Cardiopulmonary Exercise Testing in Heart Failure

Rajeev Malhotra, MD,a Kristian Bakken, NP,b Emilia D’Elia, MD, PhD,c,d Gregory D. Lewis, MD2,b

ABSTRACT

Exercise intolerance, indicated by dyspnea and fatigue during exertion, is a cardinal manifestation of heart failure (HF). Cardiopulmonary exercise testing (CPET) precisely defines maximum exercise capacity through measurement of peak oxygen uptake (VO₂). Peak VO₂ values have a critical role in informing patient selection for advanced HF interventions such as heart transplantation and ventricular assist devices. Oxygen uptake and ventilatory patterns obtained during the submaximal portion of CPET are also valuable to recognize because of their ease of ascertainment during low-level exercise, relevance to ability to perform activities of daily living, independence from volitional effort, and strong relationship to prognosis in HF. The ability of peak VO₂ and other CPET variables to be measured reproducibly and to accurately reflect HF severity is increasingly recognized and endorsed by scientific statements. Integration of CPET with invasive hemodynamic monitoring and cardiac imaging during exercise provides comprehensive characterization of multisystem reserve capacity that can inform prognosis and the need for cardiac interventions. Here, we review both practical aspects of conducting CPETs in patients with HF for clinical and research purposes as well as interpretation of gas exchange patterns across the spectrum of preclinical HF to advanced HF. (J Am Coll Cardiol HF 2016;4:607-16)

M I N I - F O C U S I S S U E : E X E R C I S E A N D H E A R T F A U L E R

S T A T E - O F - T H E - A R T P A P E R

Cardiopulmonary Exercise Testing in Heart Failure

In patients with heart failure (HF), the functional reserve capacity of the integrated metabolic machinery required to perform exercise is impaired at multiple levels. Starting with oxygen (O₂) uptake in the lungs, the requisite increase in ventilation is challenged by frequently abnormal lung mechanics and diffusing capacity. The need for increased convective O₂ transport to skeletal muscle is limited by prevalent anemia as well as abnormal cardiac output (CO) augmentation arising from chronotropic incompetence, inability to augment ventricular contractility, and functional mitral regurgitation. Shortening of diastole during heart rate (HR) elevation and increased venous return can lead to sharp increases in filling pressures during exercise; impaired vasoactivity further contributes to dynamic ventriculovascular uncoupling.

Upon delivery of O₂ to the periphery, diffusive O₂ conductance and utilization is limited by reduced capillary density, impaired sympatholysis, decreased mitochondrial volume, and selective loss of type 1 muscle fibers having oxidative fatigue-resistant properties (1). Finally, exaggerated ventilatory responses to exercise signaled through intramuscular afferents (i.e., ergoreflex signaling) are present in HF. It therefore comes as no surprise that exercise intolerance is the cardinal manifestation of HF. Careful measurement of ventilatory and O₂ uptake patterns in HF can quantify disease severity and prognosis while shedding light on relative contributions of organ systems to exercise intolerance.

From the aCardiology Division, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; bPulmonary and Critical Care Unit of the Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; cCardiovascular Department, Hospital Papa Giovanni XXIII, Bergamo Italy; and the dUniversity of Pavia, Pavia, Italy. Dr. Malhotra is supported by the KO8HL121501 grant of the National Heart, Lung, and Blood Institute (NHLBI) and the Wild Family Foundation; and has received consultant fees from Mallinckrodt, Inc. Dr. Lewis is supported by the American Heart Association Award 15GPSGC24800006, NHLBI R01 HL131029-01, and the Hassenberg Clinical Scholar Award; and has received research grant support from Abbott Vascular, Stealth Peptides, Biogen, Pfizer, Shape Medical Systems, and Novartis. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received June 17, 2015; revised manuscript received February 26, 2016, accepted March 2, 2016.
Cardiopulmonary exercise testing (CPET) provides breath-by-breath gas exchange measures of 3 variables: O₂ uptake (VO₂), carbon dioxide output (VCO₂), and ventilation (VE). These 3 measures are used to derive various other gas exchange patterns that reflect organ-specific maladaptive responses to exercise, particularly when CPET is coupled with standard exercise variables (HR, blood pressure, electrocardiogram), cardiac imaging, and invasive hemodynamic measurements during exercise.

Recent consensus statements and guideline documents have provided an overall summary of the utility of CPET (2–4). An approach to using CPET in patients with HF is provided in the Online Appendix. Here, we provide an overview on interpretation of CPET with a specific focus on the HF population. Table 1 summarizes the current clinical indications for performing CPET. Online Table 1 describes gas exchange patterns easily and reproducibly derived from non-invasive CPET, their physiologic relevance, and their clinical significance in HF.

**O₂ UPTAKE VARIABLES**

**PEAK VO₂.** Measured VO₂ during a maximal symptom-limited CPET is the most objective method to assess functional capacity and consists of the following components (2):

\[ \text{Peak VO₂} = \text{HR}_{\text{MAX}} \times \text{SV}_{\text{MAX}} \times (\text{CaO₂} - \text{CVO₂})_{\text{MAX}} \]

where SV is stroke volume, and (CaO₂ - CVO₂) is the net oxygen extraction of the peripheral tissues and is dependent on the hemoglobin concentration (Figure 1). Peak VO₂ is an important predictor of prognosis in HF patients (2). Mancini and colleagues (5) conducted a landmark study in 114 ambulatory patients with HF and reduced ejection fraction (HFpEF) that established a peak VO₂ cutoff of ≤14 ml/kg/min as a criterion for which 1-year survival was significantly lower than that achieved through transplantation (i.e., 70%). In contrast, individuals with a peak VO₂ >14 ml/kg/min had 6% 1-year mortality, suggesting that transplantation could be safely deferred in this subgroup of symptomatic HF patients. There was no difference in resting left ventricular ejection fraction or cardiac index between the groups. Multivariate analysis identified peak VO₂ as the best predictor of survival in this HF population. Recent studies have demonstrated that peak VO₂ potently risk stratifies the contemporary HF (HFrEF and HF and preserved ejection fraction [HFpEF]) populations: Weber classes A, B, C, and D corresponding to peak VO₂ >20, 16 to 20, 10 to 16, and <10 ml/kg/min was associated with 3-year transplant and mechanical circulatory support-free survival of 97%, 93%, 83%, and 64%, respectively (Central Illustration) (6). In the HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) trial, of multiple CPET variables that were assessed, peak VO₂, percent predicted peak VO₂, and exercise duration had the strongest ability to predict mortality in HFrEF (7). Peak VO₂ retains its prognostic significance in HFpEF patients on beta-blockers (8,9) and when natriuretic peptides and other clinical variables are considered (10). Peak VO₂ is also an important predictor of mortality in HF patients with preserved left ventricular ejection fraction (HFpEF) (11,12).

Peak VO₂ is influenced by noncardiac factors such as age, gender, and muscle mass (13); therefore, it is appropriate to interpret peak VO₂ normalized to age, gender, and weight-based normative values (14). The Wasserman-Hansen percent-predicted equation offers optimal HF prognostication among peak VO₂ percent-predicted equations, with a peak VO₂ <47% of predicted serving as an optimal cutpoint for determining mortality risk in HF (15). Obesity reduces VO₂ in ml/kg/min out of proportion to HF severity and has led to examination of peak VO₂ corrected for lean body mass (LBM), where LBM was defined as: actual body weight × (1 – % body fat/100) in ml/min/kg of LBM. When corrected for LBM, a peak VO₂ ≥19 ml/kg/min outperformed standard peak VO₂ ≥14 ml/kg/min in predicting transplant-free survival within a HFpEF population with a 37% prevalence of obesity (as defined by body mass index [BMI] >30 kg/m²) (16).

**SUBMAXIMAL O₂ UPTAKE MEASUREMENTS.** Interestingly, among patients with HF, submaximal exercise gas exchange variables have emerged that rival or even exceed the prognostic utility of peak VO₂ (17–19). Submaximal CPET variables (Online Table 1) are particularly attractive to study based on ease of

<table>
<thead>
<tr>
<th>TABLE 1 Clinical Indications for Cardiopulmonary Exercise Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Scenario</strong></td>
</tr>
<tr>
<td>Unexplained or multifactorial dyspnea/exercise intolerance</td>
</tr>
<tr>
<td>Established advanced cardiac or pulmonary disease</td>
</tr>
<tr>
<td>Valvular or congenital heart disease</td>
</tr>
<tr>
<td>Initiation of an intervention (clinical trial)</td>
</tr>
</tbody>
</table>
ascertainment during low-level exercise, relevance to ability to perform activities of daily living, independence from volitional exercise effort, and close relationship to prognosis in HF. We recently reported that O2 uptake kinetics, as measured by mean response time (MRT) (Online Table 1, Figure 2A), were only modestly related to peak VO2 and more accurately reflected the ability to augment CO during low-level exercise, indicating its complementary role to peak VO2 in signaling different aspects of cardiac reserve capacity (20). An MRT >60 s was related to reduced exercise right ventricular [RV] ejection fraction (RVEF) and increased transpulmonary gradient-CO slope, which supports the notion that MRT reflects RV-pulmonary vascular function during exercise (20). O2 uptake efficiency slope (OUES) (Figure 2F), which is the relationship between VO2 and log VE throughout exercise, is highly reproducible; differs by <2% if derived from 75%, 90%, or 100% of exercise duration; and outperformed peak VO2 in a multivariate analysis of predictors of outcome in 243 HFREF patients, conferring an ~2-fold increase in mortality at values <1.47 l/min (21).

VO2 at the ventilatory threshold (VT) is another measurement of O2 uptake that provides valuable information at submaximal exercise (Figure 2B). Gitt and colleagues demonstrated that a VT <11 ml/kg/min was associated with a 5.3-fold increased odds of death at 6 months in 223 patients with HFREF (22). A plateau in the VO2/HR (oxygen pulse) increment (23) indicates failure to augment the stroke volume-Cavo2 (CaO2 – CvO2) product throughout exercise (Figure 2C). Assuming a linear increment in Cavo2 throughout exercise, this pattern suggests dynamic cardiac dysfunction and has been observed with inducible myocardial ischemia (24) as well as RV-pulmonary...
vascular uncoupling (25). Aerobic efficiency describes the relationship of O₂ utilization to the amount of work performed (Figure 2D). A normal VO₂-work rate relationship during the incremental ramp portion of CPET is 10 ± 1.5 ml/min/W (26), with lower values being characteristic of HF with greater than usual dependence on anaerobic metabolism to perform the work of exercise.

Ascertainment of these submaximum O₂ uptake parameters (Online Table 1) becomes particularly important in grading HF severity when patients fail to fulfill criteria for a maximum volitional effort study.
as indicated by a respiratory exchange ratio (RER) < 1.0 to 1.1 (Central Illustration).

VENTILATORY EFFICIENCY AND STABILITY DURING EXERCISE IN HF

The modified alveolar equation describes the determinants of VE/VCO2 slope (27):

$$ \frac{VE}{VCO2} = \frac{863}{1 - \frac{VD}{VT}} \times \frac{1}{\text{PaCO}_2} $$

where $V_D$ is dead space, $V_T$ is tidal volume, and $\text{PaCO}_2$ is arterial CO2 tension. High ventilatory drive in the setting of pulmonary edema leads to reduced $\text{PaCO}_2$, whereas lung hypoperfusion from RV dysfunction results in a worsening of VQ mismatch with elevated fractional dead space. Reduced $\text{PaCO}_2$ and increased fractional dead space, as seen in the previous equation for ventilatory efficiency, cause an abnormal elevation in $VE/VCO2$. Our group showed that impaired ventilatory efficiency (high $VE/VCO2$ slope) was associated with resting and exercise pulmonary vascular resistance and inversely associated with RVEF in HFrEF (28).

Others have related $VE/VCO2$ slope to lower tricuspid
annular plane systolic excursion (TAPSE) (29), reduced RV fractional area change, and impaired RV metabolism (30). \( V_{E}/V_{CO2} \) slope is a powerful predictor of events in HF patients (Central Illustration) (17,31,32). A \( V_{E}/V_{CO2} \) slope >34 to 36 identifies high-risk HF patients and provides prognostic information above and beyond peak VO\(_2\) (13,17). \( V_{E}/V_{CO2} \) slope as a continuous variable also predicted major cardiac events in 448 patients with chronic HF (HFrEF and HFpEF), with a particularly poor prognosis in those with a slope \( \geq 45 \) (17).

Periodic breathing is a form of irregular breathing characterized by regular cyclic variation of ventilation with a period of approximately 1 minute (Figure 3) (33). Periodic breathing, as described by Cheyne and Stokes in the resting state, has been recognized as a feature of HF for almost 2 centuries (34,35). Periodic breathing during exercise, termed exercise oscillatory ventilation (EOV), is present in a large percentage of HF patients (19,36,37). The presence of periodic breathing purports a poor prognosis, whether at rest (38), during sleep (39), or during exercise (EOV) (19,33,36).

A discussion of CPET-based multivariate models for determining prognosis in HF is provided in the Online Appendix.

**CPET WITH INVASIVE HEMODYNAMIC MONITORING.** CPET coupled with hemodynamic assessment using radial and pulmonary arterial catheters enables highly detailed patient phenotyping. First, arterial line placement permits accurate blood pressure assessment and oxyhemoglobin measurement, in contrast to cutaneous pulse oximetry probes that can yield misleading data resulting from probe displacement, peripheral vasoconstriction, or calloused skin (40). Second, simultaneous measurement of VO\(_2\) and arterial as well as mixed venous blood gases during linear ramp exercise permits Fick CO derivation and evaluation of relative increases in each of the 3 components of VO\(_2\) (i.e., HR, SV, and arterio-venous oxygen content difference) (Figure 1).

Two patients with HF and identical peak VO\(_2\) values
1-year survival (41). Measurements of pulmonary stroke volume) was the most powerful predictor of outcomes in HFpEF (42) and HFrEF (43). Hemodynamic measurements during exercise also provide incremental prognostic value to resting hemodynamic measurements. In patients with HFrEF, peak stroke work index (in which stroke work is defined as the product of mean arterial pressure and stroke volume) was the most powerful predictor of 1-year survival (41). Measurements of pulmonary artery pressure (PAP) and pulmonary artery wedge pressure patterns during exercise also independently predict outcomes in HFpEF (42) and HFrEF (43).

We recommend at least 4 measurements of PAP and pulmonary artery wedge pressure along with CO during incremental ramp testing to permit determination of accurate pressure-flow relationships during exercise. A mean PAP-flow relationship $>3$ mm Hg/l/min is increasingly recognized as a robust indicator of a pulmonary hypertensive response to exercise (44). Simultaneous measurement of invasive hemodynamics with PAP responses and gas exchange (i.e., peak VO$_2$ indicative of functional capacity) can significantly aid in decision making regarding surgical interventions for valvular or congenital heart diseases.

Invasive CPET has an emerging role in patient selection for left ventricular assist device (LVAD) implantation and potentially explantation. Invasive CPET probes the ability of the right ventricle to accommodate increased flow and to augment PAP and RV stroke work index throughout exercise. Failure of the right ventricle to progressively augment PAP (i.e., a PAP plateau indicative of RV-PA uncoupling) purports a poor prognosis in HFrEF (43). When coupled with a steep rise in right atrial pressure and a fall in RVEF, the finding of a PAP plateau suggests that the RV is unable to adequately accommodate increased blood flow to the right heart from the LVAD.

In addition to invasive hemodynamic monitoring, CPET can be combined with noninvasive cardiac imaging, and a discussion of this is provided in the Online Appendix.

**SYNOPSIS OF PRACTICAL APPROACH TO CPET INTERPRETATION IN PATIENTS WITH HF.** A synopsis approach to CPET interpretation in HFrEF is provided in the Central Illustration. Because VO$_2$ is the gold standard of cardiorespiratory fitness and is integral to cardiovascular health and functional capacity, assessment of VO$_2$ is central to CPET interpretation. Delineation of volitional effort level should determine whether to focus on peak VO$_2$ or on O$_2$ uptake parameters with values independent of volitional effort (e.g., OUES and VO$_2$ at the VT). Once stratified by O$_2$ uptake parameters, hemodynamic patterns such as failure to augment systolic blood pressure or slow HR recovery (with thresholds between 6 to 12 beats/min shown to incrementally predict HF outcomes) serve to further identify cardiac-specific abnormalities while risk stratifying the HF population. Ventilatory efficiency and stability reflect HF severity, with $V_E$/VCO$_2$ slope in excess of 34 to 36 and the presence of EOV both consistently indicating 1-year mortality rates $>20\%$ (Central Illustration). Conversely, efficient ventilation without EOV, particularly with relatively preserved peak VO$_2$, signals excellent event-free survival. An approach that integrates O$_2$ uptake parameters, hemodynamic responses to exercise, and ventilatory efficiency and stability is what we recommend to risk stratify HF patients, particularly those with intermediate values of peak VO$_2$.

**CPET IN HF RESEARCH.** In designing clinical trials, debate often arises regarding whether to assess functional capacity with CPET or 6-minute walk tests (6MWT). The 6MWT has the advantage of ease of administration and minimal cost. However, CPET, unlike 6MWT, permits assessment of the organ system limiting gas exchange. This is particularly relevant to HFpEF, which tends to occur in older individuals with comorbidities that can result in primary pulmonary mechanical or orthopedic limitations to exercise that obscure ascertainment of a treatment effect from a cardiovascular intervention. CPET also permits precise assessment of volitional effort by determining whether the RER exceeds 1.0 to 1.1 during exercise, indicating that a subject has surpassed his or her anaerobic threshold (14). Furthermore, peak VO$_2$, unlike the 6MWT, has been shown to be immune to a training or familiarization effect with repeated measures in HF (45).

A direct association between improvement in peak VO$_2$ and higher survival rates was observed in a study of ambulatory HFrEF patients listed for cardiac transplantation (46). One meta-analysis found that therapy-induced changes in peak VO$_2$ in HF clinical trials did not uniformly predict the corresponding intervention’s effect on mortality in larger phase 3 trials (47). However, trials in this analysis showing discordant effects of an intervention on
peak VO2 and mortality often included fewer than 50 individuals undergoing CPET evaluation (47). In larger studies (i.e., >200 subjects) using peak VO2 as an endpoint, concordant changes in peak VO2 and mortality were apparent for interventions such as cardiac resynchronization therapy (+/– for change in VO2 and improvement in mortality, respectively) (48,49), isosorbide dinitrate/hydralazine (+/–) (50), and prazosin (-/–) (50). In the HF-ACTION Trial, for every 6% increase in peak VO2 (~1 ml/kg/min), a 5% lower risk of mortality or hospitalization was observed (51). A notable exception is that small trials with beta-blockers in HFpEF (0/+–) demonstrated neutral effects on peak VO2 (52,53) (likely resulting from negative chronotropic effects), yet beta-blockers clearly prolong survival in HFpEF. LVAD therapy may also represent an exception, in that studies looking at improvements in peak VO2 post-implantation have yielded mixed results with small sample sizes (54,55). Furthermore, unlike changes in alternative trial endpoints such as circulating biomarkers or echocardiographic parameters, there is significant intrinsic value in improving exercise capacity for patients.

CPET is commonly used to characterize the physiologic effects of emerging therapies in HF. Treatments currently undergoing evaluation or recently approved by the U.S. Food and Drug Administration for HF, including ivabradine (56), intravenous iron (57), and inorganic nitrate (58), have all been shown to improve peak VO2. As with any measurement, CPET necessitates attention to detail with metabolic cart testing, uniformity across sites coordinated by a core laboratory, appropriate training of CPET laboratory staff, and willingness of subjects to comply with testing. Compliance with repeated maximum exercise testing may be a potential concern, particularly in advanced HF patients, but in a recent HFpEF trial, completion rates for CPET were similar to those for 6MWT and echocardiography at the final study visit (59).

FUTURE DIRECTIONS

We envision an expanding role for CPET in evaluating patients with early stages of HF and conditions that predispose to HF. Population-based studies are currently planned to determine the capacity of CPET measurements to predict future cardiovascular disease, including HF. If CPET measurements are found to predict future HF in the community, they could expand the armamentarium used to evaluate HF risk beyond standard cardiovascular disease risk factors, which do not adequately capture or reflect “cardiac fitness.” That CPET measures can now be measured with handheld devices in an office-based setting will further facilitate the routine use of CPET for initial and serial patient evaluations (60).

Recent studies have begun to combine CPET responses with assessment of circulating metabolites and microRNAs that are rapidly modulated by exercise (61,62). This circulating profile of metabolites and microRNAs during exercise may provide molecular signatures of acute adaptations to exercise that complement CPET and provide insights into early forms of HF and other cardiovascular disease.

Overall, CPET has become an established method for diagnosing cardiopulmonary diseases and their severity, providing prognostic information, gauging response to clinical therapy, and serving as a potential tool for assessing early states of disease to better identify and optimize therapeutic interventions.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Gregory D. Lewis, Heart Failure and Cardiac Transplantation Unit, Massachusetts General Hospital, Bigelow 800, 55 Fruit Street, Boston, Massachusetts 02114. E-mail: glewis@partners.org.
34. Cheyne J. A case of apoplexy in which the fleshly part of the heart was converted in fat. Dublin Hosp Rep 1816;2:216–9.
35. Stokes W. The Disease of the Heart and Aorta. Dublin: Hodges and Smith, 1854.


KEY WORDS cardiopulmonary exercise testing, exercise physiology, heart failure, oxygen uptake, ventilatory efficiency

APPENDIX For supplemental material, references, and a table, please see the online version of this article.