Role of cardiopulmonary stress testing
in heart failure management

Nandini Nair MD PhD, Enrique Gongora MD

INTRODUCTION

Heart failure (HF) is a global problem of epidemic proportions. In the United States HF affects more than 5 million people currently, with 500,000 newly diagnosed cases every year. It is a syndrome of multiple etiologies and can involve systolic and/or diastolic dysfunction. The risk of death due to HF has increased partly because advances in technology have decreased the age-adjusted death rates for cardiac diseases, especially those of ischemic origin, and, therefore, increased the prevalence of HF through longer survival.

Direct measurement of ventilation and gas exchange during exercise is called a cardiopulmonary stress test (CPX). Cardiopulmonary stress testing measures multiple parameters that vary with alterations in cardiac and pulmonary function. The most important variables are expiratory ventilation (VE), pulmonary gas exchange expressed as oxygen uptake (VO₂), carbon dioxide output (VCO₂), cardiac rate and rhythm, and blood pressure. A composite set of variables measured by CPX links cardiovascular and pulmonary responses to the metabolic demands of exercise. Exercise intolerance is a characteristic feature of HF with symptoms, such as shortness of breath, fatigue, or both, which are usually out of proportion to the level of exertion. Therefore, the assessment of exercise intolerance can be used to predict the degree of cardiac impairment, stratify risk, and optimize therapy.

The use of CPX in HF patients began with the classic investigation by Mancini et al in 1991. Currently, CPX is used for diagnosis, risk stratification, and prognostication (Figure 1). This review focuses on use of CPX in the assessment of disease severity and clinical management of HF with reduced ejection fraction (HFrEF) as well as preserved ejection fraction (HFpEF).

ASSESSMENT OF DISEASE SEVERITY, RISK STRATIFICATION, AND PROGNOSIS

In HFrEF the most important use of CPX is to triage patients at the appropriate time to advanced HF therapies, such as implantation of ventricular assist devices (VADs) and cardiac transplantation. In HFpEF it is used to determine disease severity by unmasking symptoms with exercise. In both cases it is also used to guide management toward optimal medical regimens or to triage to advanced surgical therapies for HF.

The New York Heart Association (NYHA) functional class is a subjective classification addressing a patient’s functional capacity. To overcome the subjectivity of this classification exercise testing, such as CPX, has been used to make objective decisions about the treatment of chronic HF. Peak oxygen consumption (VO₂) has been shown to correlate with functional capacity and mortality. This relationship between oxygen consumption and outcomes was first reported by Mancini et al. More recently, other measurements obtained during metabolic exercise tests have been shown to predict mortality in patients with end stage HF. The slope of the relationship between ventilation and carbon dioxide production (VE/VCO₂ slope), the end tidal carbon dioxide (CO₂), the oxygen uptake efficiency slope (OUES), and the rate of heart
rate recovery have all been found to be useful predictors of outcome.\textsuperscript{8-10} Russell \textit{et al} showed that the NYHA functional class predicts exercise parameters and can be used for assessing disease severity and outcomes.\textsuperscript{11} The study by Russell also demonstrated that there is a significant difference in the peak \(\dot{V}O_2\), \(\dot{V}E/\dot{V}CO_2\) slope, and exercise time in patients with NYHA functional class II symptoms compared to those with NYHA functional class III/IV symptoms.\textsuperscript{11}

In the era of evidence-based medicine, risk stratification using multivariable scores has reliable, robust scores using CPX as one of the parameters.\textsuperscript{15-22} The Heart Failure Survival Score by Aaronson \textit{et al} has proved to be better than using peak oxygen consumption alone.\textsuperscript{18} The score by Myers \textit{et al}\textsuperscript{16,17} also used \(\dot{V}O_2\), \(\dot{V}E/\dot{V}CO_2\) slope, end-tidal CO\(_2\) pressure, OUES, and heart rate recovery. The \(\dot{V}E/\dot{V}CO_2\) slope was the strongest predictor of cardiovascular risk for mortality. Poor ventilatory control in heart failure can manifest as a crescendo-decrescendo pattern without interposed apnea called exercise oscillatory ventilation (EOV). Peak circulatory power is the product of peak \(\dot{V}O_2\) and peak systolic blood pressure. Therefore addition of these extra parameters such as Exercise Oscillatory Ventilation (EOV), the lowest \(\dot{V}E/\dot{V}CO_2\) ratio, peak circulatory power, \(\dot{V}E/\dot{V}CO_2\) slope, and OUES, produced an optimal score for predicting the risk for mortality in this population.\textsuperscript{23,24}

Exercice ventilatory power (EVP) is the ratio between peak systolic blood pressure and the \(\dot{V}E/\dot{V}CO_2\) slope. Forman \textit{et al}\textsuperscript{25} showed that using \(\leq 3.5\) mmHg for the EVP as a cutoff for high risk had better prognostic discrimination capability and predict survival. Subsequently, Borghi-Silva \textit{et al}\textsuperscript{26} used Doppler echocardiographic recordings throughout the CPX tests in patients with HFrEF and showed that lower EVPs indicated severely impaired peak \(\dot{V}O_2\) and cardiac output response to exercise with consequent impairment of right heart function and hemodynamics affecting the pulmonary system. This result showed that a lower EVP indicated increased disease severity.

The relative increase in \(\dot{V}O_2\) to maximal work
rate (WR) (change in $\dot{V}O_2$/change in WR) has been proposed as an indicator of cardiac efficiency and aerobic generation of adenosine triphosphate. In normal subjects this increases linearly and represents a surrogate index of cardiac output. In ventricular dysfunction during exercise, this parameter may plateau and fail to reach a value $\geq 10$ mL/min/W. Additionally, a flat $\Delta \dot{V}O_2/\Delta \dot{WR}$ was associated with increased systolic pulmonary artery pressure and decreased RV systolic function.$^{27,28}$

The Exertional Oscillatory Ventilation (EOV) has been found to be an important prognostic index in HF. The pathophysiological mechanisms of EOV are still not fully understood. Several factors, including decreased cardiac output, suboptimal chemoreceptor responses, reduced ventilator control, RV dysfunction, abnormal pulmonary hemodynamics, and delayed information transfer related to arterial $CO_2$ levels from the pulmonary capillaries to peripheral and central chemoreceptors secondary to impaired ventricular function, probably affect the EOV. Hence, the addition of EOV to CPX parameters would be useful for better risk stratification and prognostication. The utilization of the Metabolic Exercise test data combined with Cardiac and Kidney Indexes (MECKI) score for prognostication helps identify cardiovascular mortality and the requirement of heart transplantation. The MECKI score consists of six laboratory values, such as hemoglobin, sodium, creatinine clearance calculated by the Modification of Diet in Renal Disease (MDRD) equation, the left ventricle ejection fraction (LVEF), the percentage of $\dot{V}O_2$ max, and the $\dot{VE}/\dot{VCO}_2$ slope.$^{29-38}$

The Ventilatory Threshold (VT), also called the anaerobic threshold, assesses exercise intensity, ventilation, and metabolism and has potential use in therapeutic interventions. In HF, aerobic exercise training should be performed below the VT. Intermittently, exercise above VT can be done but with caution.$^{51,52}$ Hence assessment of VT can be used to determine exercise prescriptions in HF. In a small study CPX guided exercise rehabilitation was safe and effective for patients with HF.$^{53}$

**Summary**

Cardiopulmonary exercise testing has evolved considerably since the first report of its use in HF in 1991. The test has multiple uses in HF, including defining right ventricular failure and secondary pulmonary hypertension.$^{54-56}$ Multiple small studies have demonstrated the utility of CPX in diagnosis, risk stratification, and therapy.
tion for mortality, and prognostication of HFrEF and HFpEF. The use of CPX in grading diastolic dysfunction has been reported in a small study of individuals with HFpEF. Future research investigations may be needed to conclusively include the newer parameters discussed (EOV, OUES, EVP and circulatory power) before these can be used routinely in CPX assessments. CPX is, therefore, a highly useful, comprehensive test to evaluate, risk stratify, and guide therapy in the present day management of HF.

**Keywords:** Cardiopulmonary stress test, HFpEF, HFrEF, \( \dot{V}O_2 \) max, VE/\( VCO_2 \)

---

**Table 1: Selected studies investigating utility of CPX in HFrEF and HFpEF**

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Type</th>
<th>Type of HF</th>
<th>Subjects (n)</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Borghi-Silva et al(^a) 2014</td>
<td>Prospective</td>
<td>HFrEF</td>
<td>86</td>
<td>Lower EVP suggests higher disease severity</td>
</tr>
<tr>
<td>Foreman et al(^b) 2012</td>
<td>Prospective</td>
<td>HFrEF</td>
<td>875</td>
<td>Ventilatory power was the strongest prognostic factor</td>
</tr>
<tr>
<td>Bandera et al(^c) 2014</td>
<td>Prospective</td>
<td>HFrEF, HFpEF</td>
<td>136</td>
<td>A flat ( \Delta V/O_2/\Delta W R ) reflects impaired functional phenotype</td>
</tr>
<tr>
<td>Lewis et al(^d) 2008</td>
<td>Prospective</td>
<td>HFrEF</td>
<td>30</td>
<td>Significant correlation between VE/VCO(_2) and PVR , RVEF</td>
</tr>
<tr>
<td>Moore et al(^e) 2007</td>
<td>Prospective</td>
<td>HFrEF, HFpEF</td>
<td>147</td>
<td>VE/VCO(_2) slope is significantly higher in patients with SHF compared with DHF</td>
</tr>
<tr>
<td>Kite et al(^f) 2006</td>
<td>Prospective</td>
<td>HFrEF, HFpEF</td>
<td>216</td>
<td>Patients with DHF have exercise tolerance between that of patients with SHF and controls</td>
</tr>
<tr>
<td>Guazzi et al(^g) 2010</td>
<td>Prospective</td>
<td>HFpEF</td>
<td>22</td>
<td>CPX parameters can be used for assessment of the degree of DD</td>
</tr>
</tbody>
</table>

SHF-systolic HF, DHF-diastolic HF, DD-diastolic dysfunction, HFrEF-heart failure with reduced ejection fraction, HFpEF-heart failure with preserved ejection fraction

**Author Affiliation:** Nandini Nair is a transplant cardiologist in the Department of Internal Medicine/Division of Cardiology at Texas Tech University Health Sciences Center in Lubbock, TX. Enrique Gongora is a cardiothoracic/transplant surgeon at Memorial Cardiac and Vascular Institute in Hollywood, FL.

**Received:** 03/10/2015

**Accepted:** 06/18/2016

**Reviewers:** Aliakbar Arvandi MD

**Published electronically:** 07/15/2016

**Conflict of Interest Disclosures:** None
Figure 2  Suggested algorithm for risk stratification in advanced heart failure

<table>
<thead>
<tr>
<th>Initial evaluation for advanced heart failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Beta Blocker</td>
</tr>
<tr>
<td>On Beta Blocker</td>
</tr>
</tbody>
</table>

- **VO2 max >14 VE/VO2<34**
- **VO2 max <14 VE/VO2>34**
- **VO2 max <12 VE/VO2>34**
- Medical Management

Evaluation for Advanced HF surgical therapies—Mechanical Circulatory Support/Cardiac Transplantation

### References


10. Guazzi M, Labate V, Cahalin LP, Arena R. Cardiopulmonary exercise testing reflects similar pathophysiology and disease se-


