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
- 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.

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 (VO₂), and the volumes of carbon dioxide (VCO₂) 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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
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<tbody>
<tr>
<td><strong>Peak VO₂</strong></td>
<td>Highest oxygen uptake obtained (aerobic capacity) Values vary widely with age, sex, activity level, weight, and disease (&lt; 20 mL/kg/min in elderly; &gt; 90 in elite athletes) Nonspecific but starting point for interpretation and stratification Peak VO₂ ≥ 85% of predicted is generally favorable; ≤ 14 mL/kg/min carries a poor prognosis in heart failure (&lt; 10 if on beta-blockers)</td>
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<tr>
<td><strong>Ventilatory threshold</strong></td>
<td>Point at which anaerobic metabolism increases VO₂ at ventilatory threshold typically is 40%–60% of peak VO₂ A low value is consistent with deconditioning or disease; a high value is consistent with athletic training</td>
</tr>
<tr>
<td><strong>VE/VO₂ slope</strong></td>
<td>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</td>
</tr>
<tr>
<td><strong>Peak respiratory exchange ratio (VCO₂/VO₂)</strong></td>
<td>Reflects substrate metabolism Normal &lt; 0.8 at rest; progressively increases during exercise Value &gt; 1.1 signifies physiologically maximal response; lower value suggests submaximal effort</td>
</tr>
<tr>
<td><strong>Peak heart rate</strong></td>
<td>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</td>
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<tr>
<td><strong>Heart rate reserve</strong></td>
<td>(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</td>
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<tr>
<td><strong>Heart rate recovery</strong></td>
<td>Maximum heart rate minus rate at 1 minute recovery Recovery ≥ 12 bpm is normal; &lt; 12 is abnormal across all populations; &lt; 6 is threshold in heart failure scoring system</td>
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<tr>
<td><strong>VO₂/work slope</strong></td>
<td>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</td>
</tr>
<tr>
<td><strong>O₂-pulse</strong></td>
<td>Oxygen delivered per heart beat; a surrogate for stroke volume Curvilinear increase with exercise Norms based on predicted peak VO₂, 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</td>
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<tr>
<td><strong>End-tidal PCO₂</strong></td>
<td>Reflects perfusion: better cardiac output = better CO₂ diffusion In heart failure, values &gt; 33 mm Hg at rest and &gt; 36 mm Hg at ventilatory threshold are favorable; low values = poor prognosis</td>
</tr>
<tr>
<td><strong>Exercise oscillatory breathing</strong></td>
<td>Abnormal breathing pattern often seen in heart failure; no universal definition Sustained breathing fluctuations in ventilations support a poorer prognosis</td>
</tr>
<tr>
<td><strong>Oxygen uptake efficiency slope</strong></td>
<td>Additional logarithmic model of ventilatory efficiency In heart failure, values &lt; 1.4 carry a poor prognosis</td>
</tr>
<tr>
<td><strong>Peak respiratory rate</strong></td>
<td>Rarely exceeds 50/min High value suggests pulmonary limitation or exceptional effort Value &lt; 30 suggests submaximal effort</td>
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<tr>
<td><strong>Peak VO₂/MVV</strong></td>
<td>Ventilatory reserve: peak exercise ventilations (VE) divided by predicted or measured maximum voluntary ventilations (MVV) 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</td>
</tr>
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Adapted from information in references 4–7.
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.

**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/VO\(_2\) 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 1.** Diagram of response to work. Impairment from any cause will lower the peak VO\(_2\) and ventilatory threshold.
Gas analysis data augment information gathered from conventional stress tests

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 VO₂, VCO₂, and VE data (Figure 2).

**VE/VCO₂ 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 (Ve/Vco₂ 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 Ve/Vco₂ 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 VO₂ is low in indexed terms (22.3 mL/kg/min; 74% of predicted) but 90% of predicted in absolute terms (2.8 L/min), re-
reflecting the contribution of his obesity. His ventilatory threshold is near the lower end of normal (50% of peak \( \text{VO}_2 \)), 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 \( \text{VO}_2 \) (23.7 mL/kg/min; 69% of predicted). The \( \text{Ve}/\text{Vco}_2 \) slope is substantially elevated at 43. Other measures of cardiopulmonary impairment and ventilatory inefficiency such as the end-tidal \( \text{PCO}_2 \) response, oxygen uptake efficiency slope, and oxygen-pulse relationship (\( \text{O}_2 \)-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 \( \text{VO}_2 \) (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 \( \text{VO}_2 \) is low (15 mL/kg/min). The \( \text{Ve}/\text{Vco}_2 \) slope is elevated at 32 (normal < 30), and end-tidal \( \text{PCO}_2 \) 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.

### CPET’s Role in Heart Failure
Over 2 decades ago, the direct measure of peak \( \text{VO}_2 \) 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 \( \text{VO}_2 \) 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.\(^{7,15-17}\)

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**TABLE 3**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
<th>Points</th>
</tr>
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<tbody>
<tr>
<td>Ventilation/carbon dioxide (Ve/Vco₂) slope</td>
<td>≥ 34</td>
<td>7</td>
</tr>
<tr>
<td>Heart rate recovery</td>
<td>≤ 6 bpm</td>
<td>5(^b)</td>
</tr>
<tr>
<td>Oxygen uptake efficiency slope</td>
<td>≤ 1.4</td>
<td>2</td>
</tr>
<tr>
<td>Peak ( \text{VO}_2 )</td>
<td>≤ 14 mL/kg/min</td>
<td>2</td>
</tr>
</tbody>
</table>

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%.

\(^*\) Maximum heart rate minus heart rate at 1 minute in recovery.

\(^b\) 2 points if on a beta-blocker.

Information from reference 24.
An elevated \( \text{Ve/VCO}_2 \) 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 \( \text{PCO}_2 \)
- 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
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.

REFERENCES


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