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MINI-FOCUS ISSUE: EXERCISE AND HEART FAILURE

STATE-OF-THE-ART PAPER

Cardiopulmonary Exercise Testing in Heart Failure

Rajeev Malhotra, MD,[a] Kristian Bakken, NP,[b] Emilia D'Elia, MD, PhD,[c,d] Gregory D. Lewis, MD[a,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 (VO_2). Peak VO_2 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 VO_2 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)

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 (O_2) uptake in the lungs, the requisite increase in ventilation is challenged by frequently abnormal lung mechanics and diffusing capacity. The need for increased convective O_2 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 vasoreactivity further contributes to dynamic ventriculovascular uncoupling.

Upon delivery of O_2 to the periphery, diffusive O_2 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 O_2 uptake patterns in HF can quantify disease severity and prognosis while shedding light on relative contributions of organ systems to exercise intolerance.

From the [a]Cardiology Division, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; [b]Pulmonary and Critical Care Unit of the Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; [c]Cardiovascular Department, Hospital Papa Giovanni XXIII, Bergamo Italy; and the [d]University of Pavia, Pavia, Italy. Dr. Malhotra is supported by the K08HL111210 grant of the National Heart, Lung, and Blood Institute (NHLBI) and the Wild Family Foundation; and also has received consultant fees from Mallinckrodt, Inc. Dr. Lewis is supported by the American Heart Association Award 15GPSGC24800006, NHLBI R01 HL131029-01, and the Hassenfeld Clinical Scholar Award; and has received research grant support from Abbott Vascular, Stealth Peptides, Biomarin, 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.

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ABBREVIATIONS AND ACRONYMS

CaO_2 = arterial concentration of oxygen

CvO_2 = mixed venous concentration of oxygen

$CavO_2$ = (CaO_2 - CvO_2) difference

CPET = cardiopulmonary exercise testing

EOV = exercise oscillatory ventilation

MRT = mean response time

OUES = oxygen uptake efficiency slope

PAP = pulmonary artery pressure

PAWP = pulmonary artery wedge pressure

RER = respiratory exchange ratio

VCO_2 = carbon dioxide output

VE = ventilation

VO_2 = oxygen uptake

Cardiopulmonary exercise testing (CPET) provides breath-by-breath gas exchange measures of 3 variables: O_2 uptake (VO_2), carbon dioxide output (VCO_2), and ventilation (V_E). 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 noninvasive CPET, their physiologic relevance, and their clinical significance in HF.

O_2 UPTAKE VARIABLES

PEAK VO_2. Measured VO_2 during a maximal symptom-limited CPET is the most objective method to assess functional capacity and consists of the following components (2):

$$\text{Peak } VO_2 = HR_{MAX} \times SV_{MAX} \times (CaO_2\text{-}CvO_2)_{MAX}$$

where SV is stroke volume, and (CaO_2 - CvO_2) is the net oxygen extraction of the peripheral tissues and is dependent on the hemoglobin concentration (**Figure 1**). Peak VO_2 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 (HFrEF) that established a peak VO_2 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 VO_2 >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 VO_2 as the best predictor of survival in this HF population. Recent studies have demonstrated that peak VO_2 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 VO_2 >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 VO_2, percent predicted peak VO_2, and exercise duration had the strongest ability to predict mortality in HFrEF (7). Peak VO_2 retains its prognostic significance in HFrEF patients on beta-blockers (8,9) and when natriuretic peptides and other clinical variables are considered (10). Peak VO_2 is also an important predictor of mortality in HF patients with preserved left ventricular ejection fraction (HFpEF) (11,12).

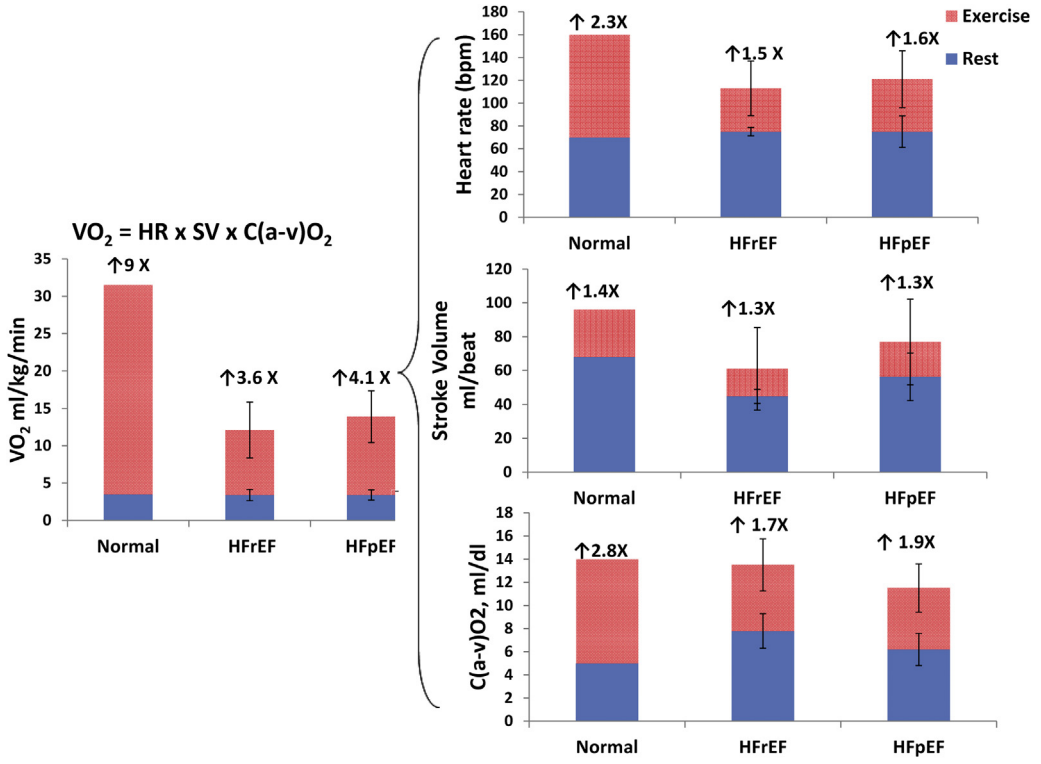
Peak VO_2 is influenced by noncardiac factors such as age, gender, and muscle mass (13); therefore, it is appropriate to interpret peak VO_2 normalized to age, gender, and weight-based normative values (14). The Wasserman-Hansen percent-predicted equation offers optimal HF prognostication among peak VO_2 percent-predicted equations, with a peak VO_2 <47% of predicted serving as an optimal cutpoint for determining mortality risk in HF (15). Obesity reduces VO_2 in ml/kg/min out of proportion to HF severity and has led to examination of peak VO_2 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 VO_2 ≤19 ml/kg/min outperformed standard peak VO_2 ≤14 ml/kg/min in predicting transplant-free survival within a HFrEF population with a 37% prevalence of obesity (as defined by body mass index [BMI] >30 kg/m^2) (16).

SUBMAXIMAL O_2 UPTAKE MEASUREMENTS. Interestingly, among patients with HF, submaximal exercise gas exchange variables have emerged that rival or even exceed the prognostic utility of peak VO_2 (17–19). Submaximal CPET variables (Online Table 1) are particularly attractive to study based on ease of

TABLE 1 Clinical Indications for Cardiopulmonary Exercise Testing

Clinical Scenario	Objective
Unexplained or multifactorial dyspnea/exercise intolerance	To define the organ system(s) limiting gas exchange
Established advanced cardiac or pulmonary disease	To grade severity of disease, prognosticate, and prioritize patients for heart transplantation and mechanical circulatory support
Valvular or congenital heart disease	To determine whether to intervene, particularly with cardiac surgical interventions, and to estimate perioperative risk
Initiation of an intervention (clinical trial)	To precisely evaluate the functional response to an intervention (i.e., change in peak oxygen uptake with a novel treatment)

FIGURE 1 Values of VO_2 and its Subcomponents of Heart Rate, Stroke Volume, and $CavO_2$ at Rest and Peak Exercise in Normal, HFrEF, and HFpEF Patients

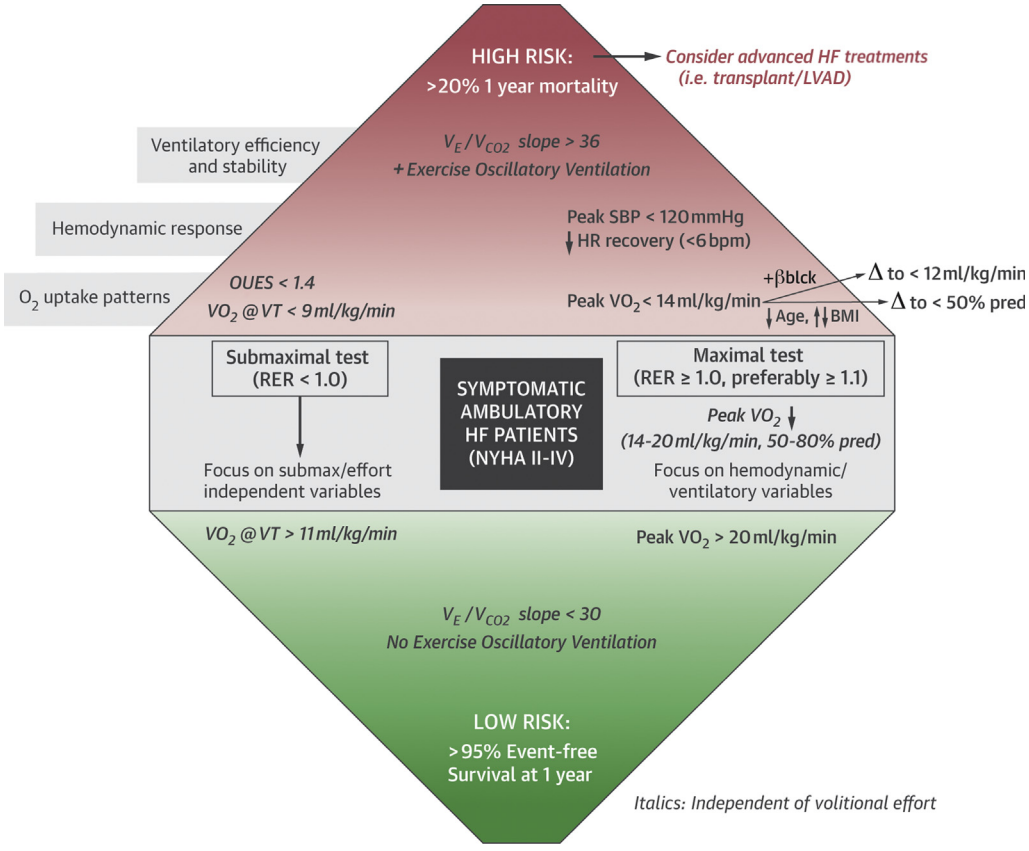


The left panel illustrates representative values for VO_2 at rest **(blue bars)** and change in VO_2 during maximum incremental exercise **(red bars)** for a normal 60-year-old man (5 feet 10 inches and normal body mass index of 21.5) derived using Wasserman's percentage predicted equation (14). Normal values are depicted in comparison to patients with HFrEF and HFpEF from a recent study that measured individual components of peak VO_2 (11). Right panels: Blue bars indicate resting values, and red bars illustrate the dynamic range in each Fick equation variable (HR, SV, and $CavO_2$) in response to maximum incremental exercise. $CavO_2$, (CaO_2 - CvO_2) difference; HFpEF = heart failure and preserved ejection fraction; HFrEF = heart failure and reduced ejection fraction; HR = heart rate; SV = stroke volume; VO_2 = oxygen uptake.

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 O_2 uptake kinetics, as measured by mean response time (MRT) (Online Table 1, **Figure 2A**), were only modestly related to peak VO_2 and more accurately reflected the ability to augment CO during low-level exercise, indicating its complementary role to peak VO_2 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). O_2 uptake efficiency slope (OUES) (**Figure 2F**), which is the relationship between VO_2 and log V_E throughout exercise, is highly reproducible; differs by <2% if derived from 75%, 90%, or 100% of exercise duration; and outperformed peak VO_2 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).

VO_2 at the ventilatory threshold (VT) is another measurement of O_2 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 VO_2/HR (oxygen pulse) increment (23) indicates failure to augment the stroke volume-$CavO_2$ (CaO_2 - CvO_2) product throughout exercise (**Figure 2C**). Assuming a linear increment in $CavO_2$ throughout exercise, this pattern suggests dynamic cardiac dysfunction and has been observed with inducible myocardial ischemia (24) as well as RV-pulmonary

CENTRAL ILLUSTRATION **Integrated Assessment of CPET Variables for Risk Stratification in HF**



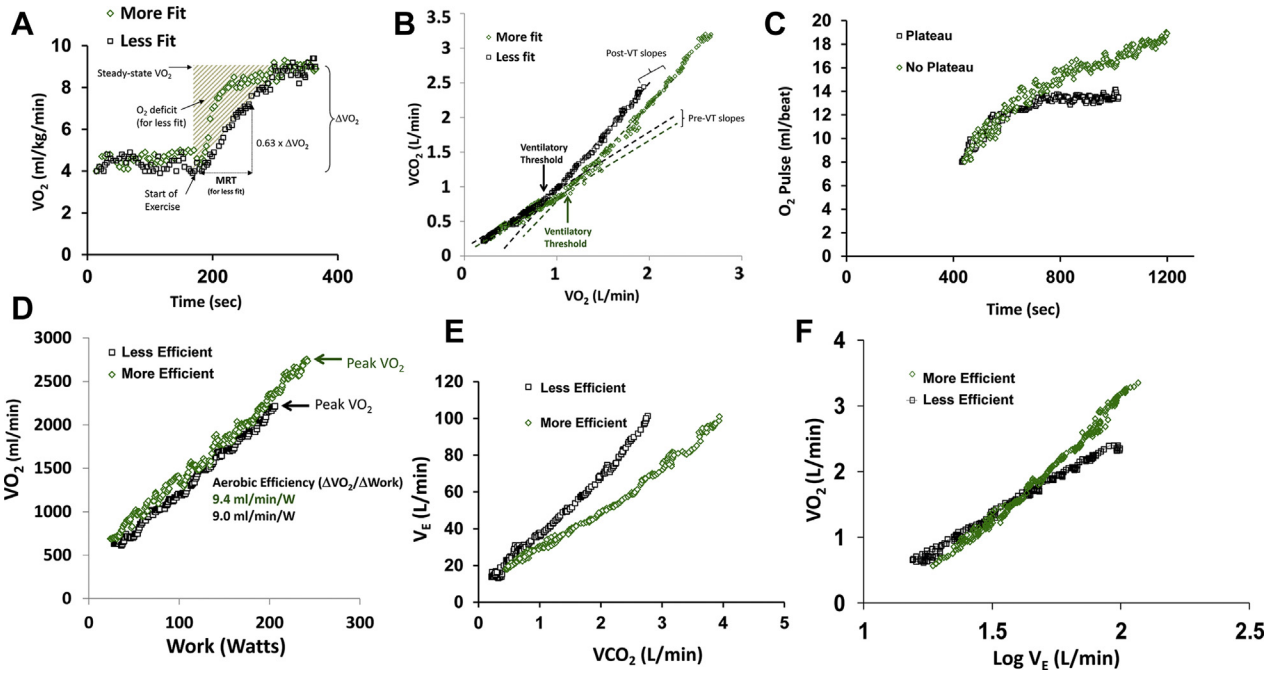
Malhotra, R. et al. J Am Coll Cardiol HF. 2016;4(8):607–16.

CPET evaluation should start with an assessment of whether there was maximum volitional effort, as indicated by RER >1.0 to 1.1. Heart rate >85% of predicted also signals maximum effort but is often not achieved in patients with HF on nodal agents and/or with chronotropic incompetence. VO_2 responses: peak VO_2 remains the gold standard metric of fitness and should be a focal point of CPET interpretation if maximum effort was achieved. Peak VO_2 <14 ml/kg/min purports poor prognosis (5,6), although a lower threshold value of <12 ml/kg/min should be used in patients tolerating beta-blockade (8). For young patients and those with high or low BMI, peak VO_2 should be interpreted as a % of predicted, with values < ~50% indicating a poor prognosis (15). For patients who do not achieve maximum effort, the focus should shift to O_2 uptake variables that are independent of volitional effort (i.e., OUES <1.4 and VO_2 at VT <9 ml/kg/min indicating a poor prognosis) (19). Hemodynamic responses: failure to achieve SBP >120 mm Hg (63) and failure to augment SBP with exercise is associated with poor prognosis, particularly when coupled with a peak VO_2 <14 ml/kg/min (63) or reduced cardiac output augmentation (64). Both chronotropic incompetence and slow heart rate recovery (<6 beats/min) also purport a poor prognosis (65). Ventilatory efficiency and stability: Steep V_E/VCO_2 slope (indicative of inefficient ventilation) and EOV are among the most potent predictors of poor outcome in HF. The presence of EOV is consistently associated with a 1-year mortality >20% (36,66). The combination of high VE/VCO_2 slope and EOV represents a particularly high-risk population, with 1 study indicating 6-month HF hospitalization (40%) and death (15%) in excess of that in the referent group (16% and 1%, respectively) (19). BMI = body mass index; CPET = cardiopulmonary exercise testing; EOV = exercise oscillatory ventilation; HF = heart failure; LVAD = left ventricular assist device; O_2 = oxygen; OUES = oxygen uptake efficiency slope; RER = respiratory exchange ratio; SBP = systolic blood pressure; VCO_2 = carbon dioxide output; V_E = ventilation; VO_2 = oxygen uptake; VT = ventilatory threshold.

vascular uncoupling (25). Aerobic efficiency describes the relationship of O_2 utilization to the amount of work performed (**Figure 2D**). A normal VO_2-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 O_2 uptake parameters (Online Table 1) becomes particularly important in grading HF severity when patients fail to fulfill criteria for a maximum volitional effort study,

FIGURE 2 Measurements of VO_2 and Ventilatory Efficiency in CPET



(A) The VO_2 onset kinetics panel (VO_2 vs. time at the beginning of exercise) shows the rise in VO_2 during onset of exercise (0-3 min), which reflects the ability of the cardiovascular system to augment cardiac output early in exercise. (MRT is 63% of the duration required to reach steady state VO_2; lower MRT reflects a more responsive cardiovascular system.) **Black squares** = abnormal MRT of 71 s; **green diamonds** = normal MRT of 32 s. **(B)** Illustration of VCO_2 vs. VO_2 relationship used to derive the VT by the V-slope method. VO_2 and VCO_2 increase proportionately during early aerobic exercise. Upon onset of anaerobic metabolism and lactate buffering by bicarbonate, there is a disproportionate increase in VCO_2 relative to VO_2 that is responsible for the steeper slope of the VCO_2-VO_2 relationship. The patient with the pattern illustrated by black squares has an earlier VT (less fit) than the patient illustrated by the green diamonds. **(C)** The ratio of VO_2 and heart rate (termed oxygen pulse) is equal to the product of stroke volume and $CavO_2$ and most often reflects dynamic conditions that cause premature leveling or decrease in stroke volume in response to exercise (i.e., myocardial ischemia or ventriculovascular uncoupling). The normal response **(green diamonds)** is contrasted with an abnormal plateau pattern **(black diamonds)**. **(D)** The aerobic efficiency panel reflects the relationship of utilization of oxygen (i.e., VO_2) to amount of work performed. A normal VO_2-work rate relationship during the incremental ramp portion of CPET is 10 ± 1.5 ml/min/W. The more efficient individual **(green diamonds)** demonstrates higher peak VO_2 and VO_2-work slope, whereas the less efficient individual **(black squares)** has a slightly lower VO_2-work slope indicative of greater reliance on anaerobic metabolism to perform work throughout exercise. This figure also demonstrates the linear relationship that exists between VO_2 and work during incremental ramp CPET. **(E)** The V_E/VCO_2 slope is a measure of the amount of ventilation required to exchange 1 l/min of CO_2. It reflects ventilation-perfusion matching during exercise as well as neural reflexes controlling dyspnea and hyperventilation. The **green diamonds** reflect more efficient ventilation (V_E/VCO_2 slope 22) in comparison to the **black squares** (V_E/VCO_2 slope 33), indicative of less efficient ventilation. **(F)** OUES indicates the total amount of oxygen uptake for each equivalent of total ventilation (V_E). VO_2 increases in proportion to the logarithm of V_E; a higher value reflects improved adaptation of the cardiopulmonary circuit to deliver oxygen for a given amount of ventilation. Representative patterns for a more efficient individual **(green diamonds)** and a less efficient individual **(black squares)** are depicted. CPET = cardiopulmonary exercise testing; O_2 = oxygen; OUES = oxygen uptake efficiency slope; MRT = mean response time; VCO_2 = carbon dioxide uptake; V_E = ventilation; VT = ventilatory threshold; other abbreviations as in Figure 1.

as indicated by a respiratory exchange ratio (RER) <1.0 to 1.1 (Central Illustration).

VENTILATORY EFFICIENCY AND STABILITY DURING EXERCISE IN HF

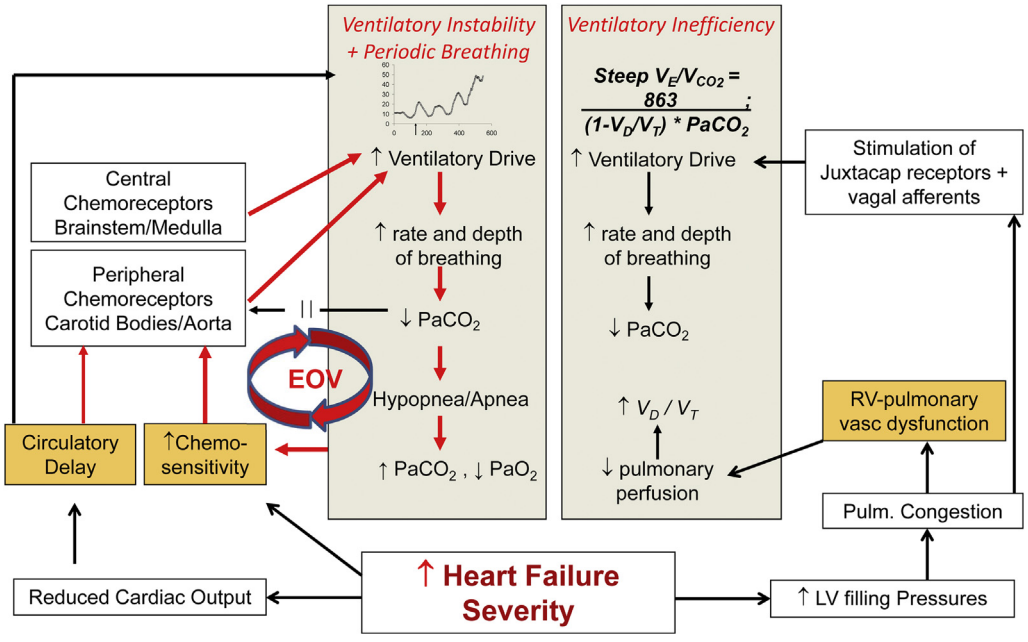
The modified alveolar equation describes the determinants of V_E/VCO_2 slope (27):

$$\frac{V_E}{VCO_2} = \frac{863}{(1\text{-}V_D/V_T)\times PaCO_2}$$

where V_D is dead space, V_T is tidal volume, and $PaCO_2$ is arterial CO_2 tension. High ventilatory drive in the setting of pulmonary edema leads to reduced $PaCO_2$, whereas lung hypoperfusion from RV dysfunction results in a worsening of VQ mismatch with elevated fractional dead space. Reduced $PaCO_2$ and increased fractional dead space, as seen in the previous equation for ventilatory efficiency, cause an abnormal elevation in V_E/VCO_2 slope (Figures 2E and 3).

Our group showed that impaired ventilatory efficiency (high V_E/VCO_2 slope) was associated with resting and exercise pulmonary vascular resistance and inversely associated with RVEF in HFrEF (28). Others have related V_E/VCO_2 slope to lower tricuspid

FIGURE 3 Mechanistic Basis for the Development of Ventilatory Instability and Ventilatory Inefficiency in Heart Failure



Ventilatory instability is reflected by exercise oscillatory ventilation (EOV) **(red arrows)**, where reduced cardiac output and circulatory delay during exercise results in increased ventilatory drive triggered by chemoreceptors sensing increased local $PaCO_2$ levels. The resultant drop in $PaCO_2$ from increased ventilation triggers relative hypopnea. These cyclical changes in $PaCO_2$ and PaO_2 are the hallmark of EOV. Ventilatory inefficiency is reflected by both a high ventilatory drive that leads to reduced $PaCO_2$ and lung hypoperfusion from RV dysfunction resulting in a worsening of ventilation-perfusion mismatch with elevated fractional dead space. These 2 factors contribute to the steep V_E/VCO_2 slope observed with ventilatory inefficiency. Adapted in part with permission from Dhakal et al. (33). EOV = exercise oscillatory ventilation; $PaCO_2$ = partial pressure of carbon dioxide; PaO_2 = partial pressure of oxygen; RV = right ventricular; VCO_2 = carbon dioxide output; V_D = ventilatory dead space; V_E = ventilation; V_T = tidal volume; other abbreviations as in Figures 1 and 2.

annular plane systolic excursion (TAPSE) (29), reduced RV fractional area change, and impaired RV metabolism (30). V_E/VCO_2 slope is a powerful predictor of events in HF patients (**Central Illustration**) (17,31,32). A V_E/VCO_2 slope >34 to 36 identifies high-risk HF patients and provides prognostic information above and beyond peak VO_2 (13,17). V_E/VCO_2 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 ≥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

of 14 ml/kg/min may have markedly different levels of impairment in the reserve capacity of each Fick variable. We and others have observed significantly reduced peak exercise arterio-venous oxygen content difference in at least a subset (i.e., 40% in a recent study) of HFpEF patients (11,12), whereas other HFpEF patients are primarily limited by chronotropic incompetence or failure to augment stroke volume.

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 VO_2 and mortality often included fewer than 50 individuals undergoing CPET evaluation (47). In larger studies (i.e., >200 subjects) using peak VO_2 as an endpoint, concordant changes in peak VO_2 and mortality were apparent for interventions such as cardiac resynchronization therapy (+/+ for change in VO_2 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 VO_2 (~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 HFrEF (0/+) demonstrated neutral effects on peak VO_2 (52,53) (likely resulting from negative chronotropic effects), yet beta-blockers clearly prolong survival in HFrEF. LVAD therapy may also represent an exception, in that studies looking at improvements in peak VO_2 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 VO_2. 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.

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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.