JACC: HEART FAILURE
VOL. 4, NO. 8, 2016

ISSN 2213-1779/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jchf.2016.03.022

MINI-FOCUS ISSUE: EXERCISE AND HEART FAILURE

STATE-OF-THE-ART PAPER

Cardiopulmonary Exercise Testing in Heart Failure

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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.

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Manuscript received June 17, 2015; revised manuscript received February 26, 2016, accepted March 2, 2016.

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)