening on hard clinical outcomes.<sup>207,313</sup> Routine exercise testing is therefore not recommended in asymptomatic patients who have diabetes mellitus and who wish to begin light to moderate levels of exercise.<sup>221</sup>

### **Peripheral Artery Disease**

Exercise testing has several potential uses in patients with PAD. First, it is the most objective method of quantifying walking capacity in those with exercise-induced claudication or suspected PAD. In such patients, walking capacity also serves as the basis for exercise prescription. Given the high prevalence of CAD in patients with PAD, exercise testing is also indicated to detect CAD. Finally, exercise capacity is an important prognostic variable in these patients.

The specific exercise test variables used to assess PAD functional severity are distance or time to onset of claudication pain and peak exercise distance or time. The test should have small progressive increases in workload, typically with constant speed. One common protocol uses a constant speed of 2 mph with 2% increases in grade every 2 minutes.<sup>314</sup> Measurement of ankle-brachial index immediately after exercise testing can help diagnose PAD in difficult cases and also can determine the extent of circulatory impairment. Because the pressure distal to an obstructive arterial lesion falls during exercise as a result of dilation of distal arterioles, the ankle-brachial index typically decreases from  $\approx 0.7$  at rest to  $\approx 0.3$  immediately after exercise. A decline after exercise has a sensitivity >95% for detecting significant PAD.<sup>315</sup>

Treadmill exercise capacity is markedly reduced in patients with PAD, with peak  $\dot{V}O_2$  typically 12 to 15 mL kg<sup>-1</sup> min<sup>-1</sup>. In such patients, both shorter treadmill exercise time and lower 6-minute walk distance have been correlated with greater superficial femoral artery plaque burden.<sup>316,317</sup> Because exercise-induced claudication often causes test termination before an adequate HR is achieved, alternative testing such as arm ergometry or pharmacological stress testing with dobutamine or vasodilators is usually required for diagnosis of CAD. Arm exercise testing often fails to elicit ischemic ST-segment depression or angina because the patient is limited by fatigue.<sup>52</sup>

Exercise performance appears to be a powerful prognostic indicator in patients with PAD. In 444 such individuals, those in the lowest quartile of 6-minute walk distance demonstrated increased risk of cardiovascular (hazard ratio = 5.6) and total (hazard ratio = 2.4) mortality versus those in the highest quartile, independent of ankle-brachial index and other important covariates.<sup>318</sup>

### **The Physically Disabled**

Special protocols are available for testing<sup>319</sup> subjects with musculoskeletal disabilities, especially those with hemiplegia or paresis after stroke or those with lower-limb amputation or spinal cord injury. Many testing protocols use arm cycle ergometry with the subject sitting to optimize the exercise load, but some protocols consist of arm-leg or leg cycle ergometry. Safe and effective testing can be performed by most of these subjects. If arm ergometry is considered, the protocol should begin at a resistance of 20 W and be increased by 10 W per stage. Electronically braked ergometers allow for constant workloads at various cranking revolutions per minute. Each stage should last 2 consecutive minutes, with a 1-minute rest period before beginning the next stage.<sup>319,320</sup> Unfortunately, exercise capacity can be limited to the degree that such testing modalities are inadequate to uncover abnormal responses, and thus pharmacological testing could be preferable.

### ***Evaluation of Chest Pain in the Emergency Department***

Detailed recommendations for exercise testing among patients who present to the emergency department (ED) or chest pain centers are presented in the AHA science advisory on "Safety and Utility of Exercise Testing in Emergency Room Chest Pain Centers,"<sup>321</sup> the "ACC/AHA 2002 Guideline Update for Exercise Testing,"<sup>58</sup> and the AHA scientific statement on "Testing of Low-Risk Patients Presenting to the Emergency Department With Chest Pain."<sup>322</sup> Patients who present to the ED are a heterogeneous population with a large range of pretest probabilities of CAD. In accord with Bayesian principles, the greatest incremental diagnostic value occurs in intermediate-risk clinical patient subsets. Exercise treadmill testing should be considered in patients who present to the ED with symptoms such as chest discomfort when they are classified as "low risk," which includes the following: Two sets of cardiac enzymes at 4-hour intervals are normal; ECG at the time of presentation and before the exercise test shows no significant changes; the resting ECG has no abnormalities that preclude accurate assessment of the exercise ECG; and the patient is asymptomatic or has minimal atypical chest pain from admission to the time results are available from the second enzyme set.<sup>323</sup>

Early exercise testing has been applied in patients with chest pain who are identified as low risk by clinical assessment, which has been implemented by using 2 approaches. In most studies, it is performed soon after presentation after an acute coronary syndrome has been excluded. Acute coronary syndromes are ruled out by an accelerated diagnostic protocol, which is usually performed within a 6- to 12-hour interval with serial cardiac serum markers and ECGs. In the second, less common, strategy, selected low-risk patients undergo "immediate" exercise testing to stratify the group into those who can be discharged directly from the ED and those who require admission. Both methods have thus far been shown to be safe, informative, and cost-effective, although experience with the latter is considerably more limited than with the former.

The feasibility of "early" exercise testing after excluding an acute coronary syndrome has been demonstrated by a number of studies involving 100 to >400 patients presenting with chest pain and negative results on an accelerated diagnostic protocol.<sup>324-329</sup> Patients with negative exercise tests were discharged, and those with positive results were admitted. No adverse effects of exercise testing were reported. Direct discharge of patients after a negative exercise test reduced hospital admissions for the initial presentation by  $\approx 50\%$ .<sup>324,326</sup> A negative exercise test was associated with no cardiac events at 30 days<sup>325</sup> and at 5-month<sup>328</sup> follow-up. Compared with patients with a positive test, those with negative tests had equivalent<sup>324,326</sup> or fewer readmissions<sup>327</sup> at 1 to 6 months. Substantial cost savings also have been demonstrated with an accelerated management protocol that included exercise testing.<sup>325,326</sup>

In further studies from one center, exercise testing was used in low-risk ED patients presenting with chest pain who had normal, near-normal, or unchanged ECGs.<sup>323,330-332</sup> This procedure has been applied in >1000 patients<sup>332</sup> with no reported adverse effects of exercise testing. All of those in the group with negative exercise tests were discharged directly from the ED, and follow-up at 30 days revealed a cardiac event in <1%. However, this approach has been associated with a small risk

(<1.0%) of inadvertent exercise testing of patients with evolving, non-ST-elevation MI, but it has been associated with no complications.<sup>332</sup> When performed after ruling out MI, early exercise testing in the ED or in chest pain units seems to be safe, accurate, and cost-effective.

SPECT imaging and dobutamine echocardiography have also been used in the ED for the noninvasive identification of myocardial ischemia and its effects on regional myocardial function.<sup>333,334</sup> Direct noninvasive visualization of coronary artery stenoses with 64-slice coronary computed tomography angiography performed well for predicting absence of acute coronary syndrome in an observational cohort study and could become an important triage alternative to traditional exercise testing in ED patients with acute chest pain syndromes.<sup>335,336</sup>

### ***Known or Suspected Arrhythmias***

Comprehensive ACCF/AHA/ European Society of Cardiology guidelines for management of patients with ventricular arrhythmias were published in 2006.<sup>337</sup> Class I recommendations for exercise testing include adult patients with ventricular arrhythmias who have an intermediate or greater probability of having coronary disease and patients (regardless of age) with known or suspected exercise-induced ventricular arrhythmias, for provocation, to make a diagnosis, and to evaluate the response to tachycardia. Exercise testing is considered useful, Class IIa, for evaluating the response to medical or ablation treatment in patients with known exercise-induced ventricular arrhythmias. Class IIb recommendations include patients with arrhythmias but a low probability of CAD and for the evaluation of isolated ventricular premature beats in greater than middle-aged patients without other evidence of CAD. In a scientific statement on risk for sudden cardiac death, assessment of functional capacity by peak oxygen consumption and by the 6-minute walk test was considered more accurate than clinical variables such as functional classification for the prediction of death and sudden death in chronic heart failure.<sup>338</sup>

The application of other available guidelines to exercise testing in patients with known or suspected arrhythmias but nonatherosclerotic heart diseases was recently reviewed by Morise.<sup>339</sup> Specifically considered were hypertrophic cardiomyopathy (HCM), valvular heart disease, atrial fibrillation, documented VT, pacemakers, and T-wave alternans. Class I indications for exercise testing include the assessment of HR-adaptive pacemakers and individuals with congenital complete heart block who are contemplating increased physical activity or competitive sports. Class IIa indications include arrhythmia provocation in patients with known or suspected exercise-induced arrhythmias, including evaluation of medical, surgical, or catheter ablation therapy in such individuals; evaluation of ventricular rate response and suspected myocardial ischemia in patients with atrial fibrillation; and in combination with T-wave alternans testing in patients with or at risk for life-threatening ventricular arrhythmias.

In some individuals, arrhythmias can occur primarily in relation to vigorous exercise. The prototype for such arrhythmias is catecholaminergic VT, a disorder first described in 1975, which occurs in genetically predisposed people without structural heart disease. In these individuals, the arrhythmia is often not inducible by programmed electrical stimulation but

is nearly always inducible by exercise testing.<sup>340</sup>  $\beta$ -Adrenergic blockade can be lifesaving in these patients. In patients with long-QT interval syndrome, exercise testing may elicit QT prolongation, which can be useful in risk stratification.<sup>341</sup>

T-wave alternans represents macroscopic or measurable microscopic alternation in electrocardiographic T-wave amplitudes or morphology that can be related to potential electrical instability. T-wave alternans testing performed in conjunction with exercise testing can be useful in identifying patients at risk for developing life-threatening ventricular arrhythmias. Numerous studies and a meta-analysis have shown low positive predictive value but high negative predictive value for such testing in predicting these arrhythmias.<sup>342–344</sup> Thus, a negative test is reassuring, whereas a positive test suggests that further risk stratification is needed.

In patients with rate-adaptive pacemakers, exercise testing can help to optimize the HR response and increase exercise capacity.<sup>58</sup> Such testing can be especially useful in patients whose exercise intolerance is not improved by pacing or empirical pacemaker adjustments.

Patients with atrial fibrillation not uncommonly demonstrate exaggerated ventricular rate responses to low-level exercise even when resting HR appears well controlled. Exercise testing can identify such individuals and can be used to titrate ventricular rate response through medication adjustment to optimize exercise capacity. Exercise testing also can detect QRS widening after initiating Class IC antiarrhythmic drugs in patients with atrial fibrillation.

### **Heart Failure**

CPX is now a well-established clinical assessment procedure in patients with heart failure.<sup>19</sup> Although the general approach to exercise testing in the heart failure population is similar to other groups, selection of the optimal testing protocol for the individual patient warrants special consideration. Given that most patients with heart failure have a significantly diminished functional capacity, the exercise test protocol should typically be conservative in nature.<sup>19</sup> Both peak  $\dot{V}O_2$  and variables reflecting ventilatory efficiency, such as the  $\dot{V}E/\dot{V}CO_2$  slope, have been shown consistently to reflect disease severity, to be strong prognostic markers, and to serve as useful gauges of therapeutic efficacy.<sup>345,346</sup> Although both variables provide independent predictive value, a combined peak  $\dot{V}O_2 < 10 \text{ mL kg}^{-1} \text{ min}^{-1}$  and a  $\dot{V}E/\dot{V}CO_2$  slope  $> 40$  portend a particularly poor prognosis and reflect advanced heart failure severity.<sup>19</sup> Other ventilatory expired gas and traditional exercise test variables have also demonstrated additive prognostic value through multivariate modeling,<sup>347</sup> although additional research is needed before solidifying recommendations for clinical practice.

### **Pulmonary Hypertension**

The role of CPX in assessing pulmonary hemodynamics is a rapidly emerging field demonstrating a great deal of clinical promise.<sup>19,348,349</sup> Patients diagnosed with pulmonary arterial hypertension typically present with a level of diminished aerobic capacity, correlating with disease severity. Perhaps more importantly, measures of ventilatory efficiency, specifically the  $\dot{V}E/\dot{V}CO_2$  slope or ratio and the partial pressure of end-tidal  $CO_2$  during exercise, reflect the degree of elevation in pulmonary arterial pressure and therefore disease severity.

These latter variables are particularly important in this patient population, given their association with pulmonary ventilation–perfusion mismatching, a primary consequence of pulmonary arterial hypertension. Initial evidence indicates that these CPX variables are both prognostic and gauge therapeutic efficacy in patients with pulmonary arterial hypertension.<sup>348</sup> Also, in patient populations in whom pulmonary hypertension could become a secondary consequence, such as in heart failure, HCM, chronic obstructive lung disease, and interstitial lung disease, ventilatory inefficiency (abnormally elevated  $\dot{V}E/\dot{V}CO_2$  and abnormally diminished partial pressure of end-tidal  $CO_2$  during exercise) appears to accurately identify an elevated pulmonary artery pressure.<sup>350</sup>

### **Adult Congenital Heart Disease**

Adults with congenital heart disease usually have cardiovascular issues that are distinct from those encountered among other adult cardiology patients. The role of exercise testing in the assessment and management of this unique group therefore differs substantially from that associated with typical adult cardiology patients. In general, the primary goal of exercise testing in adults with congenital heart disease is not the detection or evaluation of CAD. Rather, purposes of the test include the following:

- Assessment of the patient's exercise capacity
- Identification of factors that limit exercise performance
- Derivation of information on risk of cardiovascular and all-cause death
- Objective determination, based on serial testing, of whether there has been a change in clinical status or exercise capacity
- Assessment of the impact of therapeutic interventions on exercise function

These assessments are productively informed by data acquired at peak exercise during CPX testing ( $\dot{V}O_{2\text{max}}$ , peak HR, peak work rate, and the oxygen pulse at peak exercise). The validity of these data depends on adequate effort expenditure by the patient. Therefore, for most adult congenital heart disease patients, it is inappropriate to arbitrarily terminate an exercise test when the patient achieves 85% of predicted peak HR or any other preconceived HR threshold. In addition, many adult patients with congenital heart disease have abnormal sinus node function as a result of their underlying defects, prior surgeries, or current medications. Using a patient's peak HR as an indicator of effort is therefore unreliable.<sup>268</sup> It is preferable to rely on the respiratory exchange ratio; if the respiratory exchange ratio is  $< 1.09$ , it is unlikely that a patient has approached his or her cardiovascular limit.<sup>351</sup>  $\dot{V}O_{2\text{max}}$  has been found to be an independent predictor of death or hospitalization in a variety of congenital heart defects, including tetralogy of Fallot,<sup>352</sup> repair of transposition of the great arteries,<sup>353</sup> and Fontan physiology.<sup>354</sup> Similarly, in a recent study, Fontan patients with a peak HR  $< 123$  bpm were found to have a 10.6-fold greater risk of death during a follow-up period of  $4.0 \pm 2.0$  years.<sup>354</sup> In that study, however, almost all of the patients with a low peak HR had undergone treatments for serious rhythm disturbances. Thus, it is unclear whether the low peak HR was an independent risk factor for death or merely a marker for a history of serious arrhythmias.



If a patient with adult congenital heart disease has impaired exercise performance, it is helpful to determine whether the impairment is likely attributable to an impaired chronotropic response, reflected by a depressed peak HR, or an impaired stroke volume response, reflected by a low oxygen pulse at peak exercise. It also should be noted that in the presence of significant chronotropic impairment there should be a compensatory increase in stroke volume and oxygen pulse, solely on the basis of the Frank-Starling mechanism. Under these circumstances, an oxygen pulse at peak exercise that is “only normal” is, in fact, abnormal.<sup>20</sup>

Data acquired at submaximal exercise (eg, the ventilatory threshold and the  $\dot{V}_E/\dot{V}_{CO_2}$  slope) have also been found to be useful in patients with congenital heart disease. In general, the prognostic value of ventilatory threshold data is similar to but less well established than  $\dot{V}_{O_{2max}}$  data. In patients with repaired tetralogy of Fallot, the  $\dot{V}_E/\dot{V}_{CO_2}$  slope has been found to be a sensitive predictor of death.<sup>352</sup> In these patients, the elevated  $\dot{V}_E/\dot{V}_{CO_2}$  slope is probably due, at least in part, to pulmonary blood flow maldistribution secondary to pulmonary artery stenoses.<sup>355</sup> These stenoses can have a particularly deleterious effect on the physiology of the postoperative tetralogy patient and a strong, negative impact on prognosis. Effective relief of these stenoses has been found to improve exercise capacity and the  $\dot{V}_E/\dot{V}_{CO_2}$  slope.<sup>356</sup> An elevated  $\dot{V}_E/\dot{V}_{CO_2}$  slope has also been associated with an increased risk of death in patients with atrial repairs of transposition of the great arteries.<sup>353</sup> In these patients, the elevated  $\dot{V}_E/\dot{V}_{CO_2}$  slope can arise (as it does in patients with heart failure) secondary to pulmonary blood flow maldistribution and ventilation-perfusion mismatch, which in turn develop as a result of the elevated pulmonary capillary wedge pressure associated with the progressive systemic (right) ventricular dysfunction often encountered in these patients as they age.

Right-to-left shunting also increases the  $\dot{V}_E/\dot{V}_{CO_2}$  slope, probably as a consequence of the shunting of hypercapnic venous blood into the systemic circulation. Elimination of a right-to-left shunt almost invariably reduces the  $\dot{V}_E/\dot{V}_{CO_2}$  slope.<sup>357</sup> An elevated  $\dot{V}_E/\dot{V}_{CO_2}$  slope has also been associated with increased risk of death in mixed cohorts of patients with a variety of congenital heart diseases.<sup>358,359</sup> However, it has not been shown to be associated with increased risk of death in patients with Fontan circulations. In these patients, in whom  $\dot{V}_E/\dot{V}_{CO_2}$  slope elevation is almost always present, the elevation is probably attributable to pulmonary blood flow maldistribution and ventilation-perfusion mismatch secondary to the absence of a pulmonary ventricle, rather than to progression of disease.<sup>354</sup>

### **Hypertrophic Cardiomyopathy**

Although exercise testing is generally contraindicated in patients with HCM who have high resting LV outflow tract (LVOT) gradients, such testing could have clinical utility in identifying higher-risk subsets among those without high resting gradients who develop an abnormal blood pressure response to exercise, a provokable LVOT gradient, or exercise-induced ventricular tachyarrhythmias.<sup>339</sup> Several studies have shown that a blunted increase in systolic pressure, typically defined by an increase <20 to 25 mm Hg, predicts an increased risk of sudden cardiac death; although the negative predictive

value of such an exercise response is 95% to 98%, the positive predictive value is only  $\approx 15\%$ . The abnormal pressure response appears to be mediated by a decrease in stroke volume attributable to systolic dysfunction.

Although nonsustained VT (NSVT) during ambulatory electrocardiographic monitoring is associated with increased risk of sudden cardiac death in patients with HCM, the role of exercise-induced NSVT in predicting adverse outcomes is less clear. In a cohort of 1380 such patients referred to a cardiomyopathy clinic, 27 (2%) developed NSVT ( $n=24$ ) or ventricular fibrillation ( $n=3$ ) during exercise testing. These individuals had more severe septal hypertrophy and larger left atria than those without such arrhythmias. On multivariate analysis, however, the combination of NSVT and ventricular fibrillation, but not NSVT alone, was associated with an increased risk of sudden death (hazard ratio = 3.1) over a mean follow-up of 54 months.<sup>360</sup>

Exercise echocardiography can be useful in eliciting a hemodynamically significant LVOT gradient in patients with HCM with no or minimal gradient at rest. In 1 study of 256 patients with resting LVOT gradients <30 mm Hg, 52% developed a significant gradient ( $80\pm 43$  mm Hg) with exercise. Only 40% of these latter individuals developed a gradient >30 mm Hg with Valsalva.<sup>361</sup> Whether these patients with high LVOT gradients provokable only with exercise share a similar increased risk of adverse outcomes as those with resting gradients remains unclear.

The safety of exercise testing in patients with HCM has been demonstrated in several studies, some of which were discussed previously in this document. In >3000 such patients tested over 10 years, the only serious event was a single case of sustained VT, successfully terminated by cardioversion.<sup>362</sup> In another report, only one episode of sustained VT occurred with exercise in 263 patients, and no patients experienced syncope.<sup>363</sup> Thus, exercise testing appears safe and might be useful in identifying HCM patients with no or minor resting LVOT gradients who could be at higher risk because of a provokable gradient or ventricular tachyarrhythmia during exercise.

### **Cardiac Transplantation**

During maximal treadmill or cycle ergometer testing, cardiac transplant recipients demonstrate lower-than-predicted peak HR, systolic blood pressure,  $\dot{V}_{O_2}$ , exercise time, stroke volume, and cardiac output and increased ventilatory equivalent. The reduced stroke volume is secondary to blunting of preload reserve, the end-diastolic volume.<sup>364</sup> Cardioacceleration is blunted and delayed because of cardiac denervation but persists longer into recovery because of elevated catecholamine levels. Peak  $\dot{V}_{O_2}$  in untrained transplant recipients is substantially impaired, averaging  $\approx 20$  mL  $\text{kg}^{-1} \text{min}^{-1}$ .<sup>365</sup>

A major late complication of heart transplantation is diffuse coronary artery allograft atherosclerosis, which is generally not accompanied by angina pain attributable to cardiac denervation. The sensitivity of the exercise ECG for detecting myocardial ischemia is also very low in this population.<sup>366</sup> Radionuclide scintigraphy, echocardiography, and other imaging techniques performed at rest are also relatively insensitive, but their sensitivity could be improved when combined with pharmacological stress testing.<sup>366</sup>

**Valvular Heart Disease**

The utility of exercise testing in clinical decision-making for patients with valvular heart disease has been discussed in detail in recent guidelines.<sup>58,367</sup> Exercise testing has been used in subjects with valvular heart disease to quantify disability, to reproduce exercise-induced symptoms, and to evaluate responses to medical and surgical interventions.<sup>58,367,368</sup> The exercise test also has been used to identify concurrent CAD, but the prevalence of false-positive responses (ST depression not attributable to ischemia) is high because of frequent baseline electrocardiographic abnormalities and LV hypertrophy.

**Aortic Stenosis**

Effort syncope in subjects with aortic stenosis is an important and well-appreciated symptom.<sup>369,370</sup> Practice guidelines for exercise testing list symptomatic severe aortic stenosis as an absolute contraindication for testing because of concern about syncope and cardiac arrest. Proposed mechanisms for exercise-induced syncope in subjects with aortic stenosis include carotid hyperactivity, LV failure, arrhythmia, and LV baroreceptor stimulation.

Exercise testing might be useful, however, in asymptomatic patients with severe aortic stenosis for the purpose of eliciting symptoms or an abnormal blood pressure response.<sup>339</sup> Several studies have concluded that exercise testing is safe in both pediatric and adult subjects with aortic stenosis when performed appropriately. Protocols less intense than the standard Bruce protocol should be used, especially in older or deconditioned individuals. Attention should focus on the subject's symptoms, minute-by-minute response of blood pressure, slowing HR, and ventricular and atrial arrhythmias. Testing should be terminated if angina, dizziness, decrease in systolic blood pressure, complex ventricular arrhythmias, or >2 mm ST-segment depression occurs. In the presence of an abnormal blood pressure response, the subject with aortic stenosis should take at least a 2-minute cool-down walk at a lower stage of exertion to avoid acute LV volume overload, which could occur when the subject lies down. In an analysis of 7 studies encompassing 491 patients with severe asymptomatic aortic stenosis, no sudden death occurred over an average follow-up of  $\approx 1$  year in people with a normal exercise response, whereas sudden death occurred in 5% of those with abnormal test responses.<sup>371</sup>

**Aortic Regurgitation**

Subjects with aortic regurgitation<sup>372</sup> usually maintain a normal exercise capacity for a longer time than those with aortic stenosis. During exercise, the decreases in diastolic duration and regurgitation volume favor forward output. As the myocardium fails, peak HR tends to slow, and ejection fraction and stroke volume decrease. Exercise testing can be useful in patients with asymptomatic severe aortic regurgitation to assess functional capacity and symptom response. Surgery is usually indicated if unequivocal symptoms are elicited at a low workload.<sup>373</sup>

**Mitral Stenosis**

Subjects with mitral stenosis<sup>374</sup> can show either a normal or an excessive increase in HR during exercise. Because stroke volume cannot be significantly increased, the normal rise of cardiac output is attenuated, and cardiac output eventually can fall during exercise; this is frequently accompanied by exercise-induced hypotension. Exercise testing with Doppler

echocardiography can be useful in 2 settings: asymptomatic patients with moderate to severe mitral stenosis with resting pulmonary artery systolic pressure <50 mmHg, and symptomatic individuals with mild mitral stenosis. In either situation, exercise-induced increase of pulmonary artery systolic pressure >60 mmHg would qualify the patient for balloon valvulotomy, where feasible, or for mitral valve replacement.<sup>373</sup>

**Mitral Regurgitation**

Subjects with mild to moderate mitral regurgitation<sup>375</sup> maintain normal cardiac output during exercise. Blood pressure, HR, and electrocardiographic responses are usually normal. Subjects with severe mitral regurgitation do not necessarily have a decreased cardiac output and limited exercise capacity. However, a hypotensive response can develop, and arrhythmias frequently occur. In asymptomatic patients with severe mitral regurgitation and preserved LV function, exercise testing with Doppler echocardiography is reasonable to assess exercise capacity and the effect of exercise on pulmonary artery pressure. In such patients, mitral valve surgery should be considered if pulmonary artery systolic pressure exceeds 60 mmHg during exercise.<sup>373</sup>

**Drugs and Electrolytes in Exercise Testing** **$\beta$ -Blockers**

Subjects with angina who receive  $\beta$ -blockers could achieve a higher exercise capacity with less ST-segment depression and less angina if the drugs prevent them from reaching their ischemic rate-pressure product and, therefore,  $\beta$ -blockers could translate into a reduction in diagnostic accuracy. Maximum HR-systolic blood pressure product likely would be reduced. The time of ingestion and the dosage of these medications before testing should be recorded. Whether to discontinue  $\beta$ -blockers before testing was discussed in the prior section "Subject Preparation."

**Digitalis**

ST-segment depression can be induced or accentuated during exercise in individuals who are taking digitalis, including both normal subjects and subjects with CAD.<sup>376</sup> Low specificity as a result of a high prevalence of false-positive test outcomes is the main reason exercise ECG without imaging is not recommended for patients taking digitalis. A normal QT interval is associated with digitalis-induced ST changes, whereas prolonged QT intervals occur with ischemia, other type 1 anti-arrhythmic drugs, electrolyte imbalance, and other medical problems. Exercise-induced ST-segment depression can persist for 2 weeks after some preparations of digitalis are discontinued.

**Diuretics**

Most diuretics have little influence on HR and cardiac performance but do decrease plasma volume, peripheral resistance, and blood pressure. Diuretics can cause hypokalemia, which can result in muscle fatigue, ventricular ectopy, and, rarely, ST-segment depression.

**Hormones****Menstrual Cycle**

Research on the impact of the menstrual cycle on various physiological indices is complex because of pulsatile secretion

of sex hormones, large inter- and intra-individual variations in sex hormone levels between and within the various phases of the cycle, variable duration of the follicular phase, and intermittent anovulatory cycles, which might not be apparent on the basis of bleeding pattern. The available literature suggests that there are probably no major differences in muscle contractile characteristics, maximum oxygen uptake, or substrate utilization during exercise between phases of the menstrual cycle, but it has been suggested that the elevated body temperature during the luteal phase of the cycle could limit exercise in hot environments.<sup>377</sup>

Variable effects of the menstrual cycle on the exercise ECG have been reported among women with normal coronary arteries. One study reported shorter time to ST-segment depression more frequently during the menstrual and preovulatory phases of the cycle than during the high-progesterone postovulation phase,<sup>378</sup> whereas another found more frequent ST-segment depression and shorter exercise duration during the luteal phase of the cycle.<sup>379</sup> The exercise test findings correlated best with the estradiol-to-progesterone ratio ( $r=0.29$  for time to ST-segment depression).<sup>379</sup> An effect of estrogen on the ST-segment response is further suggested by the observation that false-positive stress tests among young women tend to convert to normal after bilateral hystero-salpingo-oophorectomy, an effect not seen after unilateral oophorectomy.<sup>380</sup>

Among women with angina, ischemia might be more easily inducible (as documented by shorter times to ST-segment depression) in the early follicular phase (a low-estrogen state) than in the late follicular phase, mid-cycle, and late luteal phase.<sup>381</sup> Time to ischemia did not appear to depend on progesterone concentrations.<sup>381</sup>

#### *Exogenous Sex Hormones*

In 1977, a study described “worsening” of baseline exercise-induced ST-segment depression among men and women supplemented with estrogen and amelioration of postexercise ST-segment depression among men supplemented with testosterone.<sup>382,383</sup> In the Lipid Research Clinics Program Prevalence Study, oral contraceptive users were more likely to have abnormal exercise ECGs, whereas the difference in ST-segment depression between postmenopausal women on and not on hormone replacement did not quite reach statistical significance.<sup>384</sup> The proportion of women on estrogen therapy who demonstrate abnormal exercise electrocardiographic response varies by study but has been reported to be as high as 39% among postmenopausal hormone users with concomitant normal myocardial perfusion imaging.<sup>385</sup> Specificity of the exercise ECG might be improved in women taking combined estrogen-progestin therapy versus women taking estrogen monotherapy.<sup>386</sup> Abnormal ST-segment responses in response to postural change and hyperventilation have also been reported with exogenous estrogen therapy.<sup>387</sup> The mechanism for these estrogen-induced electrocardiographic changes remains unclear. Changes in vasomotor tone, changes in autonomic tone, and a digitalis-like effect have been proposed.<sup>387</sup>

### **The Exercise Electrocardiographic Test Report**

The exercise test report should describe information relevant to diagnosis and prognosis. This would include the reason for

terminating exercise, such as fatigue; more specific symptoms like angina, leg pain or dyspnea; or a sign like a drop in systolic blood pressure or arrhythmia. Resting, exercise, and recovery HRs and blood pressures should be tabulated according to stages, and peak exercise values should be stated. There should be a specific statement with regard to the presence or absence of chest pain at peak exercise and whether this was the reason for termination of the test. Patient effort can be defined by percent maximum predicted HR achieved or by use of a chronotropic index. Additionally, it is useful to describe effort capacity as percent of maximum predicted MET workload equivalents, adjusted for age and for sex.<sup>22</sup> Peak end-exercise or recovery-phase ST-segment deviation should be described, and the test should be defined as positive, negative, or equivocal according to standard ST-segment criteria.<sup>91</sup> Depending on further experience and validation, additional diagnostic electrocardiographic findings that extend beyond the ST segment should be considered for inclusion in the routine report.<sup>3</sup> In addition to effort capacity, prognostic information might routinely incorporate the Duke Treadmill Score and information about chronotropic response to exercise and HR recovery.<sup>3</sup>

## **Exercise Training**

### **Exercise and Health**

Recent physical activity recommendations from the Centers for Disease Control and Prevention,<sup>388</sup> the American College of Sports Medicine,<sup>389</sup> and the US Surgeon General<sup>390</sup> affirm the primary role of exercise in preventing chronic disease and in maintaining health throughout the age span. Several principles emerge from these statements, including that any exercise is better than none, more exercise is better than less, different types of exercise (aerobic versus resistance) yield distinct favorable outcomes, and activity recommendations should be enabling and flexible and avoid setting up barriers.

The goal of this section on exercise training is to provide an evidence base for the medical benefits of long-term physical activity, where exercise can be viewed as a preventive medical treatment, like a “pill” that should be taken on an almost daily basis. Care is taken to merge the public health benefits of exercise with the medical model, such that medical evaluation is not set up as a barrier to exercise, yet selected higher-risk individuals are properly evaluated before they initiate an exercise program to avoid an increase in adverse outcomes. In particular, patients with established heart disease or other selected chronic medical conditions should undergo a medical evaluation to ensure clinical stability, to provide specific activity recommendations, and to guide a safe progression with exercise training.

### **Exercise Training Response in Apparently Healthy Individuals**

Exercise training in apparently healthy people affects several physiological markers of health, including  $\dot{V}O_2\text{max}$ , central hemodynamic function, autonomic nervous system function, peripheral vascular and muscular function, and submaximal exercise capacity. Collectively, these adaptations result in an exercise training effect, which allows an individual to exercise longer, to higher peak workloads, with lower HRs at submaximal levels of exercise.



*Maximal Oxygen Uptake*

Aerobic exercise training increases  $\dot{V}O_{2\max}$  through an increase in the capacity of the cardiovascular system to deliver oxygen to muscles (increased cardiac output) and of the muscles to extract and utilize oxygen, as reflected by a greater arteriovenous  $O_2$  difference [ $A-\dot{V}O_{2\text{diff}}$ ].<sup>4</sup> It has been suggested that older people demonstrate primarily an improved  $A-\dot{V}O_{2\text{diff}}$ .<sup>391</sup> In subjects who achieved a physiological maximal HR at initial testing, a higher cardiac output after training is usually brought about by an increase in stroke volume because maximal HR does not typically increase after training in normal individuals.

*Central Hemodynamic Changes*

Although a greater maximal cardiac output can be achieved as a result of exercise training, values at fixed submaximal external workloads are unchanged or slightly diminished. This is explained by a combination of reduced submaximal HR with a concomitant increase in stroke volume where unchanged submaximal values are reported, and/or a resultant increase in  $A-\dot{V}O_{2\text{diff}}$ , thus requiring less cardiac output at a given submaximal workload.

*Peripheral Muscular, Vascular, and Autonomic Changes*

**Muscular.** Skeletal muscle changes after exercise training include more and larger mitochondria and increased oxidative enzyme activity, which allow for a greater sustained level of aerobic capacity with lower blood lactate levels.<sup>5</sup> In addition, trained muscle exhibits increased utilization of fatty acids during submaximal exercise, which extends endurance. Muscle fiber type and size adaptations reflect changes that enhance aerobic potential. Each of these adaptations contributes to greater capacity to use oxygen and improve endurance. Endurance training enhances the ability to perform exercise at both submaximal and maximal intensities but is specific to those muscle groups that have undergone training (training specificity). This is reflected either by the ability to exercise longer at a similar workload or by an increase in the workload attained at a given HR. Furthermore, the results of these adaptations increase the anaerobic threshold (the point at which blood lactate begins to accumulate). Adaptation to submaximal exercise is also associated with a lower HR–systolic blood pressure product for a given exercise task, reflecting reduced myocardial oxygen demand for that level of work.

**Vascular.** Exercise training directly affects arterial shear stress, a stimulus to antiatherogenic adaptations in vascular function and remodeling. When considered along with evidence indicating increased coronary artery size and dilation capacity in trained subjects, studies strongly support the contention that exercise training is associated with improved vascular function. The mechanisms for these responses appear to be endothelium and nitric oxide dependent. That is, pursuant to the repeated increases in arterial wall stress with repeated bouts of exercise, nitric oxide synthase expression and activity in the arterial endothelium are increased.<sup>392,393</sup> Additionally, training increases the number of circulating endothelial progenitor cells, leading to endothelial regeneration and improved endothelial function.<sup>394,395</sup> These findings indicate that maintaining a high level of fitness or undertaking exercise training could prevent or attenuate the typical age-related decline in indices of vascular function.<sup>396</sup>

**Autonomic Nervous System.** It is well established that cardiac autonomic regulation can be altered by exercise conditioning.<sup>397</sup> Blood and urinary catecholamine levels are lower at rest and during submaximal exercise after training, reflecting less sympathetic nervous system activity.<sup>398</sup> The arterial baroreflex, the afferent fibers of which originate from the carotid sinus and aortic arch, regulates blood pressure on a beat-to-beat basis by continually adjusting HR, stroke volume, and peripheral resistance. During exercise, baroreflex function is reset to operate around the higher blood pressures achieved during physical activity.<sup>399</sup> Parasympathetic tone also can be increased and, with sympathetic adjustments, could account for the slower HR and lower arterial blood pressures seen after training.

*Preventive Value of Regular Physical Activity in Health and Disease*

Public health and medical authorities generally agree that reduced physical activity during leisure time and on the job increases the risk of fatal and nonfatal CAD events, obesity and type 2 diabetes mellitus, and all-cause death.<sup>388–390,400,401</sup> Thus, physical inactivity is considered a treatable or modifiable coronary risk factor.<sup>400</sup> National surveys during the past decade consistently have reported that >50% of American adults have insufficient physical activity for deriving health benefits.<sup>402,403</sup> Regular aerobic exercise is independently associated with a lower risk for developing CAD, and it also works dependently to reduce CAD risk by inducing favorable effects on other risk factors, such as hypertension, dyslipidemia, obesity, type 2 diabetes mellitus, insulin resistance, and thrombogenic factors.<sup>404</sup>

More than 40 epidemiological and observational studies provide the primary basis documenting the inverse relationship between physical activity and risk of CAD. There have been >100 published reports from such studies, with nearly 75% of them supporting an inverse relationship between physical activity or fitness and risk of an initial fatal or nonfatal MI.<sup>405–407</sup> The populations studied consisted predominantly of initially healthy, middle-aged or older white men; fewer than 10 studies included women. Few studies involve racial and ethnic minority groups. Meta-analyses reveal that the sedentary participants in these studies generally had about twice the incidence of death from CAD of their more active counterparts.<sup>408,409</sup> Longitudinal studies that assessed cardiorespiratory fitness by exercise testing have almost uniformly shown an inverse relationship between fitness and risk of CAD and total mortality in both men and women.<sup>410</sup> The least fit men and women demonstrated a >5-fold increased risk of death from CAD or CVD versus the most fit individuals.<sup>411</sup> Accordingly, on the basis of these data, a consensus has been reached that a minimum of 30 minutes of moderate-intensity physical activity (continuous or in 10-minute increments) is required on most (preferably all) days of the week to optimally reduce the risk of CAD events.<sup>403,412</sup> This is equivalent to roughly 1.5 miles/d of brisk walking at an energy cost of 150 kcal/d for an average-sized person. It is notable that lesser amounts of ongoing physical activity, such as 15 minutes/d or 90 minutes/wk, are associated with a survival benefit compared with physical inactivity.<sup>413</sup>

Epidemiological and experimental studies have identified plausible biological mechanisms that help to explain the

apparent effects of physical activity and cardiorespiratory fitness on preventing CAD. These mechanisms are reviewed in detail elsewhere<sup>405,414,415</sup> and can be classified as the following:

- Antiatherogenic effects
- Anti-inflammatory effects
- Effects on vascular endothelial function
- Effects on blood clotting
- Autonomic functional changes
- Anti-ischemic effects
- Antiarrhythmic effects
- Reduction in age-related disability

#### *Antiatherogenic Effects of Exercise Training*

Antiatherogenic effects of exercise occur primarily through the effects of exercise training on established cardiovascular risk factors.

**Exercise Training and Blood Lipid Profiles.** Cross-sectional studies show that greater physical activity and fitness correlate with lower total and low-density lipoprotein (LDL) cholesterol levels, higher high-density lipoprotein (HDL) cholesterol levels, and lower triglyceride levels throughout the lifespan.<sup>416–418</sup> Longitudinal changes in lipid profiles as a function of changing activity and fitness levels are more difficult to demonstrate, in part because of confounding by changes in body weight and dietary intake. In the Coronary Artery Risk Development in Young Adults (CARDIA) study, changes in physical fitness and activity were only weakly correlated with lipid levels, whereas changes in body weight were more strongly associated with lipid changes.<sup>419</sup> In the ARIC (Atherosclerosis Risk in Communities) study, increases in physical activity level over 9 years of follow-up were associated with increases in HDL cholesterol among white and black women and men, whereas decreases in triglycerides were evident only among white participants and changes in LDL cholesterol only among women, especially among black women.<sup>420</sup> Whether the heterogeneity of these results reflects true sex and ethnic differences or residual confounding by other lifestyle factors is unclear.

Clinical trials of exercise training as a means to modify blood lipid levels show heterogeneous results, in part dependent on characteristics of study participants; baseline lipoprotein profiles; differences in intensity, frequency, duration, and type of the exercise intervention; and any concomitant interventions as they occur in more comprehensive risk reduction programs. A meta-analysis of 48 clinical trials of exercise-based cardiac rehabilitation in patients with established CAD<sup>421</sup> reported a weighted mean difference in total cholesterol of  $-0.37$  mmol/L [ $-14.3$  mg/dL] (95% confidence interval [CI]:  $-0.63$  to  $-0.11$  mmol/L [ $-24.3$  to  $-4.2$  mg/dL]) and in triglyceride level of  $-0.23$  mmol/L [ $-20.4$  mg/dL] (95% CI:  $-0.39$  to  $-0.07$  mmol/L [ $-34.5$  to  $-6.2$  mg/dL]); information on HDL cholesterol and LDL cholesterol changes was not available in these trials. In the Training Level Comparison Study, a 1-year randomized trial in men with coronary heart disease that assessed 2 different intensities of exercise (50% and 85% of maximal oxygen consumption, respectively), modest changes in triglycerides were observed, but no significant impact on HDL or LDL cholesterol occurred in either exercise intensity group.

Adherence to either regimen correlated with improvement in lipid levels.<sup>422</sup> Another group conducted an 8-month exercise training study with different exercise intensities, taking care not to change body weight.<sup>423</sup> They also found little change in LDL cholesterol levels but observed beneficial changes in LDL subfractions, triglyceride levels, and very-low-density lipoprotein concentrations; increases in HDL cholesterol; and improvements in HDL subfractions. They similarly concluded that the amount of exercise, not the intensity of exercise or change in fitness, best correlated with improvements in these lipoproteins.<sup>423</sup> A meta-analysis of 25 exercise trials found overall modest increases in HDL cholesterol of 2.5 mg/dL and suggested that the minimal exercise volume to achieve improvements in HDL cholesterol was  $\approx 900$  kcal of energy expenditure per week or 120 minutes of exercise weekly, with significant additional increases in HDL cholesterol for every 10 minutes of exercise duration.<sup>424</sup> Another group investigated the impact of exercise on lipids and lipoproteins in specific populations in a series of meta-analyses. Benefits of exercise on lipoproteins extended to older individuals<sup>425</sup> and women,<sup>426</sup> whereas among overweight and obese individuals, only decreases in triglycerides reached statistical significance.<sup>427</sup> Whether resistance training can achieve similar benefits as aerobic training is less clear because 2 different meta-analytic approaches by the same authors reached different conclusions.<sup>428,429</sup>

**Exercise Training and Hypertension.** After early seminal observations,<sup>430,431</sup> the inverse relationship between physical activity, physical fitness, and incident hypertension has been reproduced in a number of population-based cohort studies. In the ARIC study, leisure-time physical activity among middle-aged adults was strongly associated with incident hypertension in white males but not in women or in blacks.<sup>432</sup> This unexpected finding remains unexplained but could be related to methodological issues in activity assessment in the latter 2 groups. Among young adults enrolled in the CARDIA study, both physical fitness and physical activity showed strong inverse and independent relationships to incident hypertension among whites and blacks and in both sexes.<sup>433</sup> The protective effect of greater physical activity appears to be independent of body weight in both sexes.<sup>434</sup> Even among the very fit, higher physical activity level and cardiorespiratory fitness are independently predictive of lower risk of incident hypertension.<sup>435</sup> The odds of developing hypertension were reduced in those who remained vigorously active and were increased in those whose vigorous activity declined over time.<sup>436</sup>

Exercise training lowers resting blood pressure in normotensive and hypertensive individuals and in patients with and without CVD. A meta-analysis of 54 trials of aerobic exercise training, which enrolled 2419 participants, reported a significant reduction in mean systolic and diastolic blood pressures ( $-3.84$  mmHg [95% CI:  $-4.97$  to  $-2.72$  mmHg] and  $-2.58$  mmHg [95% CI:  $-3.35$  to  $-1.81$  mmHg], respectively).<sup>437</sup> Moderate-intensity resistance training leads to blood pressure reductions of similar magnitude.<sup>438</sup> An “optimal” dose of exercise for blood pressure lowering has not been defined, but among previously sedentary adults, even modest increases in activity, such as walking 30 to 60 minutes per week, have measurable benefit.<sup>439</sup> Among 8940 patients with CAD enrolled in

48 trials of exercise-based cardiac rehabilitation, another group reported a weighted mean difference in systolic blood pressure of  $-3.2$  mm Hg (95% CI:  $-5.4$  to  $-0.9$  mm Hg).<sup>421</sup>

**Exercise Training and Obesity.** Overweight and obesity have reached epidemic proportions in the United States, with recent data from the National Health and Nutrition Examination Survey documenting a prevalence of overweight (BMI  $>25$ ) of 68% and a prevalence of obesity (BMI  $>30$ ) of 34%.<sup>440</sup> In that body weight is determined by the balance between energy intake (food) and energy expenditure (resting metabolic rate, thermic effect of food [digestion], and physical activity-related energy expenditure), exercise plays a major role in weight management. Current high rates of obesity are determined by both a high rate of physical inactivity and an increase in caloric intake.<sup>401,441</sup> Optimally, weight reduction in overweight/obese individuals is attained by a combination of reduced food intake and increased caloric expenditure (physical activity and exercise training), but weight reduction can be accomplished by diet alone or exercise alone.<sup>442</sup> Antiatherogenic effects of exercise and weight loss relate to favorable effects on insulin sensitivity, blood pressure, lipid profiles, inflammation, and blood clotting.<sup>442,443</sup> It is also notable that the best predictor of successful long-term weight loss maintenance is the presence of an ongoing exercise program with a high level of caloric expenditure.<sup>444</sup>

In patients with established CAD, participation in cardiac rehabilitation is generally not associated with substantial weight loss, probably because the caloric expenditure of exercise is relatively low at 750 to 800 kcal/wk,<sup>445</sup> and because behavioral weight loss programs are generally not offered. High-caloric-expenditure exercise (daily longer-distance walking) in combination with behavioral weight loss in cardiac rehabilitation has been demonstrated to result in substantial weight reduction over 4 months ( $>8$  kg) that is maintained at 1 year, in association with favorable effects on cardiac risk factors, including insulin sensitivity, blood pressure, lipid profiles, inflammation, and blood clotting.<sup>443</sup> Exercise and weight reduction in overweight patients with CAD have also been demonstrated to improve endothelial-dependent flow-mediated vasodilatation, a predictor of long-term prognosis.<sup>446</sup>

**Exercise Training and Insulin Sensitivity.** Physical activity has beneficial effects on both glucose metabolism and insulin sensitivity, including increased sensitivity to insulin, decreased production of glucose by the liver, a larger number of muscle cells that use more glucose than adipose tissue, and reduced body fat.<sup>447</sup> Exercise has both a short-term effect and a long-term effect that enhances insulin sensitivity and prevents type 2 diabetes mellitus. The effect of exercise on insulin sensitivity is enhanced by concomitant weight reduction. In the Diabetes Prevention Program, a combination goal of 150 minutes per week of aerobic exercise and weight reduction of 7% led to a 58% reduction in the incidence of type 2 diabetes mellitus, as compared with a control group, over 2.8 years of follow-up.<sup>448</sup> Lifestyle treatment was also more effective in preventing type 2 diabetes mellitus than was metformin, which in turn was more effective than placebo.<sup>433</sup>

**Exercise Training and Type 2 Diabetes Mellitus.** In individuals with established type 2 diabetes mellitus, a meta-analysis of published randomized controlled trials of exercise training revealed that exercise significantly improves glycemic control and reduces visceral adipose tissue and plasma triglycerides, but not plasma cholesterol, in people with type 2 diabetes mellitus, even without weight loss.<sup>449</sup> A structured exercise program is more effective than simply providing physical activity recommendations.<sup>450</sup> In the LookAHEAD (Action for Health in Diabetes) trial, a goal of 175 minutes of exercise per week and behavioral weight loss led to improved fitness and a 6% weight loss at 4 years, associated with lower levels of hemoglobin A<sub>1c</sub>, lower blood pressure, improved lipid measures, and less use of glucose-lowering medications, compared with usual care.<sup>451</sup>

#### *Anti-inflammatory Effects of Exercise Training*

Studies of the relationship between inflammation and physical activity and occasional and ongoing exercise were summarized in a systematic review in 2005.<sup>452</sup> Inflammatory markers, including high-sensitivity C-reactive protein (hs-CRP), increase soon after vigorous exercise, possibly mediated by cytokine increases or in response to muscle injury. This acute-phase response, which appears to be proportional to the amount of activity and extent of muscle injury, tends to abate within a few days and is less pronounced in trained than in untrained individuals.<sup>452</sup>

Many, but not all, cross-sectional epidemiological studies have reported an independent inverse association between physical activity level and hs-CRP levels over a broad range of physical activity levels, including ultra-marathon running.<sup>452,453</sup> The relationship might differ by type of physical activity.<sup>454</sup> In a long-term longitudinal study among older men, changes in physical activity level correlated with a decrease in hs-CRP levels, suggesting that benefits of exercise on hs-CRP are not sustained among those who become inactive and, conversely, that sedentary individuals can lower their hs-CRP levels through regular physical activity even at advanced ages.<sup>455</sup> Inverse associations have also been reported between hs-CRP levels and physical fitness, a measure less subject to bias than self-reported physical activity.<sup>456</sup>

Prospective data on the relationship between exercise training and inflammatory markers (eg, interleukins and cytokines) are more limited but suggest that exercise training (both aerobic and resistance training) can favorably affect hs-CRP levels and other inflammatory markers both in healthy populations and among individuals with metabolic disorders such as diabetes mellitus.<sup>452,457–459</sup> Whether this effect of exercise training occurs independently of weight loss remains controversial, and the mechanisms by which exercise might lower inflammatory markers are unknown.<sup>452,459</sup>

#### *Exercise Training and Vascular Function*

Numerous observational and interventional studies have shown salutary effects of aerobic exercise training on arterial function. Aging, even in healthy adults, is accompanied by an increase in intimal-medial thickness<sup>460</sup> and stiffness of larger arteries<sup>461</sup> and a reduction in endothelium-mediated arterial vasodilator capacity.<sup>462</sup> Endurance-trained individuals demonstrate lower measures of carotid artery intimal-medial



thickness and large-artery stiffness and greater endothelium-mediated vasodilator function than their sedentary age peers. For example, men 55 to 75 years of age who regularly competed in road races demonstrated  $\approx 30\%$  lower aortofemoral pulse-wave velocity and carotid augmentation index than untrained men of similar age.<sup>461</sup> As noted previously, aerobic exercise interventions lower blood pressure significantly; this reduction is generally greater in hypertensive individuals.<sup>437</sup> Endurance training in adults induces remodeling of conduit arteries, resulting in reduced wall thickness and increased lumen diameter.<sup>463</sup>

#### *Exercise Training and Blood Clotting*

Plasma levels of most coagulation factors increase with age in sedentary people, but this increase is attenuated in physically active individuals. After 16 weeks of aerobic training, coagulation factor levels were generally decreased, but these beneficial changes disappeared after only 2 weeks of “detraining.”<sup>464</sup> In sedentary overweight adults 50 to 75 years of age, favorable effects of endurance training include reduced tissue plasminogen activator antigen levels and plasminogen activator inhibitor-1 levels.<sup>465</sup> Men with claudication attributable to PAD exhibited elevated baseline levels of plasminogen activator inhibitor-1, which were reduced by 23% after 6 months of treadmill exercise training; tissue plasminogen activator activity increased 28% over this period.<sup>466</sup> Thus, ample evidence indicates that aerobic training has beneficial effects on fibrinolytic coagulation factors, especially in older adults with CVD.

#### *Exercise Training and Autonomic Function*

The balance between sympathetic and parasympathetic activity modulates cardiovascular activity. Enhanced sympathetic nervous system activity is associated with an increased risk of cardiac events, particularly in patients with known heart disease. A reduction of HR variability (HRV) has been reported in several cardiac conditions, such as after MI, in heart failure, and in diabetic neuropathy.<sup>467</sup>

Using measures of HRV, cross-sectional studies of healthy men reported higher parasympathetic activity among those who were physically trained and fit than among those who were not.<sup>468</sup> Exercise has been proposed to be an effective and nonpharmacological way to enhance cardiac electrical stability and serve as an antiarrhythmic intervention in humans.<sup>469</sup> Improved measures of HRV and baroreflex sensitivity with exercise training have been shown in patients after infarction.<sup>470,471</sup> It is also evident that exercise training improves the HRV in patients with chronic heart failure.<sup>472</sup> Benefit of exercise training in patients with chronic heart failure is in part mediated by significant reduction in central sympathetic outflow.<sup>473</sup>

#### *Anti-ischemic Effects of Exercise Training*

Although maximal exercise HR and blood pressure do not usually change significantly with aerobic training, HR and systolic blood pressure at fixed submaximal work rates are reduced by training, as noted earlier. Because the rate–pressure product is a major determinant of myocardial oxygen demand, the reduced rate–pressure product resulting from training will substantially lower oxygen demand, mimicking the anti-ischemic effects of  $\beta$ -blockers and nondihydropyridine calcium channel blockers. In addition, exercise training enhances arterial nitric oxide

production, thereby enhancing exercise-induced coronary vasodilation and myocardial blood flow.<sup>474</sup> Consistent with these favorable effects on myocardial oxygen demand and supply, studies have demonstrated training-induced improvements in myocardial perfusion and reduction in ischemia in patients after MI<sup>475,476</sup> and those with chronic CAD.<sup>477</sup> These beneficial effects of training on myocardial perfusion are observed in both the infarct zone and remote regions.

#### *Antiarrhythmic Effects of Exercise Training*

A risk of ventricular fibrillation or sudden cardiac death during isolated bouts of strenuous exercise in the presence of CAD is well documented, although the risk in screened patients is exceedingly low.<sup>234</sup> In the long-term setting, exercise training–induced improvements in the myocardial oxygen supply–demand balance and concomitant reduction in sympathetic tone and catecholamine release are postulated to attenuate the risk of ventricular fibrillation. The effects of exercise training on heart variability reflect in part decreased sympathetic and increased parasympathetic tone.<sup>478,479</sup> This could explain the lower rate of sudden cardiac death observed in physically active individuals with known or suspected CAD or at high risk of CAD.<sup>415,480–482</sup> Studies in animals after MI demonstrate an increased threshold for inducible ventricular fibrillation after exercise training.<sup>483</sup>

#### *Prevention of Aging-Related Disability*

Because regular exercise plays an important role in maintaining mobility, exercise training is a logical intervention to reduce or prevent age-associated disability. In a systematic review of exercise interventions, it was found that trials that offered a multicomponent exercise program involving endurance, strength, flexibility, and balance training generally reported significant reductions in disability.<sup>484</sup> Longer duration of the intervention and follow-up and interventions in more functionally limited individuals were associated with greater likelihood of benefit.<sup>484</sup> Interventions limited to lower-extremity strength training showed little to no benefit. The ongoing multicenter Lifestyle Interventions for Independence in Elders (LIFE) study will provide additional information on this topic. In the LIFE Pilot Study, a comprehensive physical activity intervention in 424 individuals at risk for disability (70–89 years of age) resulted in improved measures of physical performance and a lower incidence of major mobility disability, as reflected by inability to complete a 400-meter walk.<sup>485</sup>

### **Exercise Prescription for Apparently Healthy Individuals**

#### *Preexercise Screening*

The need for formal medical screening before the initiation of an exercise program depends on several factors, including the intensity of exercise to be undertaken, the age and cardiac risk factor status of the individual, and the presence or absence of established CVD. Healthy adults who wish to undertake a low- to moderate-intensity walking program or equivalent moderate-intensity exercise generally do not need a formal medical screening. Indeed, most are primarily formalizing a walking program that was already tolerated as a part of daily activities. Requiring a medical evaluation and a

stress test before undertaking walking (or equivalent) exercise in broad, healthy populations of adults has not been proven to be useful and could serve as a barrier to undertaking healthful exercise.<sup>486</sup> This is backed by the caveat that if individuals are experiencing chest pain, dyspnea, joint pain, or lightheadedness with exercise, they should seek medical attention.

### **Medical Evaluation and Exercise Prescription**

Individuals who are planning more vigorous physical activity than walking (or equivalent) should consider a medical screening, particularly if they are in an age and cardiac risk factor classification that would indicate a higher risk of exercise-related adverse events.

- Among men <45 years and women <55 years of age who are asymptomatic without known or suspected CVD, cardiovascular work-up is generally not needed unless there are extenuating circumstances, such as a family history of sudden death at a young age, or poorly controlled cardiac risk factors.
- Among men >45 years and women >55 years of age undertaking vigorous exercise who have diabetes mellitus or 2 other risk factors for CVD, a medical evaluation is advised. This should include a medical history, a physical examination, and a risk factor profile. For most, an electrocardiographic stress test is recommended. ("Exercise Testing: Before Participation in Vigorous Exercise" section.)
- The medical history should include the following: a history of familial CAD or heart failure; presence of valvular heart disease, stable or unstable angina, congenital heart disease, stroke, sudden death, history of pulmonary disease (ie, chronic obstructive pulmonary disease or asthma); presence of symptoms including chest discomfort, dizziness, and shortness of breath (at rest or with activities of daily living) and leg discomfort (claudication) suggesting cardiovascular or pulmonary disease; changes in balance or gait; presence of orthopedic problems including joint concerns (swelling), arthritis, or changes in mobility; medication use and use of caffeine or alcohol; and prior exercise habits. Of particular interest are data in the history that indicate that unsupervised exercise could be hazardous.

The physical examination should include vital signs and examination of the cardiovascular and pulmonary systems, including evaluation of abnormal heart sounds or murmurs; presence of wheezes or other adventitious sounds; presence of elevated BMI; presence of elevated blood pressure; presence of neuromuscular disease; and presence of joint swelling or other orthopedic issues. The risk factor profile should include blood work to determine the presence of dyslipidemia, anemia, diabetes mellitus, or prediabetes and should use the Framingham or other risk factor instrument to determine global cardiovascular risk.

- An exercise test is selectively recommended if vigorous exercise is planned. ("Exercise Testing: Before Participation in Vigorous Exercise" section.)

If the test is normal, no further restrictions are needed from a cardiovascular point of view. If the test is abnormal, further work-up should follow, according to symptoms and estimates

of risk. If an asymptomatic individual does not undergo an exercise test before beginning training, he or she should follow the activity guidelines outlined in Table 3. If the history or physical examination indicates significant CVD, the individual should be treated by using information detailed in the section titled "Evaluation and Exercise Prescription in Patients With CVD," with note taken that exercise is an important component of treatment and secondary prevention in individuals with CAD.

In the health/fitness facility setting, screening procedures should take place as detailed in the "Recommendations for Cardiovascular Screening, Staffing, and Emergency Policies at Health/Fitness Facilities."<sup>239</sup> This involves the use of screening questionnaires such as the Physical Activity Readiness Questionnaire (PAR-Q) or AHA/American College of Sports Medicine Pre-participation Screening Questionnaire. These will prompt referral for medical evaluation by a healthcare professional when indicated.

The risks of sudden cardiac arrest during intense exercise in the general population have been estimated at roughly 1 death per 80 000 to 159 000 participants during marathon running<sup>487–489</sup> and at 1 death per 67 000 participants during triathlons, with almost all triathlon deaths occurring during the swim portion.<sup>490</sup>

### **Classification of Cardiovascular Risk**

Individuals can be classified by risk on the basis of their age and cardiac risk factor characteristics. This classification is provided in detail in Tables 3 through 6, which are used to determine the need for subsequent supervision and the level of monitoring required.

## **Exercise Training Techniques**

### **Elements of an Exercise Training Session**

Exercise training sessions are typically arranged with brief periods of warm-up and cool-down (low-intensity aerobic and stretching movements) before and after a more intense and prolonged phase of conditioning of either endurance or resistance training (Table 7<sup>491,491a</sup>). Often, endurance training is

**Table 3. Risk Classification for Exercise Training: Class A: Apparently Healthy Individuals**

This classification includes:

1. A-1: Children, adolescents, men <45 years of age, and premenopausal women who have no symptoms or known presence of heart disease or major coronary risk factors
2. A-2: Men ≥45 years of age and postmenopausal women who have no symptoms or known presence of heart disease and with <2 major cardiovascular risk factors
3. A-3: Men ≥45 years of age and postmenopausal women who have no symptoms or known presence of heart disease and with ≥2 major cardiovascular risk factors

Activity guidelines: No restrictions other than basic guidelines

Supervision required: None\*

Electrocardiographic and blood pressure monitoring: Not required

\*It is suggested that persons classified as Class A-2 and particularly Class A-3 undergo a medical examination and possibly a medically supervised exercise test before engaging in vigorous exercise. Reproduced with permission from Fletcher et al.<sup>1</sup> © 2001 American Heart Association, Inc.

**Table 4. Risk Classification for Exercise Training: Class B: Presence of Known, Stable CVD With Low Risk for Complications With Vigorous Exercise, But Slightly Greater Than for Apparently Healthy Individuals**

This classification includes individuals with any of the following diagnoses:

1. CAD (MI, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, angina pectoris, abnormal exercise test, and abnormal coronary angiograms); includes patients whose condition is stable and who have the clinical characteristics outlined below
2. Valvular heart disease, excluding severe valvular stenosis or regurgitation, with the clinical characteristics as outlined below
3. Congenital heart disease; risk stratification for patients with congenital heart disease should be guided by the 27th Bethesda Conference recommendations<sup>145</sup>
4. Cardiomyopathy: ejection fraction  $\leq 30\%$ ; includes stable patients with heart failure with clinical characteristics as outlined below but not HCM or recent myocarditis
5. Exercise test abnormalities that do not meet any of the high-risk criteria outlined in Class C (Table 5)

Clinical characteristics (must include all of the following):

1. New York Heart Association class I or II
2. Exercise capacity  $>6$  METs
3. No evidence of heart failure
4. No evidence of myocardial ischemia or angina at rest or on the exercise test at or below 6 METs
5. Appropriate rise in systolic blood pressure during exercise
6. Absence of sustained or nonsustained VT at rest or with exercise
7. Ability to satisfactorily self-monitor intensity of activity

Activity guidelines: Activity should be individualized, with exercise prescription provided by qualified individuals and approved by primary healthcare provider

Supervision required: Medical supervision during initial prescription session is beneficial.

Supervision by appropriate trained nonmedical personnel for other exercise sessions should occur until the individual understands how to monitor his or her activity. Medical personnel should be trained and certified in Advanced Cardiac Life Support. Nonmedical personnel should be trained and certified in Basic Life Support (which includes cardiopulmonary resuscitation).

Electrocardiographic and blood pressure monitoring: Useful during the early prescription phase of training

CAD indicates coronary artery disease; HCM, hypertrophic cardiomyopathy; MET, metabolic equivalent; MI, myocardial infarction; and VT, ventricular tachycardia. Reproduced with permission from Fletcher et al.<sup>1</sup> © 2001 American Heart Association, Inc.

performed on days that alternate with resistance training, but both modes can be combined into a single session for patients who are sufficiently vigorous and healthy to tolerate the effort. Flexibility training is an additional exercise mode that is often integrated into the warm-up or cool-down periods to provide still another dimension of benefit.

#### *Warm-Up and Cool-Down*

Both warm-up and cool-down periods entail low-intensity aerobic exercises usually for 5 to 10 minutes. Warm-up maneuvers stimulate vasodilation and increased local muscle perfusion before a more intense conditioning stimulus. This activity also increases joint range of motion (ROM) and

flexibility. After the conditioning phase, cool-down facilitates a gradual transition to exercise cessation, modulating the effects of vasodilation, high catecholamines, and potential ischemia. Cool-down helps the HR and blood pressure transition to normal levels, reducing the likelihood for hypotension and ventricular ectopy. Body heat, lactic acid, and adrenaline are dissipated with gradual restoration to baseline levels.

#### *Flexibility Exercise*

Flexibility training preserves or progressively increases ROM of joints over time. Flexibility goals usually are tailored to capacities and needs of each patient, but a well-rounded program generally includes at least one stretching exercise for each major muscle group (ie, lower back, hips, posterior thighs, and legs). Just as with endurance and resistance training, flexibility training is generally based on goals to progressively enhance performance. In the case of flexibility exercise, this entails stretching muscle beyond its normal resting length but not to the point of pain or injury. The American College of Sports Medicine recommends  $\geq 4$  repetitions for each exercise, with the stretching itself lasting about 15 seconds.<sup>45</sup> Flexibility training then progresses to increase the extent of stretching, as well as the duration and the number of stretches to achieve further ROM benefits. Flexibility training is best performed when preceded by a general warm-up to prepare the muscles that are to be stretched; therefore, it is common to incorporate flexibility training as part of the cool-down phase of exercise training.

Traditionally, stretching methods vary between 3 techniques: ballistic stretching, static stretching, and proprioceptive neuromuscular stretching. Whereas ballistic stretching entails bouncing movements to lengthen the range of muscle stretch, static stretch uses slow, sustained muscle lengthening. During proprioceptive neuromuscular facilitation, the body part is moved to the end of its ROM, but it is then moved even further by an assistant. Proprioceptive neuromuscular facilitation is most common among athletic and rehabilitation programs. Ballistic and slow static exercises are more widespread, particularly because they do not depend on assistance to achieve the training benefit. Although both ballistic and slow static techniques are well-established modes to achieve increased ROM, slow stretching is less likely to cause injury or soreness.<sup>492</sup>

#### *Endurance Exercise*

Endurance exercise entails rhythmic motion of large muscle groups in aerobic activities such as walking, jogging, cycling, and rowing (Table 7). Endurance training uses the same progressive overload principle already described in relation to flexibility training. The overriding goal is to induce progressive physiological adaptations that facilitate increased exercise capacity and its related health benefits. Endurance training is prescribed in terms of intensity, duration, frequency, progression, and modality (Table 7). The intensity of endurance training can range from 40% to 80% of baseline exercise capacity, depending on the fitness of an individual, as well as his or her training goals. ("Maximizing Fitness.") Lower-intensity regimens can constitute an adequate training stimulus for sedentary adults and those who are older or frail. However, for most adults, training intensities of 55% to 80% of the baseline exercise capacity are well tolerated and



**Table 5. Risk Classification for Exercise Training: Class C: Those at Moderate to High Risk for Cardiac Complications During Exercise or Unable to Self-Regulate Activity or to Understand Recommended Activity Level**

This classification includes individuals with any of the following diagnoses:

1. CAD with the clinical characteristics outlined below
2. Valvular heart disease, excluding severe valvular stenosis or regurgitation with the clinical characteristics as outlined below
3. Congenital heart disease; risk stratification for patients with congenital heart disease should be guided by the 27th Bethesda Conference recommendations<sup>145</sup>
4. Cardiomyopathy: ejection fraction  $\leq 30\%$ ; includes stable patients with heart failure with clinical characteristics as outlined below but not HCM or recent myocarditis
5. Complex ventricular arrhythmias not well controlled

Clinical characteristics (any of the following)

1. New York Heart Association class III or IV
2. Exercise test results
3. Exercise capacity  $< 6$  METs
4. Angina or ischemic ST depression at a workload  $< 6$  METs
5. Fall in systolic blood pressure below resting levels during exercise
6. Nonsustained VT with exercise
7. Previous episode of primary cardiac arrest (ie, cardiac arrest that did not occur in the presence of an acute myocardial infarction or during a cardiac procedure)
8. A medical problem that the physician believes could be life-threatening

Activity guidelines: Activity should be individualized, with exercise prescription provided by qualified individuals and approved by primary healthcare provider

Supervision: Medical supervision during all exercise sessions until safety is established

Electrocardiographic and blood pressure monitoring: Continuous during exercise sessions until safety is established

CAD indicates coronary artery disease; HCM, hypertrophic cardiomyopathy; MET, metabolic equivalent; and VT, ventricular tachycardia.

\*Class C patients who have successfully completed a series of supervised exercise sessions may be reclassified to Class B, providing that the safety of exercise at the prescribed intensity is satisfactorily established by appropriate medical personnel and that the patient has demonstrated the ability to self-monitor. Reproduced with permission from Fletcher et al.<sup>1</sup> © 2001 American Heart Association, Inc.

safe and more efficiently lead to improved fitness and health. Assessments of initial fitness and training intensity are usually conceptualized in relation to aerobic performance indices. For people without known or suspected CVD in whom an exercise test has not been performed, intensity can be estimated from the percentage of maximum predicted HR, derived as 220 minus age in years, assuming that the individual is not taking a  $\beta$ -adrenergic-blocking medication. CPX testing<sup>19</sup> provides the most accurate measure of maximal aerobic performance during an exercise test ( $\dot{V}O_{2\max}$ ), such that a training intensity can be established as a percentage of  $\dot{V}O_{2\max}$ . A percentage of maximal HR from an exercise test can be used as an alternative means to gauge aerobic capacity. Furthermore, training targets based on  $\dot{V}O_2$  or HR often are adjusted to account for individual differences in  $\dot{V}O_2$  and HR at rest. This is achieved

by first subtracting the resting values of  $\dot{V}O_2$  and HR from the maximum level achieved to determine the  $\dot{V}O_2$  reserve or HR reserve, respectively; training targets are then calculated by multiplying the desired training percentage with the reserve values and adding the product to the baseline  $\dot{V}O_2$  and HR values. For example, if the maximal exercise HR is 180 and the resting HR is 80, the HR reserve is 100. Training at 50% of HR reserve would have the individual training at an HR of 130 bpm ( $80 + 0.5 \times 100$ ). Even with such steps to increase training precision, measures of  $\dot{V}O_2$  and HR can vary with exercise mode as well as with medications, volume status, disease, or even psychological stress.

A simpler way of gauging exercise intensity is to base a training target on a subjective assessment of exertion. The Borg Perceived Exertion Scale<sup>219</sup> provides a well-validated gradation of exercise intensity (relative perceived exertion index of 6 to 20) (Table 2). Training at an RPE level between 12 and 16 is generally consistent with 40% to 80% HR reserve.

Although exercise training has been consistently demonstrated to be very safe, even in adults with known CVD, exercise testing constitutes an important means to formally assess overall clinical stability and to rule out myocardial ischemia, arrhythmia, or hemodynamic hazards that would otherwise contribute to exercise-related risks. Although such testing is often sufficient to assure training safety, monitoring of HR and blood pressure over the course of a training program is still important because the physiological rationale for endurance exercise depends at least in part on safely provoking these cardiovascular responses to elicit physiological adaptations. One key purpose of cardiac rehabilitation is to provide more stringent surveillance of cardiovascular responses as endurance exercise intensity is advanced in patients with known CVD. A "talk test" is considered a relatively simple way of monitoring exercise intensity. Essentially, the ability of someone to talk comfortably during exercise has been associated with overall cardiovascular safety.<sup>493,494</sup> Safety concerns also relate to the effects of endurance exercise on joints and bones. High-impact activities are more likely to result in injury, especially in overweight or deconditioned adults. Cross-training (ie, varying exercise modalities) also helps to avoid excessive use of any single joint or bone.

Ideal training goals are to exercise  $\geq 5$  days a week for 30 to 60 minutes, depending on the training intensity. Nonetheless, this extent of activity could be overwhelming to many, particularly those who are frail or deconditioned at the onset. Therefore, it is important to start with modest goals that are realistic and attainable and to slowly advance toward guideline-based training intensity, duration, and frequency. Multiple "bouts" of low-intensity physical activity (eg, slow walking) for even 10 minutes each have been shown, for example, to have meaningful physiological value for adults to yield healthful adaptations and progressive improvement in exercise tolerance. Walking is often regarded as the activity of choice because it is readily accessible, offers a range of intensities amenable to personalized regimens, and is easily regulated. Slow walking at 2 mph approximates 2 METs and can constitute sufficient training for lower-fitness subjects. Brisk walk training programs (3–4 mph) for longer durations provide high-energy activity

**Table 6. Risk Classification for Exercise Training: Class D: Unstable Disease With Activity Restriction\***

This classification includes individuals with any of the following:

1. Unstable ischemia
2. Severe and symptomatic valvular stenosis or regurgitation
3. Congenital heart disease; criteria for risk that would prohibit exercise conditioning in patients with congenital heart disease should be guided by the 27th Bethesda Conference recommendations<sup>609</sup>
4. Heart failure that is not compensated
5. Uncontrolled arrhythmias
6. Other medical conditions that could be aggravated by exercise

Activity guidelines: No activity is recommended for conditioning purposes. Attention should be directed to treating the patient and restoring the patient to Class C or better. Daily activities must be prescribed on the basis of individual assessment by the patient's personal physician.

\*Exercise for conditioning purposes is not recommended. Reproduced with permission from Fletcher et al.<sup>1</sup> ©2001 American Heart Association, Inc.

intensity that increases exercise capacity while decreasing body weight and fat stores. As the fitness level of an individual advances, the intensity of exercise training needs to advance; thus, it is important to build in prompts for both the exerciser and for the exercise supervisor to periodically reexamine the exercise prescription on the basis of the current fitness status of the individual.

Jogging or brisk walking, on level ground or a treadmill, has historically been regarded as a primary exercise mode to achieve appropriate levels of energy expenditure and derive cardiovascular benefits. Nevertheless, desirable levels of energy expenditure and cardiovascular benefits can be achieved with other exercise modes, such as cycling, aerobic dance, elliptical training, and water-based exercise modalities (water-based aerobics or walking in waist-deep water). It is particularly important to prescribe exercises that a person enjoys and that he or she tolerates comfortably to promote long-term compliance.

Aerobic interval training (AIT) is an endurance training strategy that contrasts to the traditional standard of progressive continuous training modes. Interval training is structured as intense exercise periods alternating with relatively lower-intensity recovery periods. Originally, AIT was used mostly by athletes because it improved exercise performance more rapidly than progressive continuous training. However, since the 1990s, AIT has been applied more frequently to other populations, including adults with heart disease. AIT is discussed further in a later section<sup>495,496</sup> ("Maximizing Fitness").

### Resistance Training

Resistance exercise training, which involves activities that use low- or moderate-repetition movements against resistance, has been accepted as a primary component of a comprehensive exercise program, both for apparently healthy individuals and (with appropriate screening and precautions) for subjects with CVD.<sup>491</sup> Although the effect of resistance exercise on CVD risk factor modification is less than traditional endurance exercise, the increase in strength and potential for increased muscle mass could improve the individual's ability to become more physically active, raise the basal metabolic rate, and in older people, improve the ability to perform activities of daily living and

**Table 7. General Guidelines for Endurance and Resistance Training**

Endurance training	
Frequency	≥5 d/wk
Intensity	55%–90% maximum predicted HR* or 40%–80% Vo <sub>2</sub> max or HR reserve RPE 12–16
Modality	Walking, treadmill, cycling, etc
Duration	30–60 min
Resistance training	
Frequency	2–3 d/wk
Intensity	50%–80% of 1-RM or RPE 12–16 1–3 sets of 8–15 repetitions per exercise
Modality	Lower extremity: leg extensions, leg curls, leg press. Upper extremity: bench press, lateral pulldowns, biceps curl, triceps extension
Duration	30–45 min

HR indicates heart rate; maximum predicted HR=(220–age); RPE, rating of perceived exertion; and 1-RM, single-repetition maximal lift.

\*The HR range recommendation assumes that the individual is not taking β-adrenergic-blocking medications. Modified from Shephard and Balady.<sup>491a</sup> ©1999 American Heart Association, Inc.

decrease fall risk (Table 7<sup>491,491a</sup>). People initiating a resistance training program should be carefully screened for both cardiovascular limitations and preexisting orthopedic and musculoskeletal problems. In addition, individuals should be provided with careful recommendations with regard to the specific components of the resistance training program, including proper technique, number and types of exercises, and safety precautions.

Detailed guidelines for resistance training can be found elsewhere.<sup>45,491,497</sup> An outline of progressive resistance training programming is presented in Table 7. Programs including a single set of 8 to 10 different exercises (eg, chest press, shoulder press, triceps extension, biceps curl, pull-down, lower back extension, abdominal crunch/curl-up, quadriceps extension or leg press, and leg curls/calf raise) that train the major muscle groups, when performed 2 to 3 days per week, will elicit favorable adaptations and improvement (or maintenance thereof). Intensity of training (training load) is prescribed relative to the 1-repetition maximum (1-RM), which is the highest weight or load an individual can lift for a specific exercise only once when using proper technique. To achieve a balanced increase in both muscular strength and endurance, a repetition range of 8 to 12 is recommended for healthy participants <50 to 60 years of age (60%–80% of 1-RM), and a range of 10 to 15 repetitions at a lower relative resistance (40%–60% of 1-RM) is recommended for cardiac patients and healthy older participants. The reason for the increased repetition range at a lower relative effort for older or debilitated subjects is injury prevention. The relative load should be increased when the individual can comfortably exceed the repetition range.

### Behavioral Aspects of Initiating and Sustaining an Exercise Program

The promotion of physical activity for adults requires some understanding of the principles of behavior change and of habit development. Additionally, barriers to physical activity and

correlates of success with long-term exercise should be considered. An evaluation of an individual's readiness for change is appropriate before considering a major behavior change such as embarking on an exercise program.<sup>498</sup> Five components of behavior change and self-regulation include: (1) setting of realistic and simple goals, (2) self-monitoring of personal behaviors linked to goal attainment, (3) feedback about progress toward goals, (4) self-evaluation of progress, and (5) corrective behavior leading to effective movement toward goals.<sup>499</sup> These principles are relevant whether an individual is embarking on exercise in a home-based or in a group format. In adults >55 years of age, more than two thirds of individuals perceive barriers to physical activity, including weather, neighborhood safety, and quality of sidewalks, in addition to lack of time, energy, and motivation.<sup>500–502</sup> Exercises that are most likely to be successful in the long term are moderate in intensity, relatively inexpensive, simple, and convenient and include a social component.<sup>503</sup>

### **Evaluation and Exercise Prescription in Patients With CVD**

Exercise training in patients with CVD has been documented to increase exercise capacity,<sup>504,505</sup> reduce or eliminate angina pectoris,<sup>506</sup> and markedly increase walking distance in patients with claudication.<sup>507</sup> Meta-analyses suggest that exercise-based cardiac rehabilitation reduces total deaths, cardiovascular deaths, and hospital readmissions by roughly 25% in patients after an MI.<sup>421,508</sup> A randomized, controlled clinical trial in patients with systolic heart failure documented an 11% reduction in total mortality or hospitalization in patients randomized to exercise training versus sedentary controls after adjustment for selected baseline variables.<sup>509</sup> Exercise training in patients with CVD has multiple other therapeutic benefits.<sup>404</sup> Despite such beneficial effects, exercise training is not consistently prescribed for patients with CVD, as evidenced by the fact that only 14% to 35% of qualified patients are referred to cardiac rehabilitation programs after MI<sup>510–512</sup> and ≈31% after bypass surgery.<sup>511</sup> The reasons for such underutilization are unclear but probably include provider-related factors (eg, lack of training in exercise therapeutics, underestimation of therapeutic benefits, lack of time), medical system factors (eg, poor hospital-to-outpatient transition, ever-shortening index hospitalizations), and patient-related factors (eg, depression, social isolation, extended travel time, lack of insurance coverage, socioeconomic status, a need to return to work). Nevertheless, nearly all patients with diagnosed heart disease can benefit from an individualized exercise training regimen. Accordingly, there is a need to design, evaluate, and implement evidence-based alternative approaches to traditional cardiac rehabilitation that help provide all appropriate patients affordable access to clinically effective secondary prevention programs.<sup>513</sup>

### **Preexercise Clinical Screening**

The clinical evaluation of patients considered for exercise training is designed to identify those in whom exercise training should be prohibited or delayed and those in whom exercise training is unlikely to produce benefit and to design an appropriate exercise prescription for participants.

### **History and Physical Examination**

Patients with CAD can initiate exercise training within a week after an acute coronary syndrome, provided the patient is

clinically stable. Consequently, the history and physical examination should ensure that the patient does not have unstable ischemic symptoms, uncontrolled heart failure, or potentially life-threatening arrhythmias that might be exacerbated by exercise training. In addition, the physical examination should determine if there are orthopedic issues that could be worsened by physical activity. Patients with lower-extremity orthopedic problems or neuropathy might benefit from non-weight-bearing forms of exercise training, such as ergometry or swimming. Patients with CAD who have undergone recent cardiac surgery should be examined for wound infections and sternal instability to ensure that they do not engage in physical activities that would hamper healing. For these patients, it is broadly accepted that there should be a delay in the initiation of an upper-extremity resistance training program after surgery (ie, 4–6 weeks). Similarly, integrity of catheterization access sites should be examined to rule out fistulae and pseudoaneurysms that could be worsened by exercise training. For patients with claudication, the physician should ensure that the patient does not have rest pain, skin ulcers of the feet, or an extremely limited exercise tolerance because such patients are unlikely to improve with exercise training alone. The physical examination in patients with peripheral vascular disease should ensure that no skin lesions exist that would be worsened with exercise or that could be attributable to extremely low perfusion. Such an examination of the lower extremities and feet is especially important in patients with CVD and diabetes mellitus.

### **Role of Exercise Tolerance Testing**

Patients with CVD should generally undergo symptom-limited exercise testing before initiating an exercise program in cardiac rehabilitation to establish a baseline fitness level, determine maximal HR, and ascertain the safety of exercise by assessing symptoms and by observing for severe electrocardiographic ischemia or cardiac arrhythmia that would contraindicate exercise training or require a different therapeutic approach. This is not an absolute requirement, however, and many programs do not require such testing in clinically stable patients with CVD to facilitate initiation of the exercise regimen. Referral to a cardiac rehabilitation program is often used as a surrogate for exercise testing in such patients, and the initial exercise session is used to benchmark the patient's symptom and exercise performance baseline. Exercise testing before exercise training is not designed for diagnosis, and therefore, patients should be tested while on their usual medication to mimic their exercise-training sessions. Patients who did not undergo exercise testing after acute coronary syndrome or surgery and are not referred to a cardiac rehabilitation program should be encouraged to initiate low-intensity exercise training, with instructions to report symptoms such as chest pain or shortness of breath to their physician.

### **Risk of Exercise Training for Patients With CVD**

The risk of a cardiac event during vigorous exercise training in individuals with established CAD can be estimated from supervised cardiac rehabilitation programs. Studies in this population indicate that there is roughly 1 cardiac arrest for every 115 000 patient-hours of cardiac rehabilitation and 1 death for



every 750 000 patient-hours of participation.<sup>421,508</sup> The observation that the incidence of cardiac arrest is 6-fold higher than the death rate indicates the value of successful resuscitation during supervised cardiac rehabilitation but also suggests that the death rate likely would be higher during unsupervised exercise.

Because cardiovascular events during supervised exercise training are rare, there are no established predictors as to which CVD patients will suffer exercise-related cardiac events. Prognosis for patients with heart disease generally worsens with the extent of disease, reduced LV function, inducible ischemia, and the presence of cardiac arrhythmias.<sup>514</sup> Consequently, patients with an LV ejection fraction <50%, exercise-induced ischemia or complex ventricular arrhythmias, or hemodynamically significant residual coronary stenoses are likely to be at increased risk and should be considered for supervised exercise training.

### ***Supervision and Monitoring of Exercise Training***

The level of supervision and monitoring of exercise training must be considered on the basis of the type of patient, staff, facility, and resources. Details on administration and programming of cardiac rehabilitation are provided in the “Guidelines for Cardiac Rehabilitation and Secondary Prevention Programs” from the American Association of Cardiovascular and Pulmonary Rehabilitation.<sup>515</sup>

Recommendations for risk stratification are provided in Tables 3 through 6. For the apparently healthy individual, no supervision is needed (Table 3). For those with unstable disease, no activity is recommended (Table 6). Additional guidelines are provided for moderate- to high-risk and low-risk subjects.

### ***Medically Supervised Exercise***

**Moderate- to High-Risk Subjects (Class C).** Activity programs are needed to provide close medical supervision for individuals who are at moderate to high risk for a complication associated with vigorous physical activity. Such individuals are largely from Class C (Table 5). These patients require careful medical supervision and surveillance to ensure that the activity is well tolerated. A physician should be immediately available for these classes, although the presence of a properly trained and experienced nurse or exercise physiologist in the exercise room is sufficient if a physician is not in the exercise area. The qualifications of the physician may vary, but experience in the treatment of patients with heart disease is required. Training programs should be medically supervised until the safety of the prescribed activity has been established.

**Low-Risk Subjects.** Low-risk subjects (Class B) benefit from medically supervised programs because vigorous exercise can be conducted more safely, and group dynamics often help subjects comply with good health behaviors. Medical supervision of low-risk subjects can be provided by a well-trained nurse or exercise physiologist working under a physician's standard orders. If direct medical supervision by a physician is not provided, the supervisor should have successfully completed an AHA-sponsored course in Advanced Cardiac Life Support and should be able to administer emergency medications. Well-trained cardiovascular nurses usually meet these

criteria. The program should provide the same basic requirements detailed for high-risk subjects in Table 5.

All but the highest-risk patients can exercise in nonmedical settings, including the home and health/fitness facilities. Such patients should be properly instructed by appropriately trained healthcare professionals with regard to the exercise prescription and self-monitoring techniques. Details on exercise in nonmedical settings are provided in the “Recommendations for Cardiovascular Screening, Staffing, and Emergency Policies at Health/Fitness Facilities” from the AHA and American College of Sports Medicine.<sup>239</sup>

A stable patient can enter cardiac rehabilitation as early as the first 1 or 2 weeks after discharge from the hospital for a cardiac event such as MI or stent placement. Before enrolling in cardiac rehabilitation, most individuals, with their physician's guidance, may initiate a home walking program at a slow, regular pace with increasing duration, starting with one to two 5- to 10-minute periods per day and gradually working up to 30 to 60 minutes per day. Such walking programs need not be supervised. Unmonitored exercise<sup>516</sup> can also be used for conditioning after the individual has recovered from the MI ( $\geq 2$  weeks after hospital discharge) or in other cases of stable CAD, although medically supervised and monitored exercise is preferred. It should be noted that recent evidence indicates initiation of structured cardiac rehabilitation shortly after hospital discharge for a recent MI significantly improves program participation.<sup>517</sup> Clinicians should therefore strongly consider facilitation of cardiac rehabilitation as soon as possible after hospital discharge. If cardiac rehabilitation facilities are not available, activity guidelines can still be provided to cardiac subjects, and they should be encouraged to exercise. If individuals carefully watch for signs of intolerance such as chest pain or shortness of breath and are attentive to HR and RPE, this activity level is considered safe. Walking is a safe, low-impact, controllable exercise that, in most cases, generates an intensity that is 40% to 70% of  $\dot{V}O_{2\max}$ . ROM exercises and light calisthenics can be performed in an unmonitored setting. Activities are considered safe and appropriate if they meet the criterion of moderate intensity, as perceived by the physician or judged by an exercise test.

### ***Electrocardiographic Monitoring During Exercise Training***

Various recommendations exist with regard to the number of electrocardiographic-monitored sessions that are necessary and reasonable in an exercise training program. No controlled clinical trials have specifically evaluated this issue. Some programs use as few as 6 sessions, with progression in mode and intensity of the exercise during these periods,<sup>518</sup> whereas others have used as many as 36 sessions of electrocardiographic monitoring. It is recommended that the classifications outlined in Tables 4 and 5 be used as a general guideline. Importantly, the ultimate judgment must remain with the medical supervisor of the cardiac rehabilitation program and must include consideration of the patient, staff, and exercise setting. Class A (apparently healthy) individuals do not require electrocardiographic-monitored sessions because the general guidelines are adequate. Class B (low-risk) individuals should be monitored and supervised until they understand their desirable activity levels (usually 6 to 12 sessions). Class C (higher-risk)

individuals should be medically supervised with electrocardiographic monitoring until they understand the level of activity that is safe and the medical team determines that the exercise is well tolerated and effective. Usually, 12 sessions are needed.

#### *Electrocardiographic-Monitored Cardiac Rehabilitation*

Monitoring sessions ideally should be performed with continuous electrocardiographic monitoring by either hardwired apparatus or telemetry. The sessions should be conducted by personnel who understand the exercise principles involved and have a working knowledge of electrocardiography and arrhythmia detection. The sessions should also be supervised by appropriately trained healthcare professionals trained in emergency management procedures, including cardiopulmonary resuscitation. All healthcare professionals involved in the execution of cardiac rehabilitation should at a minimum have a current certification in basic life support. Standing orders for the management of a complication should be immediately available. Monitored sessions should also include symptom and RPE assessment by the staff, blood pressure recording, and instructions to subjects about selection and proper use of exercise equipment.

#### *Home-Monitored Cardiac Rehabilitation*

In a systematic review of data from 12 randomized controlled trials (1938 participants) conducted in 6 different countries, the effectiveness of home-based cardiac rehabilitation was compared with supervised traditional cardiac rehabilitation; no difference in outcomes was found among patients receiving home-based or center-based cardiac rehabilitation either in the short term (3–12 months) or longer term (up to 24 months).<sup>519</sup> Most of these studies monitored home exercise by using measures of perceived exertion to approximate exercise intensity. Transtelephonic electrocardiographic monitoring at home has been studied as a substitute for outpatient visits to the clinic.<sup>520,521</sup> Such programs have the disadvantage of lacking immediate emergency medical care but the advantage of not requiring an on-site clinic visit. These programs can be particularly useful in rural settings.<sup>522</sup> One program reported using both electrocardiographic and voice transtelephonic monitoring, which supported both the efficacy and safety of home programs.<sup>523</sup> The importance of alternative approaches with novel technologies is discussed in detail in a recent AHA science advisory on this topic.<sup>513</sup>

### **Effects of Exercise Training in Patients With CVD**

Exercise capacity and the short-term physiological responses to exercise improve with training in individuals with established CVD. The increase in peak aerobic capacity is attributable to a combination of central (or cardiac) adaptations and peripheral adaptations.

#### *Peak Oxygen Uptake*

Subjects with heart disease frequently demonstrate an increase in  $\dot{V}O_{2\max}$  with aerobic exercise training.<sup>4,524</sup> Although the absolute magnitude of the change is often less in subjects with CVD than that observed in apparently healthy individuals, the proportional increase is similar and can exceed that seen in normal individuals, favorably impacting performance of activities of daily living. In

individuals with heart failure, absolute increases in  $\dot{V}O_{2\max}$  with training are somewhat limited, but even these small changes have significant impact on the restoration of the ability to perform daily activities and are correlated with an improved prognosis.<sup>525–527</sup>

#### *Cardiac Output*

An increase in peak cardiac output can result from the subject's ability or willingness to increase peak exercise intensity, including peak HR and perhaps stroke volume, during subsequent testing as compared with an initial test. In addition, exercise training has been suggested to improve vasomotor function (eg, coronary dilation), providing the possibility of increased myocardial oxygen delivery to cardiac muscle and thereby potentially increased stroke volume.<sup>528,529</sup> Submaximal cardiac output might be lower at a given workload, primarily the result of lower HR, with maintenance of  $\dot{V}O_2$  provided by a widening of peripheral arteriovenous  $\dot{V}O_2$  difference after training. This suggests improved overall efficiency for delivery of oxygen to the tissues. In studies of high-intensity exercise training ( $\approx 90\%$   $\dot{V}O_{2\max}$ ) in patients with heart failure or CAD, there are indications that cardiac function, including ejection fraction, stroke volume, diastolic function, and wall motion parameters, is also improved.<sup>495,530–532</sup>

#### *Myocardial Oxygen Demand*

Primarily as the result of peripheral metabolic changes, exercise training for individuals with CAD promotes lower myocardial oxygen demand at any given absolute workload, resulting in lower HR, systolic blood pressure, and circulating catecholamines. The benefits of these adaptations can be demonstrated by the greater amount of work that can be done before angina or ischemic ST depression occurs. Moreover, several studies suggest that there is an improvement in myocardial oxygen supply (ie, coronary blood flow) at a given level of myocardial oxygen demand after training.<sup>528,529</sup>

#### *Autonomic Function*

HR recovery measured at exercise testing is reflective of vagal tone and is an independent marker of overall risk of death. HR recovery improves after Phase II cardiac rehabilitation and is associated with decreased risk of all-cause death.<sup>533</sup>

### **Prognostic Benefits of Exercise in Patients With CVD**

Cardiorespiratory fitness, as measured objectively by the assessment of peak oxygen uptake, is a powerful, independent predictor of death in patients with known cardiac disease.<sup>185,527,534–536</sup> One study of men with a history of heart disease demonstrated that a 1-MET increment was related to age-adjusted decreased risks of 18% and 32% for nonfatal and fatal cardiac events, respectively.<sup>535</sup> Other investigations have shown comparable findings. In patients referred for cardiac rehabilitation, peak  $\dot{V}O_2$  cut points of <15, 15 to 22, and >22 mL  $\text{kg}^{-1} \text{min}^{-1}$  were associated with multivariate-adjusted hazard ratios of 1.00, 0.62, and 0.39 for cardiac deaths and 1.00, 0.66, and 0.45 for all-cause deaths.<sup>536</sup> In patients with heart failure, a meta-analysis revealed a 39% risk reduction for death among exercise-trained patients

versus controls.<sup>537</sup> These results are similar to those of another meta-analysis, in which a 35% reduction in risk of death and a 28% reduction in the composite end point of death and hospitalization were found with exercise training.<sup>538</sup> More recently, a large multicenter trial demonstrated a multivariate-adjusted reduction of 11% in the combined end point of all-cause death and hospitalization and a 15% reduction in the combined end point of cardiovascular death and heart failure hospitalization.<sup>509</sup> Furthermore, that study also demonstrated that the volume of exercise training affected risk reduction; >4 MET-hours or >6 MET-hours per week resulted in an 18% or 26%, respectively, reduction in the combined end point of all-cause death or hospitalization. Finally, in older adults ( $\geq 60$  years of age), the highest level of cardiorespiratory fitness was associated with lower all-cause death (hazard ratio = 0.59) and death from CVD (hazard ratio = 0.57).<sup>539</sup> The impact of exercise training on fitness and ultimately on risk of death appears to be attributable to improvement in CVD risk factors, such as enhanced fibrinolysis, improved endothelial function, decreased sympathetic tone, and likely other, as yet undetermined, factors.<sup>540–543</sup>

### Targeting Exercise Prescription to Relevant Outcomes

Although general guidelines for exercise training noted in the earlier section (“Exercise Training Techniques”) provide benefits for both health and fitness for the adult population at large, the exercise prescription can be tailored with regard to individual needs, conditions, and comorbidities to attain specific health outcomes.

#### Maximizing Fitness

Exercise training programs generally are designed to improve aerobic fitness and include the prescriptive components of intensity, duration, frequency, progression, and modality, as discussed in previous sections and as outlined in detail elsewhere.<sup>45</sup> For patients with CVD, intensity usually is determined on the basis of results from the baseline exercise test by any of the following methods: 40% to 80% of peak exercise capacity with the HR reserve; in patients who have performed a CPX, 40% to 80% measured  $\dot{V}O_2$  reserve, or % peak  $\dot{V}O_2$ . The intensity may be further modified by using the subjective RPE scale of 12 to 16 on a scale of 6 to 20.<sup>219</sup> Among patients with an ischemic response during exercise, the intensity should be prescribed at an HR just below the onset of ischemic symptoms (by  $\approx 10$  beats). The ischemic threshold is most often determined as the HR at which typical angina begins to occur. The goal duration of exercise at the prescribed intensity is generally 30 to 60 minutes per session.

AIT involves alternating 3- to 4-minute periods of exercise at very high intensity (90%–95% HR<sub>peak</sub>) with 3-minute intervals at a moderate intensity (60%–70% HR<sub>peak</sub>). Such training for  $\approx 40$  minutes 3 times per week has been shown to yield greater improvements in peak  $\dot{V}O_2$  than those seen with standard continuous, moderate-intensity exercise.<sup>495,496</sup> Although AIT has long been used in athletic training and appears to have promise in patients with CVD, AIT cannot yet be broadly

recommended for such patients until further data on safety and efficacy are available.

#### Reducing Body Weight and Insulin Resistance

The primary characteristics of an exercise program targeted at reducing body weight are that the program should maximize exercise-related caloric expenditure and should be sustained for the long term. Examples of exercise programs that maximize caloric expenditure and induce weight loss have been well described and generally include almost-daily longer-distance walking.<sup>442,443</sup> To maximize caloric expenditure, non-weight-supported exercise should be favored, given that exercises such as walking or elliptical trainers will burn more calories than exercises that are weight supported, such as rowing or seated or supine ergometry.<sup>544</sup> For patients who have difficulty walking, weight-supported exercise can be substituted, at least initially, and the duration of exercise can be maximized as possible.

Aerobic exercise has both short- and long-term favorable effects on insulin sensitivity, whereas resistance exercise, particularly if it induces an increase in muscle mass, has been linked primarily to long-term improvements in insulin sensitivity. Ongoing aerobic exercise, in association with a behavioral weight loss program, has been demonstrated to significantly decrease the clinical progression from insulin resistance to type 2 diabetes mellitus<sup>448</sup> and yields improved diabetic control for individuals with established type 2 diabetes mellitus.<sup>451</sup>

#### Improving Blood Pressure and Lipids

Data demonstrating the effect of exercise on blood pressure and blood lipid levels are discussed under “Antiatherogenic Effects of Exercise.” Clinical trial evidence supports that hypertension can be modified favorably by moderate-intensity endurance exercise (40%–60% HR reserve or  $\dot{V}O_2$  reserve), which is performed for  $\geq 30$  minutes per day on most (preferably all) days of the week.<sup>545</sup> Recent preliminary data suggest that AIT could provide a great magnitude of benefit on both systolic and diastolic blood pressures.<sup>546</sup> There are not yet enough data to support this latter approach, however. Although resistance training could yield modest reductions in blood pressure, data are insufficient to support a specific resistance training regimen. Hence, endurance exercise should remain the cornerstone of an exercise training regimen to treat hypertension. Resistance training could provide some additional benefit.<sup>438</sup>

Without weight reduction, the effects of exercise training on lipids are at best modest. HDL appears to be the lipoprotein that is most favorably affected by endurance exercise. Data suggest that high-intensity training (65%–80% of % peak  $\dot{V}O_2$ )<sup>423,547</sup> at high volumes (eg, 20 miles per week)<sup>423</sup> is needed to demonstrate improvements in HDL. One preliminary study has shown AIT to be superior to moderate-intensity training in raising HDL.<sup>548</sup> There are not yet enough data to support a specific resistance training regimen in the treatment of abnormal lipids.

#### Improving Effort Tolerance in Older Patients With CVD

The superimposition of CVD on the well-known age-associated decline in aerobic capacity results in marked functional impairment in typical older patients entering cardiac rehabilitation. In 2896 patients of mean age 61 years entering cardiac rehabilitation after a recent coronary event or revascularization, peak  $\dot{V}O_2$



averaged 19.3 mL kg<sup>-1</sup> min<sup>-1</sup> in men and 14.5 mL kg<sup>-1</sup> min<sup>-1</sup> in women.<sup>524</sup> Peak  $\dot{V}O_2$  declined per age decade by 2.4 mL kg<sup>-1</sup> min<sup>-1</sup> in men and 1.2 mL kg<sup>-1</sup> min<sup>-1</sup> in women, thus approaching values typical of patients with chronic heart failure, especially in women. Nevertheless, multiple studies have shown that older adults respond to cardiac rehabilitation with relative improvements in peak  $\dot{V}O_2$  and other measures of functional capacity similar to those of younger cardiac rehabilitation patients.<sup>549–552</sup>

The exercise prescription will often require modification in patients >75 years of age, especially those with common age-related comorbidities such as arthritis, pulmonary disease, and PAD. A common theme in such individuals is to start at very low work levels and advance in small increments, often by using a type of interval training with intermittent rest periods. Patients with impaired balance or gait often are better suited to training on a cycle ergometer than on a treadmill. Strength training is an important component of exercise training in the elderly, given the decline in muscle mass and strength with aging. A growing body of literature supports the use of exercise interventions to improve function in frail elders.<sup>553</sup> In a study of 116 elders of mean age 75 years with 5.5 chronic conditions on average, increases in leg power after 16 weeks of combined aerobic–resistance training was a strong independent contributor to increased gait speed and enhanced overall physical performance.<sup>554</sup>

Perhaps the greatest barrier to the benefits of cardiac rehabilitation in older adults with CVD is their very low utilization rate of such programs. An analysis of Medicare claims documented use of cardiac rehabilitation in 13.9% of patients hospitalized for acute MI and 31% of patients after coronary bypass surgery, with lower rates in very elderly people, women, non-whites, and those with comorbidities.<sup>511</sup> A major contributor to the low utilization of cardiac rehabilitation by the elderly is the reluctance of the provider to refer them to these programs.<sup>555</sup>

### ***Exercise Training for Chronic Heart Failure and After Heart Transplantation***

Exercise training is effective in improving exercise capacity, symptoms, and quality of life in patients with impaired LV systolic function and chronic heart failure.<sup>556,557</sup> In an international randomized controlled trial of exercise training for 2331 outpatients with stable systolic heart failure (HF-ACTION; Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training), it was found that after adjustment for prognostic baseline characteristics, exercise training was associated with an 11% reduction in combined all-cause death or hospitalization ( $P=0.03$ ).<sup>509</sup> Similarly, in a meta-analysis of exercise training trials in patients with chronic heart failure, exercise training significantly reduced deaths and hospital admissions.<sup>538</sup> Accordingly, exercise training is recommended as a component of a comprehensive approach to the patient with stable chronic heart failure.<sup>558</sup> However, only a few exercise training studies have addressed patients with chronic heart failure and preserved LV ejection fraction.<sup>559</sup> Exercise training in patients with chronic heart failure has been shown to reduce HR at rest and submaximal exercise and to increase peak aerobic capacity. These favorable changes are attributable to a broad range of mechanisms. Although central hemodynamics have not consistently shown improvement, significant

peripheral changes, including those in vascular endothelial function, lead to improved leg blood flow and reduced arterial and venous lactate levels.<sup>495,560</sup> Neurohormonal abnormalities in patients with heart failure also improve after training.<sup>561</sup> Exercise training favorably affects autonomic tone, leading to enhanced vagal tone as evidenced by overall reductions in HR, increased HRV, and a decline in sympathetic nervous activity.<sup>562,563</sup> Exercise training also yields important changes in skeletal muscle fiber type and function in such patients, leading to enhanced oxidative capacity.<sup>564</sup>

The exercise prescription for patients with heart failure is similar to that outlined for patients with CVD. In most clinical studies, an intensity range of 70% to 80% of peak HR (determined from a symptom-limited exercise test) for 30 to 60 minutes, 3 times per week, is used. A few studies have used high-intensity training,<sup>565</sup> and one study used AIT exercise.<sup>495</sup> However, at this time, there are not enough data to recommend the latter. Although endurance exercise remains the focus of clinical training programs, resistance training has been shown to increase muscle strength and endurance, to reduce symptoms, and to improve quality of life in patients with heart failure. Hence, resistance training should be incorporated into the training program of these patients.<sup>566–569</sup> Data from HF-ACTION demonstrated that among 1159 patients with stable heart failure who were assigned to supervised exercise with subsequent transition to home-based unsupervised exercise, the adverse event rate was similar to that of the group assigned usual care. Thus, moderate-intensity exercise in the home setting appears to be safe for patients with heart failure.<sup>509</sup>

Patients who have undergone cardiac transplantation were often quite inactive before the procedure and remain deconditioned after the operation. The denervated donor heart has altered physiological responses to exercise, which include blunted chronotropic and inotropic responses that tend to limit exercise capacity. Nonetheless, several studies have shown that exercise training increases endurance capacity.<sup>570,571</sup> Generally, patients may enter medically supervised outpatient exercise programs as soon as they are discharged from the hospital. The exercise prescription is similar to that for other patients with CVD. However, prescription of exercise intensity can be more challenging. Because the HR in a denervated heart rises more slowly in response to exercise and can remain elevated longer after activity ceases, it is more difficult to use HR to monitor exercise intensity. The RPE in combination with other descriptors of exercise tolerance, such as workload, can be particularly helpful with this patient group. Resistance training can be useful to offset the skeletal muscle loss and weakness because of corticosteroid use.<sup>572</sup>

LV assist devices are used as a bridge to cardiac transplantation, a bridge to recovery, and, increasingly, as a destination therapy among patients with end-stage heart failure who are not eligible for cardiac transplantation. These patients tend to be profoundly deconditioned before device implantation and remain so after implantation. Early mobilization and ambulation are keys to recovery. Exercise physiology in recipients of LV assist devices is complex and depends on the type of device, device settings, function of the native left and right ventricles, and peripheral

factors.<sup>573,574</sup> Controlled trials of exercise training in the LV assist device population have not been published. Exercise training featuring gradually increasing intensity (guided by RPE and symptoms) and including both aerobic and resistance exercises appears to be safe and results in improvements in physical function.<sup>574,575</sup>

### **Exercise Training in Valvular Heart Disease**

Depending on the valvular orifice size and the resting gradient, patients with mild aortic or mitral stenosis can perform isotonic exercises, provided the response to exercise stress testing is normal. Patients with moderate stenosis can indulge in low- to moderate-intensity isotonic exercises as tolerated. Patients with severe stenosis should be restricted from intense isotonic or isometric exercises but can perform low-level activities as tolerated.<sup>576</sup>

Previous level of training, type of cardiac disease and valve replaced, and postoperative functional status can influence the exercise recommendations after valve replacement. Patients with mitral valve disease have a markedly lower exercise tolerance postoperatively than those with aortic valve disease and thus are candidates for a different, lower-level exercise training program. There is evidence available to show that the avoidance of patient–prosthesis mismatch can result in better exercise capacity for patients after aortic valve replacement.<sup>577</sup> Selected patients with very low postoperative exercise capacity should undergo echocardiography to rule out patient–prosthesis mismatch. Electrocardiographic monitoring should be considered on a case-by-case basis.

### **Exercise Training in PAD**

Patients with PAD are commonly limited in their daily activities by claudication or leg fatigue during exercise that involves dynamic motion of calf and leg muscles. An exercise treadmill test before exercise training is useful to evaluate walking capacity and the degree of exercise limitation. However, some patients could have severe symptoms that preclude the performance of an exercise test. If testing is performed, protocols that begin at low work rates and have low work rate increments per stage, including individualized ramp protocols, can be especially useful. Exercise training with treadmill walking has been used most frequently in clinical trials.<sup>578–582</sup> The treadmill walking exercise prescription for patients with PAD and symptoms of intermittent claudication consists of intermittent bouts of walking exercise at a work rate that brings on claudication until the patient has an ischemic leg pain score of mild–moderate (3–4 on a 5-point scale), followed by rest until pain completely subsides, and then resumption of exercise at a similar intensity. The rest and exercise bouts are repeated for a total of 50 minutes per day, including rest periods. Patients can progress to a higher work rate when 8-minute bouts of exercise are attained. Patients with PAD without intermittent claudication should follow the exercise prescription for patients with CVD outlined previously (“Maximizing Fitness”). In all patients with PAD, treadmill walking exercise is the preferred modality, but supplemental exercise with other exercise modalities, including resistance training as recommended for patients with CVD, could be of additional benefit. A recent multicenter randomized controlled trial documented that supervised exercise training delivered for 3 hours per week

over 6 months was superior to primary stenting for aortoiliac disease with regard to the primary outcome of peak walking time.<sup>583</sup> The topic of exercise training in PAD is discussed in detail elsewhere.<sup>515,582</sup>

### **Exercise Training in Congenital Heart Disease**

In comparison with normal subjects, the exercise function of patients with congenital heart disease is often decreased, even after reparative surgery. Although some of this exercise dysfunction could be related to residual hemodynamic defects, inactivity and deconditioning (often because of restrictions inappropriately imposed by family members, teachers, coaches, or the patients themselves) undoubtedly contribute to this problem.<sup>584,585</sup> This component of their disability should theoretically respond favorably to exercise training programs.

Several small studies have documented the short-term benefits of exercise training programs in children with congenital heart disease. On completion of a variety of training programs, peak  $\dot{V}O_2$  has been reported to increase 7% to 21% over baseline values.<sup>586–589</sup> Most of the improvement appears to be attributable to an increase in the oxygen pulse at peak exercise.<sup>589</sup> In one study, the short-term improvements were sustained 6 to 9 months after the termination of the rehabilitation program (1 year after the prerehabilitation study) and were associated with improvements in lifestyle, perceived exercise function, self-esteem, and emotional state.<sup>590</sup> Improvements in exercise function and other areas were not observed in a control group, composed of 18 children with similar diagnoses, observed over the same time period.

The benefits associated with exercise training in children with congenital heart disease (and adults with acquired heart disease) should also extend to adults with congenital heart disease. However, few studies have been undertaken to support this conjecture. One study<sup>591</sup> of 17 adults with tetralogy of Fallot (of whom 9 participated in a home/hospital-based exercise program for 12 weeks, and 8 continued to pursue their habitual daily activities) reported a small (7.8%) but statistically significant increase in peak  $\dot{V}O_2$  in the exercise group but not in the control subjects. In another study,<sup>592</sup> the exercise duration of a group of 61 adult patients with a variety of congenital heart disease diagnoses improved after a 10-week home-based exercise program. Similar beneficial effects were detected in another study of 11 patients.<sup>593</sup> Recommendations for participation in competitive sports by individuals with congenital heart disease were published in the 2005 Bethesda Conference Report.<sup>594</sup> No restrictions were placed on athletes with hemodynamically minor, unrepaired abnormalities (eg, septal defects or persistent ductus arteriosus without pulmonary hypertension or LV enlargement). Patients who have undergone successful surgical or transcatheter closure of hemodynamically significant defects may participate in all competitive sports. In the absence of other abnormalities, asymptomatic patients with mild semilunar valve stenosis (peak systolic gradient <40 mmHg) or regurgitation and those who underwent successful surgical or transcatheter relief of stenosis >3 months previously also need not be restricted. Similarly, in the absence of other abnormalities, patients with mild aortic coarctations (and those with mild residual coarctations >1 year after surgery or balloon

angioplasty) may participate in all activities. Patients with a hemodynamically excellent tetralogy of Fallot repair or arterial switch procedure for transposition of the great arteries may participate in all activities if they have normal exercise tests and no evidence of serious rhythm disturbances. Similar criteria apply to patients with mild Ebstein disease. A variable level of competitive sports participation is permitted for patients with more severe unrepaired congenital anomalies and patients with more significant residual lesions, provided they have reassuring exercise tests and ambulatory electrocardiographic monitoring. Only patients with the most serious cardiovascular conditions (eg, patients with persistent severe pulmonary hypertension, severe aortic stenosis, significant aortic dilation / wall thinning or aneurysm formation, or severe Ebstein anomaly; most patients with severe valvular insufficiency; those with moderate to severe ventricular dysfunction; and those with unrepaired cyanotic defects) are restricted from all (or virtually all) competitive sports. It should be noted, however, that the Bethesda Conference Recommendations apply only to competitive sports. The recommendations do not necessarily apply to exercise or sports participation in less intense environments and certainly do not exclude properly screened patients from participating in and deriving benefits from appropriately designed exercise programs. Indeed, there are no reports of serious adverse events among the patients with congenital heart disease who have participated in the rehabilitation studies published in the literature, even though these programs often included patients with all but the highest-risk conditions.

### ***Atrial Fibrillation***

Light to moderate physical activities, particularly leisure-time activity and walking, are associated with a significantly lower incidence of atrial fibrillation in older adults.<sup>595</sup> It should be noted that recent evidence indicates that ongoing high-intensity/high-volume endurance training could be associated with an increased incidence of atrial fibrillation.<sup>596,597</sup> Even so, in view of the multiplicity of benefits of exercise, no current recommendations discourage exercise training at a higher level to reduce atrial fibrillation risk. For those already diagnosed with atrial fibrillation, regular moderate physical activity is known to increase exercise capacity and control ventricular rate during atrial fibrillation.<sup>598</sup> Patients without structural disease and in the absence of WPW syndrome can safely perform moderate-intensity isometric and isotonic exercises, depending in part on the presence and severity of underlying CVD. Exercise training response in patients with chronic atrial fibrillation is not impaired, and exercise capacity improves.<sup>599</sup>

### ***Pacemakers***

Before exercise is prescribed, the presence and severity of underlying heart disease should be evaluated, including the severity of CAD and the adequacy of LV function. Exercise is prescribed according to the type of pacemaker implanted and the sensor used to detect activity in rate-responsive pacemakers.<sup>600</sup> Physical activity intensities in fixed-rate pacemakers must be gauged by a method other than pulse counting, such as defining specific workloads that are initially ≈40% to 60%

of peak exercise capacity, as determined by the exercise test and by the RPE. Systolic blood pressure can also be used as a measure of exercise intensity.

### ***Intracardiac Defibrillators***

An intracardiac defibrillator (ICD) uses HR as the primary method of tachycardia detection. Before initiating an exercise training program, one should know the programmed device's cutoff rate. Exercise prescription for patients with defibrillators should be limited to a maximal HR that is at least 10 to 15 beats lower than the threshold discharge rate for the defibrillator. Baseline functional status and severity of ventricular dysfunction will have an impact on exercise prescription. Patients with an ICD should undergo a standard graded exercise tolerance test for devising an individualized exercise program. Such testing can detect exercise-induced arrhythmias. ICD recipients should generally not participate in moderate- or high-intensity competitive athletics, although this depends in part on the severity of underlying cardiac disease and the original indication for implantation. Low-intensity competitive sports that do not constitute a significant risk of trauma to the defibrillator are permissible if 6 months have passed since the last ventricular arrhythmia requiring intervention.<sup>601</sup> There is evidence to suggest that exercise training in patients with an ICD increases peak  $\dot{V}O_2$ , similar to control patients.<sup>602–604</sup> In a retrospective comparative survey, it was shown that patients who participated in an exercise-based cardiac rehabilitation program received fewer total and exercise-related shocks than those who did not participate.<sup>605</sup> In a prospective cohort study of 118 patients after ICD implantation, a significant increase of exercise capacity was shown, without serious complications.<sup>606</sup> Supervised exercise training for patients with implanted defibrillators appears to be both safe and effective.<sup>604</sup>

The HF-ACTION study provides the largest single assessment of exercise in patients with stable heart failure. Among 490 patients with an ICD in the exercise group, only 1 patient experienced ICD firing during an exercise session.<sup>509</sup>

### ***Cardiac Resynchronization Therapy***

In suitable patients with chronic heart failure, cardiac resynchronization therapy leads to an improvement in exercise capacity, peak  $\dot{V}O_2$ , and quality of life. A randomized controlled study showed that exercise training leads to further improvements in exercise capacity, hemodynamic measures, and quality of life, supplemental to the improvements seen after cardiac resynchronization therapy.<sup>565</sup> A study conducted in 52 men with heart failure who received an ICD with or without cardiac resynchronization therapy demonstrated that moderate aerobic exercise training improves functional capacity, endothelium-dependent vasodilatation, and quality of life.<sup>607</sup> The investigators concluded that moderate exercise training is safe and has beneficial effects on peak  $\dot{V}O_2$  and quality of life after ICD, especially when cardiac resynchronization therapy is present. Another pilot trial of exercise training in resynchronized heart failure patients also demonstrated enhanced exercise tolerance.<sup>608</sup> Thus, for suitable patients, exercise training may be used as an adjunct to cardiac resynchronization therapy for improving cardiac and peripheral muscle function.



## Disclosures

## Writing Group Disclosures

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Paul D. Thompson	Hartford Hospital	NHLBI†; NIH-NIAMST; NIH-NCCAM†; GlaxoSmithKline†; Roche†	None	Abbott†; AstraZeneca†; GlaxoSmithKline†; Kowa†; Merck†	None	2007–2010 Witness for Plaintiff, Case of cardiomyopathy resulting in cardiac transplant	Furiex*; Merck*; Regeneron*; Roche*; Sanofi*; Takeda*	None
Mark A. Williams	Creighton University	NIH*	None	None	None	None	None	None

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives \$10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns \$10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

\*Modest.

†Significant.

## Reviewer Disclosures

Reviewer	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Expert Witness	Ownership Interest	Consultant/Advisory Board	Other
Nora Goldschlager	UCSF	None	None	None	None	None	None	None
Michael Lauer	NHLBI	None	None	None	None	None	None	None
Todd D. Miller	Mayo Clinic	None	None	None	None	None	None	None
Roberta Oka	VA Palo Alto HCS	None	None	None	None	None	None	None
Paolo Raggi	University of Alberta (CANADA)	None	None	None	None	None	None	None
Malissa J. Wood	Massachusetts General Hospital	None	None	None	None	None	None	None

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