CME CREDIT **EDUCATIONAL OBJECTIVE:** Readers will consider cardiopulmonary exercise testing to investigate the cause of unexplained shortness of breath on exertion

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Cardiopulmonary exercise testing: A contemporary and versatile clinical tool

ABSTRACT

Cardiopulmonary exercise testing (CPET) helps in detecting disorders of the cardiovascular, pulmonary, and skeletal muscle systems. It has a class I (indicated) recommendation from the American College of Cardiology and American Heart Association for evaluating exertional dyspnea of uncertain cause and for evaluating cardiac patients being considered for heart transplant. Advances in hardware and software and ease of use have brought its application into the clinical arena to the point that providers should become familiar with it and consider it earlier in the evaluation of their patients.

KEY POINTS

Technological advances and ease of use have brought CPET out of specialized centers and into the realm of daily clinical practice.

CPET is a versatile test that has unique ability to assess cardiopulmonary and metabolic responses to exercise that can reflect underlying pathology.

CPET has established value in assessing patients with exertional dyspnea and can guide clinical decision-making and help streamline patient management by focusing on the cause or excluding pathology.

CPET has useful prognostic capabilities in patients with heart failure to guide medical treatment or referral for advanced therapies.

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Cardiopulmonary exercise testing (CPET) is a versatile tool that can be useful in patient management and clinical decision-making. Many physicians are unfamiliar with it, in part because historically it was cumbersome, done mostly in research or exercise physiology centers, and used mostly in assessing athletic fitness rather than pathologic conditions. In addition, medical schools provide little instruction about it, and hands-on use has typically been relegated to pulmonologists.

Improvements in hardware and software and ease of use have brought this test into the clinical arena to the point that clinicians should consider it earlier in the evaluation of appropriate patients. It now has a class I recommendation (ie, the test is indicated) from the American College of Cardiology and American Heart Association for evaluating exertional dyspnea of uncertain cause and for evaluating cardiac patients being considered for transplant.[1] It also is a powerful prognosticator of outcomes in heart failure patients.

CARDIOPULMONARY EXERCISE TESTING MADE SIMPLE

CPET is the analysis of gas exchange during exercise. Modern systems measure, breath-by-breath, the volume of oxygen taken up (Vo_2), and the volumes of carbon dioxide (Vco_2) and air expired (VE).

Testing can be done with nearly any kind of exercise (treadmill, cycle, arm ergometry), thus accommodating patient or provider preference. Most exercise protocols involve a gradual increase in work rather than increasing stages of

TABLE 1

Selected cardiopulmonary exercise testing variables

Peak Vo_2
Highest oxygen uptake obtained (aerobic capacity)
Values vary widely with age, sex, activity level, weight, and disease (< 20 mL/kg/min in elderly; > 90 in elite athletes)
Nonspecific but starting point for interpretation and stratification
Peak Vo_2 ≥ 85% of predicted is generally favorable; ≤ 14 mL/kg/min carries a poor prognosis in heart failure (≤ 10 if on beta-blockers)

Ventilatory threshold
Point at which anaerobic metabolism increases
Vo_2 at ventilatory threshold typically is 40%–60% of peak Vo_2
A low value is consistent with deconditioning or disease; a high value is consistent with athletic training

V_E/Vco_2 slope
Ventilatory volume/carbon dioxide output; reflects ventilatory efficiency
Normal 25–30
May be slightly elevated in isolation in otherwise healthy elderly patients
Elevated value reflects ventilatory inefficiency or ventilation-perfusion mismatch
Values ≥ 34 indicate clinically significant cardiopulmonary disease (heart failure, pulmonary hypertension, chronic obstructive pulmonary disease
Higher values = worse prognosis

Peak respiratory exchange ratio (Vco_2/Vo_2)
Reflects substrate metabolism
Normal < 0.8 at rest; progressively increases during exercise
Value > 1.1 signifies physiologically maximal response; lower value suggests submaximal effort

Peak heart rate
Varies with age, fitness level, use of beta-blockers
Should increase linearly with ramped increase in work
Peak rate ≥ 85% of predicted is generally favorable

Heart rate reserve
(Maximum heart rate – resting heart rate) divided by (predicted maximum heart rate – resting heart rate)
Reflects chronotropic competence
Normal ≥ 80% if not on beta-blocker; ≥ 62% if on beta-blocker; less than this = chronotropic incompetence

Heart rate recovery
Maximum heart rate minus rate at 1 minute recovery
Recovery ≥ 12 bpm is normal; < 12 is abnormal across all populations; < 6 is threshold in heart failure scoring system

Vo_2/work slope
Oxygen uptake per unit of work
Normal is 10 ± 1.5 mL/min/watt
Validated with cycle ergometry; not valid with treadmill exercise, as unable to calculate specific unit of work
A high slope reflects increased anaerobic demand or high oxygen cost, eg, in obesity or hyperthyroidism; low slope reflects increased anaerobic work, eg, in heart failure or coronary artery disease

O_2-pulse
Oxygen delivered per heart beat; a surrogate for stroke volume
Curvilinear increase with exercise
Norms based on predicted peak Vo_2 and peak heart rate; value ≥ 85% of predicted is favorable
Blunted response or decline suggests ventricular failure; response can be falsely high if heart rate is blunted

End-tidal Pco_2
Reflects perfusion: better cardiac output = better CO_2 diffusion
In heart failure, values > 33 mm Hg at rest and > 36 mm Hg at ventilatory threshold are favorable; low values = poor prognosis

Exercise oscillatory breathing
Abnormal breathing pattern often seen in heart failure; no universal definition
Sustained visible fluctuations in ventilations support a poorer prognosis

Oxygen uptake efficiency slope
Additional logarithmic model of ventilatory efficiency
In heart failure, values < 1.4 carry a poor prognosis

Peak respiratory rate
Rarely exceeds 50/min
High value suggests pulmonary limitation or exceptional effort
Value < 30 suggests submaximal effort

Peak V_E/M_{VV}
Ventilatory reserve: peak exercise ventilations (V_E) divided by predicted or measured maximum voluntary ventilations (M_{VV})
Normal: 15%–20% reserve in most people
May be reduced or absent in elite athletes; reduced reserve suggests pulmonary limitation; excessive value suggests submaximal effort

Adapted from information in references 4–7.

CPET differs from standard stress testing in that the workload 'ramps up,' ie, increases gradually and continuously

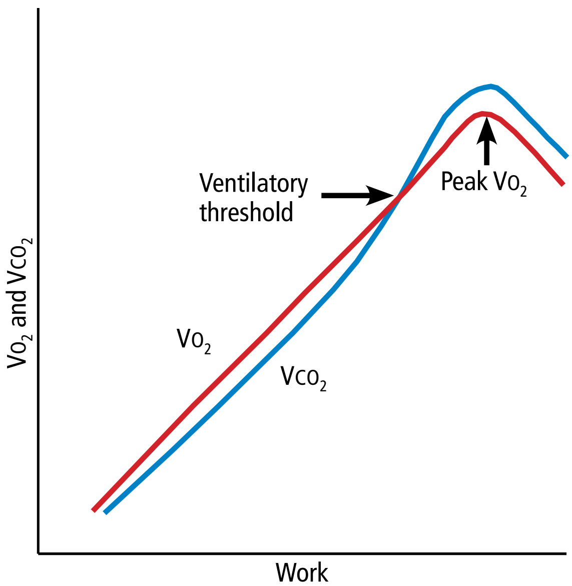

FIGURE 1. Diagram of response to work. Impairment from any cause will lower the peak VO_2 and ventilatory threshold.

work for smooth data collection, and graphical display for optimal test interpretation.

After undergoing baseline screening spirometry, the patient rides a stationary bicycle or walks on a treadmill while breathing through a nonrebreathing mask and wearing electrocardiographic leads, a blood pressure cuff, and a pulse oximeter. The test starts out easy and gets progressively harder until the patient fatigues, reaches his or her predicted peak VO_2, or, as in any stress test, experiences any other clinical indication for stopping, such as arrhythmias, hypotension, or symptoms (rare). We advise patients to wear comfortable workout clothes, and we ask them to try as hard as they can. The test takes about 10 to 15 minutes. Patients are instructed to take all of their usual medications, including beta-blockers, unless advised otherwise at the discretion of the supervising physician.

What the numbers mean

Table 1 lists common CPET variables; **Table 2** lists common patterns of results and what they suggest. Other reviews further discuss disease-specific CPET patterns.[2–5]

Peak VO_2. As the level of work increases, the body needs more oxygen, and oxygen consumption (VO_2) increases in a linear fashion up to a peak value (**Figure 1**). Peak VO_2 is the central variable in CPET. Whereas elite athletes have high peak VO_2 values, patients with exercise impairment from any cause have lower values, and average adults typically have results in the middle. Peak VO_2 can be expressed in absolute terms as liters of oxygen per minute, in indexed terms as milliliters of oxygen per kilogram of body weight per minute, and as a percentage of the predicted value.

Ventilatory threshold. Before people reach their peak VO_2, they reach a point where the work demand on the muscles exceeds the oxygen that is being delivered to them, and their metabolism becomes more anaerobic. This point is called the anaerobic threshold, or more precisely the ventila-

TABLE 2

What cardiopulmonary exercise test patterns suggest

Nonspecific: suggest significant cardiopulmonary or metabolic impairment of any sort
Peak VO_2 < 80% of predicted
VE/VCO_2 slope > 34
Ventilatory (anaerobic) threshold < 40% of peak VO_2

Deconditioning
Low-normal peak VO_2
Low ventilatory (anaerobic) threshold
Absence of any other abnormal responses

Obesity
Increased VO_2/work slope
Indexed peak VO_2 (mL/kg/min) less than predicted
Absolute VO_2 (L/min) normal or greater than predicted
Oxygen indexed to lean body mass normal or greater than predicted

Cardiac limitations
Oxygen pulse (O_2-pulse) < 80% predicted or flattened or falling curve
Chronotropic incompetence
Heart rate recovery ≤ 12 beats per minute after 1 minute of recovery
Standard electrocardiographic criteria for ischemia

Pulmonary limitations
Peak exercise respiratory rate > 50 per minute
Ventilatory reserve (peak VE/MVV) < 15%
Oxygen desaturation by pulse oximetry
Abnormal results on pretest screening spirometry
Abnormal exercise flow-volume loops

Muscular disease
Submaximal cardiac and respiratory responses
Ventilatory (anaerobic) threshold < 40% of peak VO_2
Elevated lactate at any given level of submaximal work

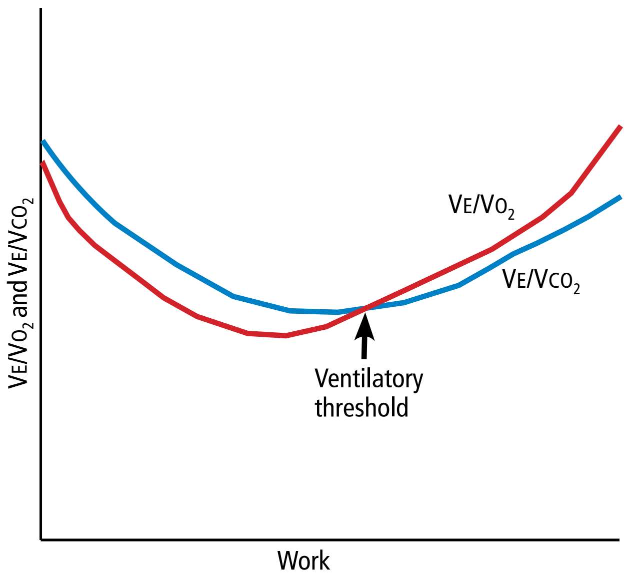

FIGURE 2. One method of determining the ventilatory threshold is to determine the intersection of the V_E/V_{O_2} and V_E/V_{CO_2} curves.

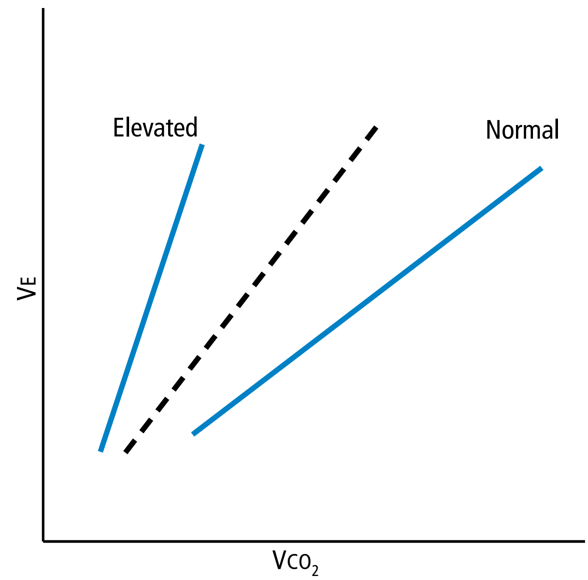

FIGURE 3. The V_E/V_{CO_2} slope is elevated in advanced heart failure and other hemodynamically significant cardiopulmonary conditions.

tory threshold. In states of deconditioning or disease, this threshold is often lower than predicted. It can be detected either directly by measuring blood lactate levels or, more often, indirectly from the V_{O_2}, V_{CO_2}, and V_E data (**Figure 2**).

Gas analysis data augment information gathered from conventional stress tests

V_E/V_{CO_2} slope. As exercise impairment advances, ventilatory efficiency worsens. Put simply, the demands of exercise result in greater ventilatory effort at any given level of work. This is a consequence of ventilation-perfusion mismatching from a milieu of metabolic, ventilatory, and cardiac dysregulation that accompanies advanced cardiopulmonary or metabolic disease.[6,7] The most validated CPET variable reflecting this is the minute ventilation-carbon dioxide relationship (V_E/V_{CO_2} slope) (**Figure 3**).

Coupled with other common CPET variables and measures such as screening spirometry, electrocardiography, heart and respiratory rate responses, pulse oximetry, and blood pressure, the V_E/V_{CO_2} allows for a detailed and integrated assessment of exercise performance.

USING CPET TO EVALUATE EXERTIONAL DYSPNEA

Shortness of breath, particularly with exertion, is a common reason patients are referred to internists, pulmonologists, and cardiologists. It is a nonspecific symptom for which a precise cause can be elusive. Possible causes range from physical deconditioning due to obesity to new or progressive cardiopulmonary or muscular disease.

If conventional initial studies such as standard exercise testing, echocardiography, or spirometry do not definitively identify the problem, CPET can help guide additional investigation or management. Any abnormal patterns seen, together with the patient's clinical context and other test results, can give direction to additional evaluation.

Table 2 outlines various CPET patterns that can suggest clinically significant cardiac, pulmonary, or muscle disorders.[8–13] Alternatively, normal responses reassure the patient and clinician, since they suggest the patient does not have clinically significant disease.

Case 1: Obesity and dyspnea

You evaluate a 53-year-old mildly obese man for dyspnea. Cardiology evaluation 1 year earlier included normal transthoracic and stress echocardiograms. He is referred for CPET.

His peak V_{O_2} is low in indexed terms (22.3 mL/kg/min; 74% of predicted) but 90% of predicted in absolute terms (2.8 L/min), reflecting the contribution of his obesity. His ventilatory threshold is near the lower end of normal (50% of peak $\dot{V}O_2$), and all other findings are normal. You conclude his dyspnea is due to deconditioning and obesity.

Case 2: Diastolic dysfunction

You follow a normal-weight 65-year-old woman who has long-standing exertional dyspnea. Evaluation 1 year ago included an echocardiogram showing a normal left ventricular ejection fraction and grade II (moderate) diastolic dysfunction, a normal exercise stress test (details were not provided), normal pulmonary function testing, and high-resolution computed tomography of the chest. She too is referred for CPET.

The findings include mild sinus tachycardia at rest and low peak $\dot{V}O_2$ (23.7 mL/kg/min; 69% of predicted). The $\dot{V}E/\dot{V}CO_2$ slope is substantially elevated at 43. Other measures of cardiopulmonary impairment and ventilatory inefficiency such as the end-tidal PCO_2 response, oxygen uptake efficiency slope, and oxygen-pulse relationship (O_2-pulse, a surrogate for stroke volume) are also abnormal. In clinical context this suggests diastolic dysfunction or unappreciated pulmonary hypertension. You refer her for right heart catheterization, which confirms findings consistent with diastolic dysfunction.

Case 3: Systemic sclerosis

A 64-year-old woman with systemic sclerosis, hypertension, diabetes, and sleep apnea is referred for CPET evaluation of dyspnea. Echocardiography 6 months ago showed a normal left ventricular ejection fraction and moderate diastolic dysfunction.

She undergoes screening spirometry. Results are abnormal and suggest restrictive disease, borderline-low breathing reserve, and low peak $\dot{V}O_2$ (20 mL/kg/min; 71% of predicted). She also has chronotropic incompetence (peak heart rate 105 beats per minute; 67% of predicted). These findings are thought to be manifestations of her systemic sclerosis. You refer her for both pulmonary and electrophysiology consultation.

Case 4: Mitral valve prolapse

A generally healthy 73-year-old woman undergoes echocardiography because of a murmur. Findings reveal mitral valve prolapse and mitral regurgitation, which is difficult to quantify. She is referred for CPET as a noninvasive means of assessing the hemodynamic significance of her mitral regurgitation.

Her overall peak $\dot{V}O_2$ is low (15 mL/kg/min). The $\dot{V}E/\dot{V}CO_2$ slope is elevated at 32 (normal < 30), and end-tidal PCO_2 response is also abnormal. The recovery heart rate is also abnormally elevated. Collectively, these findings indicate that her mitral valve regurgitation is hemodynamically significant, and you refer her for mitral valve surgery.

TABLE 3

Cardiopulmonary exercise testing scoring system for patients with heart failure

Variable	Value	Points
Ventilation/carbon dioxide ($\dot{V}E/\dot{V}CO_2$) slope	≥ 34	7
Heart rate recovery[a]	≤ 6 bpm	5[b]
Oxygen uptake efficiency slope	≤ 1.4	2
Peak $\dot{V}O_2$	≤ 14 mL/kg/min	2

Score > 15 points: annual mortality rate 12.2%; relative risk > 9 for transplant, left ventricular assist device, or cardiac death.
Score < 5 points: annual mortality rate 1.2%.
[a] Maximum heart rate minus heart rate at 1 minute in recovery.
[b] 2 points if on a beta-blocker.

Information from reference 24.

CPET'S ROLE IN HEART FAILURE

Over 2 decades ago, the direct measure of peak $\dot{V}O_2$ during exercise was found to be an important prognosticator for patients with advanced heart failure and thus became a conventional measure for stratifying patients most in need of a heart transplant.[14] To this day, a peak $\dot{V}O_2$ of 14 mL/kg/min remains a prognostic threshold—values this low or less carry a poor prognosis.

Additional CPET variables are prognostically useful, both independently and with each other. Many of them reflect the ventilatory and metabolic inefficiencies that result from the extensive central and peripheral pathophysiology seen in heart failure.[7,15–17]

TABLE 4

Suggested components of a cardiopulmonary exercise testing report

History and clinical context
Relevant medical history, specifics of exercise intolerance, prior exercise test results, relevant studies (eg, echocardiography, pulmonary function tests, complete blood cell count), relevant medications (eg, beta-blockers)

Resting data
Weight, body mass index, percent body fat, heart rate, blood pressure, pulse oximetry, screening spirometry, hemoglobin, electrocardiogram

Exercise protocol
Treadmill, cycle, or arm geometry; rate of ramp increase; peak workload

Reason for test termination
Fatigue, symptoms, abnormal electrocardiographic findings

Subjective responses
Peak rating of perceived exertion
Specific symptoms and comparison to index symptoms

Validity of test
Peak respiratory exchange ratio ≥ 1.1, rating of perceived exertion ≥ 17

Oxygen responses
Peak $\dot{V}O_2$ relative to norms, $\dot{V}O_2$ per ideal weight, $\dot{V}O_2$ at ventilatory threshold

Specific cardiac responses
Reflected in exercise and recovery heart rate, blood pressure, O_2-pulse, electrocardiogram

Specific pulmonary responses
Peak respiratory rate, ventilations; ventilatory reserve ($\dot{V}E/MVV$), pulse oximetry, blood gases

Markers of central cardiopulmonary inefficiency
$\dot{V}E/\dot{V}CO_2$ slope, end-tidal PCO_2 responses, exercise oscillatory breathing, oxygen uptake efficiency slope

Summary statement
The bottom line for referring provider; normal vs abnormal; if abnormal, suggest differential diagnoses; CPET score for heart failure (see **Table 3**)

Recommendations
To guide referring provider
Reassurance if normal
Formal exercise program for fitness or weight loss
Suggest adjunctive tests if abnormal (eg, formal spirometry, right heart catheterization, chest computed tomography, natriuretic peptide measurement)
Beta-blocker modification or pacemaker if chronotropically incompetent

An elevated $\dot{V}E/\dot{V}CO_2$ slope is a strong predictor of adverse outcomes for patients with heart failure with either reduced or preserved ejection fraction.[18,19] Other recognized prognostic indicators include[20–23]:

Low end-tidal PCO_2

Exercise oscillatory breathing

Low oxygen uptake efficiency slope. All of these are readily provided in the reports of modern CPET systems. Explanations are in **Table 1**.

Collectively, these variables are strong predictors of outcomes in heart failure patients in terms of survival, adverse cardiac events, or progression to advanced therapy such as a left ventricular assist device or transplant. A multicenter consortium analyzed CPET results from more than 2,600 systolic heart failure patients and devised a scoring system for predicting outcomes (**Table 3**). This scoring system is a recommended component of the standard evaluation in patients with advanced heart failure.[24]

EXERCISE TEST REPORTING

Currently there is no universal reporting format for CPET. Using a systematic approach such as the one proposed by Guazzi et al[5] can help assure that abnormal values and patterns in all areas will be identified and incorporated in test interpretation. **Table 4** lists suggested components of a CPET report and representative examples.

OTHER USES OF EXERCISE TESTING

CPET has also been found useful in several other clinical conditions that are beyond the scope of this review. These include pulmonary hypertension,[25] differentiation of pathologic vs physiologic hypertrophy of the left ventricle,[26] preclinical diastolic dysfunction,[27,28] congenital heart disease in adults,[29] prediction of postoperative complications in bariatric surgery,[30] preoperative evaluation for lung resection and pectus excavatum,[31,32] hemodynamic impact of mitral regurgitation,[33] and mitochondrial myopathies.[34]

COST-EFFECTIVENESS UNKNOWN

The Current Procedural Terminology code for billing for CPET is 94621 (complex pulmonary stress test). The technical fee is $1,605, and the professional fee is $250. The allowable charges vary according to insurer, but under

Medicare A and B, the charges are $258.93 and $70.65, respectively, of which patients typically must copay 20%. Total relative value units are 4.60, of which 1.95 are work relative value units.

The cost-effectiveness of CPET has not been studied. As illustrated in the case examples, patients often undergo numerous tests before CPET. While one might infer that CPET could streamline testing and management if done sooner in disease evaluation, this hypothesis has not been adequately studied, and further research is needed to determine if and how doing so will affect overall costs.

IMPLICATIONS FOR PRACTICE

Newer hardware and software have made CPET more available to practicing clinicians. CPET has proven value in evaluating patients with exertional dyspnea. If first-line evaluation has not revealed an obvious cause of a patient's dyspnea, CPET should be considered. This may avoid additional testing or streamline subsequent evaluation and management. CPET also has an established role in risk stratification of those with heart failure.

The clinical application of CPET continues to evolve. Future research will continue to refine its diagnostic and prognostic abilities in a variety of diseases. Most major hospitals and medical centers have CPET capabilities, and interested practitioners should seek out those experienced in test interpretation to increase personal familiarity and to foster appropriate patient referrals.

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