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REVIEW ARTICLE | PHYSICAL ACTIVITY AND EXERCISE SERIES

Cardiopulmonary Exercise Testing

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Abstract

Because symptoms of cardiopulmonary disease often occur with exertion, cardiopulmonary exercise testing (CPET) has a unique role in the assessment of patient symptoms, disease severity, prognosis, and response to therapy. In addition to the evaluation of cardiovascular and pulmonary physiology, CPET provides an assessment of the interaction of the cardiovascular and pulmonary systems with the musculoskeletal, nervous, and hematological systems. In this article, we review key CPET variables, protocols, and clinical indications.

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Introduction

In patients with cardiac, pulmonary, or muscular diseases, symptoms often first develop with physical activity.[1] Cardiopulmonary exercise testing (CPET) assesses a patient during exercise and provides insight into their physiology in a controlled environment. By comparing a patient's exercise response to that which is expected in a healthy individual of the same age and sex, and/or prior testing of that patient, pathological changes in the cardiopulmonary system can be discerned. This information provides objective, quantitative information to aid clinicians in making accurate diagnoses and developing comprehensive therapeutic strategies

CPET measures a patient's response to dynamic exercise with a progressive, symptom-limited protocol and provides a multivariate, integrative approach to the elements of oxygen transport from the atmosphere to the mitochondria of active skeletal muscle. Assessments are performed at both submaximal and peak exercise. The test serves as the basis for the evaluation of cardiovascular and pulmonary physiology with an assessment of their interaction with the musculoskeletal, nervous, and hematological systems. Information obtained during CPET can then be applied to clinical decision-making across a wide array of indications: assessment of patient symptoms, disease severity, prognosis, and response to therapy. CPET is particularly useful when laboratory and resting evaluations (e.g., imaging, pulmonary function testing, echocardiography) provide uncertain insight into the patient's symptoms throughout daily activities. In this review, we provide context for key CPET variables, as well as indications for CPET, clinical applications, and limitations of this testing modality.

COMMON INDICATIONS FOR CPET

Common indications for CPET are depicted in Figure 1. One of the most common clinical indications for CPET is dyspnea on exertion when the etiology is unclear. CPET is particularly useful in the evaluation of congenital heart disease, which can lead to complex

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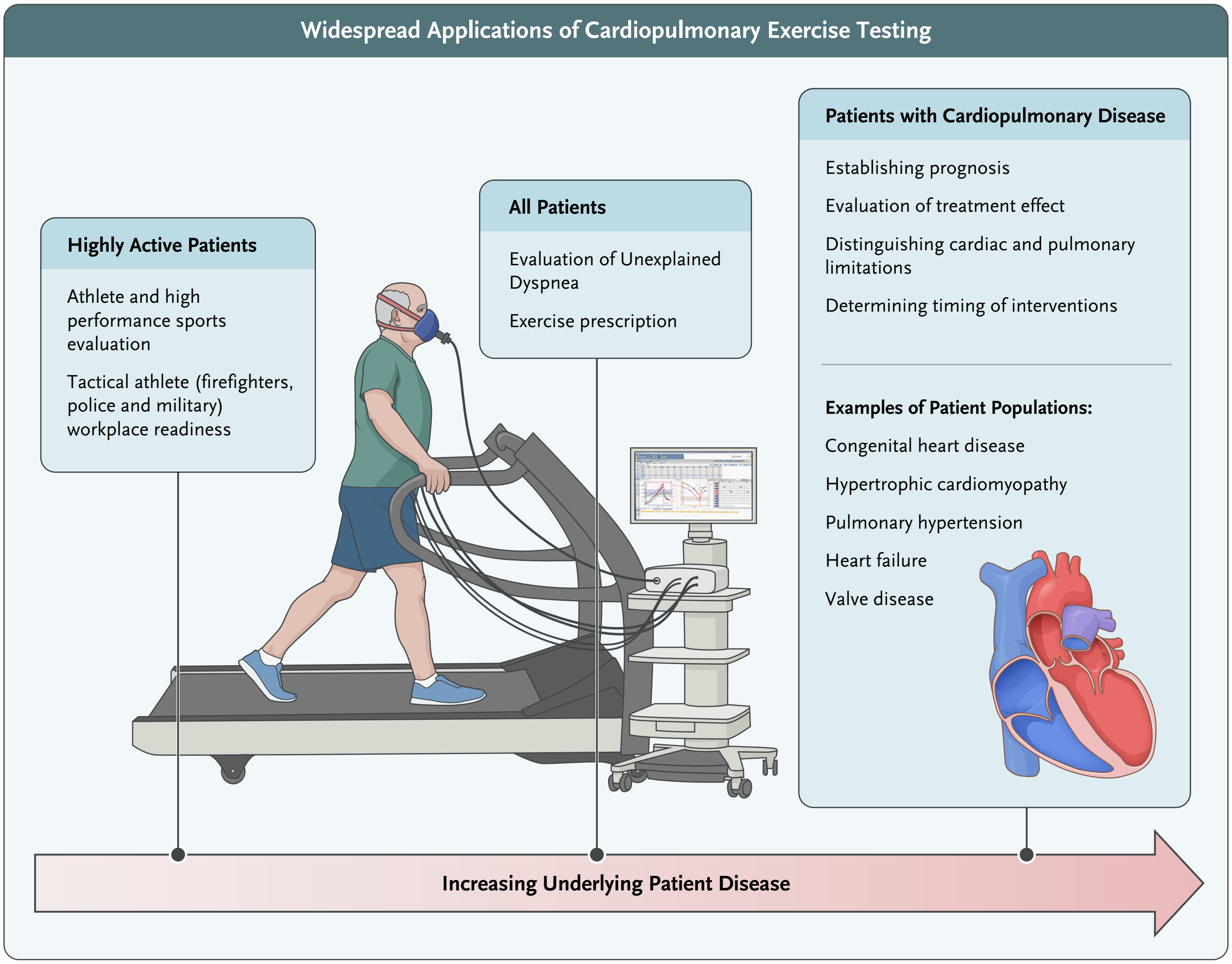

Figure 1. Cardiopulmonary Exercise Testing Applications.

cardiac limitations together with respiratory limitations due to multiple surgical interventions. CPET testing is a component of the standard of care for adults with congenital heart disease. CPET can help determine the need for valvular intervention, transplant referral, or to evaluate the response to treatment. Similarly, patients with pulmonary hypertension often have complex etiologies of dyspnea (cardiac, pulmonary, and peripheral), which can be characterized with CPET. CPET can also provide insight into the management of pulmonary vasodilators. For patients with heart failure, CPET is valuable in prognostication as well as in the determination of transplant candidacy. It is also often used for the development of personalized exercise prescriptions. Additional populations who may benefit from CPET include patients with valvular heart disease to evaluate the functional significance of regurgitation, stenosis, or the efficacy of valvular replacement. In patients who experience arrhythmias triggered by exercise, CPET can help determine the efficacy of medical therapy and is particularly useful in providing a controlled environment with full electrocardiogram (ECG) monitoring to evaluate patients with palpitations, dizziness, and near or true syncope provoked by exercise. The results of CPET may also be used for disability determination and worksite readiness for physically demanding occupations.

PROTOCOLS

Determining the most appropriate exercise testing modality for a given patient requires consideration of the patient's

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comorbidities and the health system's available resources. Treadmill exercise is preferred when possible, as daily activities require upright ambulation. Some patients may not be capable of substantial exertion on a treadmill due to gait, balance, or orthopedic limitations, and a cycle ergometer provides a reasonable alternative. Cycle ergometer maximal CPET values are typically 5 to 11% lower than those achieved with treadmill exercise in noncyclists, as less muscle mass is used during exercise.[2] Untrained individuals may terminate cycling exercise due to quadriceps muscle fatigue at oxygen uptake (VO_2) levels below those achieved on a treadmill.

To achieve sufficient granularity in the measurement of exercise capacity to provide meaningful information, the incremental ramping up of intensity must be relatively small. Large or unequal increments of work between stages may make it challenging to interpret test results and are a frequent critique of the standard Bruce protocol in which both the speed and grade of the treadmill change at each stage.[3] Multiple alternative graded maximal exercise tests exist that utilize different increments with the goal of simplifying the protocol, reducing testing duration, and/or accommodating patients of different fitness levels. The modified Astrand protocol also keeps the speed the same; however, it uses a steeper grade increase of 2% with a longer stage duration of 2 minutes.[4] In contrast, the Ellestad protocol increases only the speed each minute until the 10th minute, at which time there is a 5% grade change followed by subsequent speed increases until the attainment of a maximal value for oxygen uptake (VO_2 max[5]). VO_2 max is the gold standard measure of cardiorespiratory fitness and represents the highest level of oxygen utilization to fuel aerobic production of adenosine triphosphate achievable by an individual. A study comparing these four different protocols found that participants (51 healthy men between 35 and 55 years of age) achieved a similar VO_2 max with each test, although there was some variation with other measured physiological parameters.[4]

VO_2 max is a complex measure.[6] Indirect criteria are commonly employed to support the conclusion of VO_2 max attainment by an individual during CPET. However, repeating an exercise test at a higher workload is the only way to confirm VO_2 max definitively. Indirect criteria that are often used to approximate VO_2 max include a combination of a plateau in measured VO_2 max, the respiratory exchange ratio (RER) of expired carbon dioxide to oxygen uptake (VCO_2/VO_2), estimated maximal heart rate (HR), blood lactate levels, and Borg's rating of perceived exertion scale (RPE).[6,7] The VO_2 max plateau refers to the slowing of oxygen uptake despite an increase in workload. The observation of this plateau during CPET is inconsistent and can be influenced by protocol design, testing modality, and analysis methods.[8] The RER is a commonly used measure for an individual's effort via a noninvasive expired gas analysis. This may not hold true for individuals on extreme or restrictive diets, and it is important to gather such information through a detailed patient history. The RER increases with exercise due to muscle glycogenolysis, the buffering of lactate, and/or hyperventilation.[9] An RER value greater than 1.1 is a strong indicator of good effort in a healthy patient but is not an indication to end a VO_2 max test. The RPE provides data on a patient's subjective response to exercise, which encompasses behavioral, psychological, and physical factors that influence the CPET results.

Another valuable outcome of CPET is the maximal steady state, which is the maximal workload that is sustainable for a prolonged period of time. For example, a marathon is typically run at approximately the maximal steady state, but occupational or recreational activities that can be sustained without excessive dyspnea or fatigue may also be performed at approximately the maximal steady state. In healthy individuals, the maximal steady state occurs at 50 to 70% of VO_2 max and can exceed 90% of VO_2 max in elite athletes. The maximal steady state is useful for the evaluation of a patient's ability to perform activities of daily living and/or sustained aerobic exercise. Thus, it supports the development of exercise prescriptions and offers valuable information on functional status. It is also particularly useful as a measure of functional capacity in patients with significant limitations to achieving a VO_2 max measurement. Multiple techniques, including the Conconi HR, lactate threshold, and ventilatory threshold, are used to identify this level of exercise intensity.[9]

CLINICAL APPLICATIONS

Functional Assessment

CPET can be instrumental in determining the cause of a patient's exercise limitation or unexplained dyspnea when resting spirometry, chest imaging, and echocardiography are unrevealing or nondiagnostic. Exercise tests must be interpreted in the clinical context along with other supporting data. Comorbid conditions may make interpretation more challenging.[10,11]

Aerobic Exercise Prescription

For patients with cardiovascular disease, pulmonary disease, and many others, an aerobic exercise prescription may be useful to establish safe levels of exercise.

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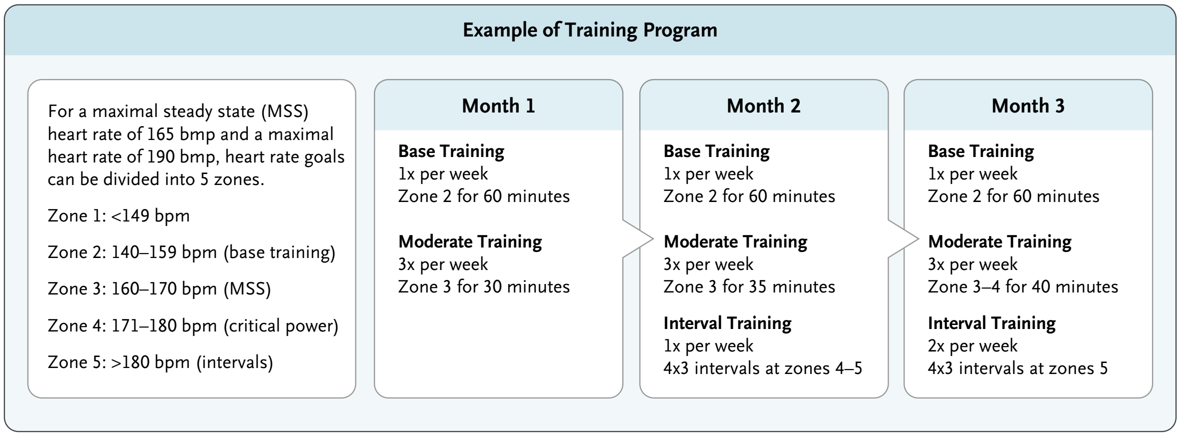

Figure 2. Example Training Program for a Patient with a Maximal Heart Rate of 190 BPM.

Training zone heart rates can vary, but five training zones are typically identified. For a maximal steady state heart rate of 165 bpm, and a max heart rate of 190 bpm: zone 1, below 140 bpm; zone 2, (base training) 140 to 159 bpm; zone 3 (MSS or threshold), 160 to 170 bpm; zone 4 (critical power), 171 to 180 bpm; and zone 5 (intervals), greater than 180 bpm. bpm denotes beats per minute; MSS, maximal steady state.

Prescriptions focus on exercise duration, intensity, and frequency.[12] Determining the HR at which the ventilatory threshold is attained defines the highest submaximal level at which the patient can sustain exercise. When writing an exercise prescription, it is important to consider the environment in which exercise will be performed and medications with a negative chronotropic effect. Identifying the exercise intensity at which a patient experiences angina or the ECG indicates myocardial ischemia can define the work rate and HR at which ischemia occurs. In this setting, the resulting prescription would be safely below the intensity at which abnormalities were detected (often defined as approximately 10 bpm below the HR at which ischemia occurred). A sample exercise prescription would define training zones based on HR and then gradually increase training volume (both by duration and intensity) to reach the desired fitness (Figure 2).

SPECIAL CONSIDERATIONS IN HEART FAILURE

Heart Failure with Reduced Ejection Fraction

CPET is especially useful and has become part of the standard clinical evaluation of heart failure with reduced ejection fraction (HFrEF), as CPET can quantify a patient's functional restrictions and provides more detailed objective data than a 6-minute walk test. Furthermore, CPET can provide information that helps clinicians determine whether or not heart failure is the cause of the patient's exercise intolerance and evaluate the patient's candidacy for advanced heart failure therapies, including left ventricular assist devices and heart transplant.[13] The results of exercise testing can guide a physical training prescription and subsequent testing can measure the patient's response to therapeutic interventions.

Numerous studies have shown the prognostic value of CPET in patients with heart failure. A VO_2 peak less than or equal to 14 ml/kg/minute (≤12 ml/kg/minute if prescribed a beta-blocker) is an indication for consideration for a heart transplant.[13] Weber et al. proposed a classification of heart failure severity based on VO_2 peak values (>20 ml/kg/minute = no to mild disease, 16–20 ml/kg/minute = mild to moderate disease, 10–15 ml/kg/minute = moderate to severe disease, and <10 ml/kg/minute = severe disease), although this classification is not widely accepted.[14] A ventilatory efficiency slope (ventilatory efficiency is the ratio of total minute ventilation to minute ventilation of carbon dioxide, V_E/VCO_2) greater than 34 has been associated with an increased risk for hospitalization due to acute decompensated heart failure.[15,16] A V_E/VCO_2 slope greater than or equal to 43 is an indication of severe disease with consideration for a heart transplant.[17]

Heart Failure with Preserved Ejection Fraction

Heart failure with preserved ejection fraction (HFpEF) is a heterogeneous disease with multiple proposed phenotypes. HFpEF is characterized by exercise intolerance, diastolic dysfunction, and elevated left-sided pressures (pulmonary capillary wedge pressure [PCWP] ≥15 mmHg at rest or >25 mmHg during exercise) due in part to a stiff

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left ventricle. In some patients, the diagnosis of HFpEF can be made based on history and supported by echocardiography or cardiovascular magnetic resonance, while right heart catheterization is helpful to confirm the diagnosis in others. In a subset of patients, central hemodynamics may be within normal limits at rest, especially in the upright position. However, PCWP increases dramatically during exercise (≥25 mmHg during supine exercise, and >15 mmHg from baseline during upright exercise),[18] though this acute increase is likely not the primary cause of patients' dyspnea.[19] Some patients with HFpEF also have reduced oxygen uptake and reduced augmentation of blood flow to skeletal muscles that contribute to their symptoms and limited exercise capacity.[20] CPET may help in the diagnosis of earlier stages of HFpEF when resting central hemodynamics may still be within normal limits and to identify patients with peripheral limitations. Research is underway to better define HFpEF phenotypes and management strategies.

LIMITATIONS OF CPET STANDARDS

Limited Data in Women

Many of the research studies on which the prognostic significance of CPET results are based were conducted primarily in men. Women typically have a lower VO_2 max than men due in part to lower average muscle mass, smaller hearts and therefore lower stroke volume, and lower blood hemoglobin mass and concentration.[21] Current guidelines do not account for these differences. Additional studies are warranted to better clarify sex-based differences across age groups and how cardiopulmonary function may be altered due to hormone-related changes during pregnancy, menopause, and in transgender individuals.

Body Fat Ratio

Obesity, which is rising in prevalence, impacts CPET results as body fat is less metabolically active than muscle mass. While scaling VO_2 max to body mass allows for comparisons between individuals, scaling to body mass will result in a lower value in heavier individuals regardless of body composition as well as those with higher percentage fat mass, including women.[21,22] This lower scaled value may then misrepresent cardiorespiratory capacity, even though it does accurately reflect the impact of body mass on functional capacity. Using fat-free mass (i.e., lean body mass) instead of total body mass to scale VO_2 may allow for better characterization of cardiorespiratory performance and it may enhance discrimination of risk for major adverse cardiovascular events.[23]

Obesity results in additional cardiac stress and muscle mass development to perform activities of daily living. As hearts are typically proportional to body size at ideal body weight, the development of obesity results in a heart that is smaller and must work harder to support a larger body. Weight loss studies following bariatric surgery demonstrate a decline in both fat and lean body mass, as well as a decline in absolute VO_2 max.[24-28] Despite no evidence of aerobic gain (thought to be due in part to lower lean body mass following substantial weight loss), exercise tolerance may improve in these patients due to lower energy demand to perform dynamic exercise (by having to move less weight through space), improved exercise capacity, and more efficient ventilatory work.[27]

Medications

Certain classes of medications may diminish the prognostic value of specific CPET measures. For example, beta-blockers will reduce VO_2 max. As a result, practitioners will need to increase their reliance on other measures from the study. It is imperative to consider a patient's complete medication list, how each medication may impact testing results, and whether or not holding a medication prior to testing would improve the study quality without increasing patient risk.

Peripheral Limitations

While cardiac output is the main limitation to oxygen uptake in most individuals, peripheral factors also contribute to reduced VO_2 max and lower cardiorespiratory fitness. The peripheral component of VO_2 is reflected in the arteriovenous oxygen difference (a–vO_2 difference), which is the amount of oxygen extracted and utilized by tissues to sustain a given level of activity. Although the mechanisms behind peripheral limitations in oxygen uptake and utilization are incompletely understood, they may include a combination of lower capillary density in skeletal muscle, atherosclerosis, endothelial dysfunction, blood flow redistribution to less active muscles or other adjacent tissues, and mitochondrial dysfunction.[29-37] Orthopedic injuries may result in lower cardiorespiratory fitness due to skeletal muscle loss, myalgias, arthralgias, and/or radiculopathies. In a subset of patients with HFpEF, lower a–vO_2 difference correlates with exercise intolerance and has been shown to improve with exercise training.[34,35] Similarly, aerobic exercise in patients with peripheral arterial disease has been demonstrated to lead to improvements in endothelial dysfunction and skeletal muscle metabolism.[38,39]

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Congenital Heart Disease

CPET has important prognostic and diagnostic value in adults with congenital heart disease. These patients often have limitations in both cardiac and pulmonary function, which makes the assessment of dyspnea on exertion particularly challenging. Interpretation of the data can be complex as there is no clear standard for CPET performance in patients with congenital heart disease.[40] Numerous evaluations have shown that VO_2 performance varies substantially by underlying cardiac anatomy as well as the era of intervention.[41] In the absence of definitive predictive data, serial testing is useful to determine the timing of interventions, strategies for competitive sports participation, or the basis for exercise prescriptions.

Conclusion

CPET provides a comprehensive, integrated approach to evaluating a patient's exercise capacity with objective diagnostic and prognostic information. These valuable insights can identify therapeutic targets across multiple organ systems and shape a patient's clinical care.

Disclosures

Author disclosures are available at evidence.nejm.org.

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