Cardiopulmonary Exercise Tests in Patients With Heart Failure and Chronic Obstructive Pulmonary Disease

Moving Beyond Risk Assessment*

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Chronic obstructive pulmonary disease (COPD) is a common comorbidity in patients with heart failure with reduced ejection fraction (HFrEF). An estimated 24 million people in the United States are affected by COPD, and its prevalence in patients with HFrEF ranges from 11% to 39% (1,2). The high prevalence of COPD in patients with HFrEF is attributable to the presence of shared risk factors, such as advanced age and smoking. A cardinal symptom of both conditions is dyspnea on exertion, and this commonality creates a unique challenge when attempting to distinguish the primary etiology of dyspnea in patients with these concomitant disorders.

Cardiopulmonary exercise tests (CPETs) are indicated for the evaluation of unexplained dyspnea, and given this test’s capacity to simultaneously evaluate circulatory and pulmonary function, it is well suited for the diagnostic evaluation of dyspnea in patients with HFrEF and COPD. Among the physiologic parameters measured in a CPET, several are recognized as important when distinguishing between circulatory and pulmonary disease; however, less is known about which parameters are most critical in this regard. In this issue of JACC Heart Failure, Barron et al. (3) present an interesting analysis that evaluates the diagnostic performance of a comprehensive list of gas exchange parameters from CPETs in patients with HFrEF and COPD.

Exercise intolerance in HFrEF is characterized by both a circulatory impairment in delivering oxygen to skeletal muscle and a peripheral impairment in oxygen utilization by active myocytes during exercise. On a progressive workload exercise test, these central and peripheral impairments result in a supply-demand mismatch of oxygen at a reduced peak workload, which is related to an insufficient amount of adenosine triphosphate (ATP) to sustain skeletal muscle contraction and continue progressive exercise. On a CPET, this pathophysiology manifests in a reduced level of peak oxygen consumption (V̇O₂), the gold standard measurement of functional capacity.

Similarly in COPD, the functional capacity is reduced and is reflected by a reduced peak V̇O₂ on a CPET; however, the pathophysiology of exercise intolerance in COPD is markedly distinct from that in HFrEF. As opposed to the circulatory impairment in oxygen delivery in HFrEF, COPD is characterized by reduced ventilatory capacity, related to both an increased airway obstruction and a reduced rate of expiratory ventilation. On a CPET, this impairment in ventilatory capacity is manifested by reduced breathing reserve at peak exercise (the difference between maximal voluntary ventilation and maximal exercise ventilation) in patients with COPD, compared to typically normal levels of breathing reserve at peak exercise in patients with HFrEF. Breathing reserve is a well-accepted CPET variable used to discriminate between certain cardiac and pulmonary disorders (4), and the findings by Barron et al. (3) reaffirm the value of this parameter in discriminating between HFrEF and COPD.

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Interestingly, the analysis by Barron et al. (3) did not confirm the discriminatory value of anaerobic threshold in the study patients, which is at odds with a putative understanding of the value of anaerobic threshold in discriminating between certain cardiac and pulmonary disorders (4). The anaerobic threshold, also referred to as ventilatory threshold on a CPET, is defined as the highest VO$_2$ that can be obtained during exercise without developing lactic acidosis. HFrEF is typically characterized by a low anaerobic threshold, consistent with its reduced capacity to deliver and utilize oxygen peripherally throughout progressive exercise. By contrast, COPD (excluding those with concomitant pulmonary vascular disease) is typically characterized by a normal anaerobic threshold.

In addition to being counter to the pathophysiologic understanding of HFrEF and COPD, the lack of discriminatory value of anaerobic threshold in the analysis by Barron et al. (3) may be disputed by a variety of other factors. First, anaerobic threshold demonstrated good discrimination between HFrEF patients and healthy controls, whereas it did not in similar analyses comparing COPD and healthy controls. Second, failure to attain anaerobic threshold occurred in 9 of 29 (31%) patients with COPD compared with 1 of 44 (2%) patients with HFrEF, suggesting that the ability to reach anaerobic threshold may offer some discriminative value between patients with HFrEF and COPD. Third, the change in VO$_2$ relative to the change in work rate (ΔVO$_2$/ΔWR), which shares a common pathophysiology to that of low anaerobic threshold in HFrEF, demonstrated moderate discriminative value between COPD and HFrEF. Finally, anaerobic threshold is subject to interpretative biases that may have affected the results of this study. As a result, while the limited discriminatory value of anaerobic threshold in this study is intriguing, the study does not exclude the importance of anaerobic threshold in patients with HFrEF.

The study does provide strong evidence of the value of oxygen uptake efficiency slope (OUES) as a novel CPET variable that can help discriminate between HFrEF and COPD. OUES is an index of cardiorespiratory functional reserve derived from the logarithmic relation between VO$_2$ and minute ventilation during incremental exercise, and it represents how effectively oxygen is extracted from the atmosphere and then ventilated (5). Higher values for OUES indicate a more favorable response, and patients with HFrEF have significantly lower OUES values compared to cohorts without HFrEF (6). Also, OUES is a valuable CPET parameter in HFrEF because it is a submaximal measurement and is a highly reproducible and prognostically significant parameter (5–7).

Several other CPET variables were evaluated, but breathing reserve and OUES were the strongest variables to discriminate between COPD and HFrEF. These findings offer important new insights into the diagnostic interpretation of CPETs. Accordingly, a flowchart using these variables was devised by the authors as a model of how clinicians might utilize breathing reserve and OUES to distinguish HFrEF versus COPD patients. Although the value of breathing reserve is clear, the inclusion of OUES as a critical discriminatory CPET variable in patients with HFrEF and COPD should undergo further validation in larger cohorts of these patients before it is more broadly utilized in clinical practice.

There are several limitations to the study, including the limited number of patients with comorbid HFrEF and COPD, which the authors describe well in their discussion; however, the study is highly important because it investigates the mechanism of dyspnea in HFrEF patients, an underexplored aspect of the role of CPET in clinical practice. Since the publication of a landmark study by Mancini et al. (8) on peak VO$_2$ in HFrEF, an increasing evidence base has accrued demonstrating the prognostic value of several parameters obtained in CPETs, including a recent analysis of 2,100 patients from the HF-ACTION (HF-A Controlled Trial Investigating Outcomes of Exercise Training), which revealed that exercise duration, peak VO$_2$, and percent predicted peak VO$_2$ are powerful predictors of mortality in HFrEF (9). However, the majority of these studies do not inform clinicians on how to use CPETs to determine the underlying cause of dyspnea in their patients.

The work by Barron et al. (3) provides evidence to support a more detailed understanding of the mechanism underlying dyspnea on exertion in individual patients and helps move the field of HFrEF toward greater personalization of medical care. For instance, HFrEF patients with low peak VO$_2$ are oftentimes considered for advanced therapies such as left ventricular assist devices; however, if their primary exercise limitation is due to COPD rather than HFrEF, then left ventricular assist devices are less likely to improve symptomatology. In addition, an understanding of the mechanism of dyspnea in patients with HFrEF and COPD could have important implications on decision making over beta blocker titration, and on determining the most appropriate exercise training interventions to be used in cardiac rehabilitation in individual patients.

In conclusion, the findings by Barron et al. (3) provide important new insights into how CPETs
should be interpreted in patients with HFrEF and COPD. More studies like this are needed to further refine how CPETs should be used to determine the primary etiology of dyspnea of exertion in patients with HFrEF, particularly those with comorbidities such as COPD. Such studies will expand the role of CPET in the clinical management of patients with HFrEF and help the move the field beyond CPETs’ already important role in risk assessment.

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**REFERENCES**


