

# Metabolic Parameters Derived From Cardiopulmonary Stress Testing for Prediction of Prognosis in Patients With Heart Failure: The Ochsner Experience

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## ABSTRACT

Cardiopulmonary parameters, particularly peak oxygen consumption, have proven utility in prognostic stratification for patients with heart failure. These have been typically corrected for total body weight as opposed to lean body mass (LBM). For practical purposes, fat consumes virtually no oxygen and receives minimal perfusion. Based on this rationale and on observations from previous studies, several investigations conducted at the Ochsner Clinic Foundation have assessed the prognostic value of metabolic parameters when corrected for LBM. Three studies reviewed in this discussion consistently found greater prognostic value for LBM-corrected parameters, especially peak oxygen consumption and oxygen pulse. These findings lead to a strong recommendation for LBM correction of cardiopulmonary exercise stress test–derived parameters for more accurate prognostic stratification in patients with heart failure, especially in the obese population. Other centers have studied additional parameters such as the ventilation to carbon dioxide production slope, oxygen uptake efficiency slope, and partial pressure of end-tidal carbon dioxide during exercise and rest. In multiple studies, these ventilation-dependent parameters have shown prognostic superiority compared with the standard peak oxygen consumption even when obtained from submaximal exercise data. However, no study to our knowledge has compared these parameters with LBM-adjusted values as described herein. The prognostic validity of cardiopulmonary exercise stress test–derived parameters requires further investigation in patients treated with  $\beta$ -blockers.

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## INTRODUCTION

Exercise stress testing is commonly used in clinical practice to evaluate the presence and severity of coronary ischemia, as well as exertional symptoms, heart rate and blood pressure responses, and estimated aerobic capacity.<sup>1–3</sup> By direct measurement of exercise respiratory gas exchange, cardiopulmonary exercise stress testing (CPX) adds important clinical information to that provided by the standard exercise stress test.<sup>1,4</sup> In particular, CPX provides precise determination of aerobic capacity, the causes of dyspnea on exertion, and prognosis in patients with systolic heart failure (HF).<sup>1</sup>

The heart, lungs, and pulmonary and systemic circulations form a single circuit for exchange of respiratory gases between the environment and the cells of the body.<sup>1,5,6</sup> Under steady-state conditions, oxygen consumption per unit time ( $\dot{V}O_2$ ) and carbon dioxide output ( $\dot{V}CO_2$ ) measured at the mouth are equivalent to oxygen ( $O_2$ ) utilization and carbon dioxide production occurring in the cell; thus, external respiration equals internal respiration.<sup>1,6</sup> CPX testing directly measures fractions of  $O_2$  and carbon dioxide in expired gas, expired air volume, or flow and calculates  $\dot{V}O_2$ ,  $\dot{V}CO_2$ , and minute ventilation (VE).<sup>1</sup> Samples of expired air are typically assessed every 15 seconds, and real-time data are expressed in tabular and graphic formats.<sup>4</sup> From these data, multiple metabolic parameters can be derived (Table 1). These parameters may be used for different diagnostic, therapeutic, and prognostic purposes (Table 2); risk stratification and prognosis in patients with systolic HF are most pertinent to this discussion.

The application of CPX in categorizing the severity of HF has been described by many investigators such as Weber and Janicki in 1985.<sup>7</sup> Subsequently, Szlachcic et al<sup>8</sup> investigated the prognostic utility of CPX for HF and found a correlation between peak  $\dot{V}O_2$  and mortality. In the Veterans Administration Heart Failure Trial (v-HEFT),<sup>9</sup> the mortality rate of patients with maximum oxygen consumption ( $\dot{V}O_{2max}$ ) not

**Table 1. Metabolic Parameters Measured or Derived From Cardiopulmonary Exercise Stress Testing (CPX)\***


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<b>Peak oxygen uptake (Peak <math>\dot{V}O_2</math>):</b>	The highest $\dot{V}O_2$ achieved during the CPX, which generally occurs near or at peak exercise. Reported as a weight-adjusted parameter as mL/kg per minute.
<b>Maximal oxygen uptake (<math>\dot{V}O_{2max}</math>):</b>	The value achieved when $\dot{V}O_2$ remains stable despite a progressive increase in the intensity of exercise. This is synonymous with peak aerobic capacity.
<b>Breathing Reserve (BR):</b>	The reserve capacity of the ventilatory system, calculated as 1 minus the ratio of peak exercise minute ventilation (VE) to maximal voluntary ventilation. A normal value would be $\geq 30\%$ .
<b>Anaerobic Threshold (AT):</b>	The highest oxygen uptake attained without a sustained increase in blood lactate concentration and lactate/pyruvate ratio. Reported as a weight-adjusted parameter in mL/kg per minute.
<b>Respiratory Exchange Ratio (RER):</b>	Related but not equivalent to its cellular counterpart, the respiratory quotient, and is defined as the ratio of $\dot{V}CO_2$ and $\dot{V}O_2$ .
<b>Oxygen saturation (<math>SpO_2</math>):</b>	The percentage of hemoglobin that is saturated with oxygen. Typically measured by pulse oximetry.
<b><math>O_2</math> pulse:</b>	The amount of $O_2$ consumed from the volume of blood delivered to tissues by each heartbeat; is calculated as $O_2$ pulse = $\dot{V}O_2$ /heart rate.
<b>Ventilation/carbon dioxide production ratio (<math>\dot{V}E/\dot{V}CO_2</math>):</b>	Also known as the ventilatory equivalent for $CO_2$ , this represents a respiratory control function that reflects chemoreceptor sensitivity, acid-base balance, and ventilatory efficiency.
<b>Peak <math>\dot{V}O_2</math> lean:</b>	The peak oxygen uptake adjusted for lean body mass. Reported as a lean body weight-adjusted parameter in mL/kg per minute.

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\* Adapted with permission from Milani et al.<sup>4</sup>  $O_2$  indicates oxygen;  $\dot{V}O_2$ , oxygen consumption.

exceeding 14.5 mL/kg per minute was double that of patients whose  $\dot{V}O_{2max}$  exceeded this value.<sup>1,4</sup> In a separate investigation of patients with HF referred for heart transplantation (HT), Mancini et al<sup>10</sup> found that peak  $\dot{V}O_2$  was the best single predictor of survival. Moreover, HT could be safely deferred in patients with peak  $\dot{V}O_2$  exceeding 14 mL/kg per minute, whose survival exceeded that of patients undergoing HT.<sup>1,4</sup> As a result of these seminal studies, CPX remains a pivotal modality in the initial evaluation of patients with advanced HF, especially those who are considered for HT.<sup>1,4</sup>

Although the peak  $\dot{V}O_2$  cutoff of 14 mL/kg per minute remains an important prognostic discriminator in patients with HF, disparities in its prognostic utility may occur when evaluating special populations, including women and obese persons.<sup>1,11–13</sup> At the Ochsner Clinic Foundation (OCF), several studies have been conducted exploring other independent

prognostic values. These include peak  $O_2$  pulse, body fat-adjusted peak  $O_2$  pulse, body fat-adjusted peak  $\dot{V}O_2$ , and percentage of predicted  $\dot{V}O_{2max}$  (an age- and sex-adjusted measure). Herein, we review the experience of the OCF in an attempt to better define a stronger prognosticator of outcome and to more accurately risk stratify patients with systolic HF.

## METHODS

We reviewed 3 studies conducted at OCF and published between 1997 and 2004. In addition to being performed at our center, these studies assessed independent predictors of survival in patients with chronic HF and compared these with the standard peak  $\dot{V}O_2$  described by Mancini et al.<sup>10</sup> CPX testing was performed on a treadmill using an individually tailored ramping protocol designed to yield a test duration of 8 to 12 minutes in all studies. Patients were encouraged to exercise until symptoms

**Table 2. Potential Indications for Cardiopulmonary Stress Testing\***


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Evaluation for exertional dyspnea
Development of an exercise prescription
Direct measurement of peak oxygen consumption per unit time (functional capacity)
Risk stratification and prognosis in heart failure
Optimization of rate-adaptive or biventricular pacemaker
Congenital heart disease (determination of need for surgical repair and response to treatment)
Disability determination (worksite readiness)
Assessment of functional significance of regurgitant valvular heart disease
Assessment of results of medical and surgical therapies

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\* Adapted with permission from Milani et al.<sup>1</sup>

of chest discomfort or dyspnea were intolerable. Breath-to-breath online gas analysis was performed using a MedGraphics CPXID metabolic card (Medical Graphics Corporation, St. Paul, Minn.).

A prospective observational study by Richards et al<sup>11</sup> was conducted between November 1992 and August 1994. It included 76 patients undergoing outpatient HT evaluation referred to a noninvasive laboratory for CPX and followed them for a mean period of 12 months (range, 9–25 months). Entry criteria included New York Hospital Association functional class II or III, left ventricular ejection fraction not exceeding 40%, no symptomatic change on maximum medical therapy for 6 weeks, and ability to exercise on a treadmill. Exclusion criteria included unstable ischemic symptoms, uncontrolled severe hypertension, and inability to undergo treadmill exercise testing. Adverse clinical events were defined as the occurrence of cardiac death or HT.<sup>11</sup> The study was designed to compare peak  $\dot{V}O_2$  with an age- and sex-adjusted measurement (percentage predicted  $\dot{V}O_2$ ) as an outcome determinant in women with HF. Percentage of predicted  $\dot{V}O_{2\max}$  was calculated using the formula by Wasserman et al.<sup>14</sup>

Osman et al<sup>15</sup> prospectively studied 225 consecutive ambulatory patients with chronic systolic HF referred for CPX between November 1995 and December 1998. Using the rationale that body fat can represent a significant portion of total body weight and that it consumes essentially no  $O_2$ , the study assessed the predictive strength of peak  $\dot{V}O_2$  adjusted to lean body mass (LBM) in determining clinical outcomes in patients with moderate to severe chronic systolic HF. It also attempted to stratify patients into high-risk and low-risk groups based on this value and to define subpopulations that may merit mandatory application of this prognostic criteria. The investigators included patients having HF for at least 6 months receiving stable dosages of medications and having no exacerbations or need for inotropic support for 4 weeks before assessment. Patients with severe peripheral vascular disease, low-threshold angina, and orthopedic limitations preventing them from exercise testing were excluded. Body fat assessment was determined by the skinfold technique using a mean of 3 skinfolds (thigh, chest, and abdomen in men and thigh, triceps, and suprailium in women). Principal outcomes assessed were death due to cardiovascular causes and need for urgent HT. Patients were followed for a median duration of 19.5 months (range, 2–40.4 months; mean [SD], 18.9 [11.3] months).

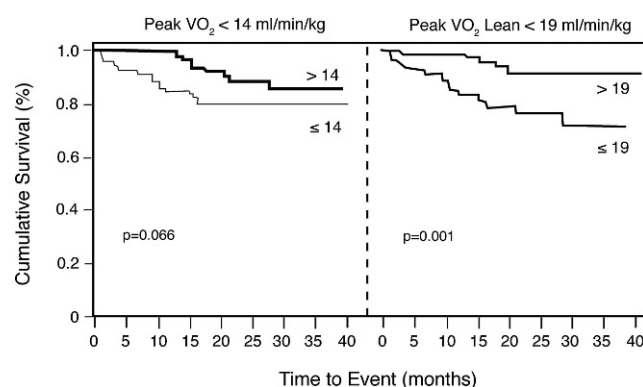
Peak exercise  $O_2$  pulse is another variable derived from CPX, and limited data were available on its prognostic ability in patients with chronic systolic

HF.<sup>16,17</sup> Lavie et al<sup>18</sup> retrospectively studied 209 consecutive ambulatory patients with chronic systolic HF (New York Hospital Association classes I–III) who underwent CPX between January 1996 and December 1998. All patients were diagnosed at a minimum of 6 months before testing and had been receiving stable dosages of medication with no exacerbations or need for inotropic support for 6 weeks. Percentage body fat was also calculated using the 3-skinfold technique. Clinical events were defined as cardiovascular death and urgent HT. The study compared multiple parameters, including anaerobic threshold (AT), ratio of ventilation to carbon dioxide production ( $\dot{V}E/\dot{V}CO_2$ ), peak  $\dot{V}O_2$ , peak  $\dot{V}O_2$  lean (corrected for LBM),  $O_2$  pulse, and  $O_2$  pulse lean. It also attempted to define the effect of  $\beta$ -blocker use on these prognostic values.

## RESULTS

The study by Richards et al<sup>11</sup> found that, despite having a lower peak  $\dot{V}O_2$  than men (18.3 vs 14.5 mg/kg per minute,  $P = .01$ ), women had a higher percentage predicted  $\dot{V}O_{2\max}$  (65.5% vs 75.4%,  $P = .03$ ). In addition, with only one clinical event, women had a higher event-free survival rate (75% vs 95%,  $P = .01$ ).<sup>11</sup> The male cohort comprised 6 of 7 urgent HTs and 8 of 8 cardiovascular deaths. These discrepancies in mean peak  $\dot{V}O_2$ , percentage predicted  $\dot{V}O_{2\max}$ , and clinical outcomes suggest that an age- and sex-adjusted value may be a more suitable prognostic tool and perhaps mandatory in certain populations.

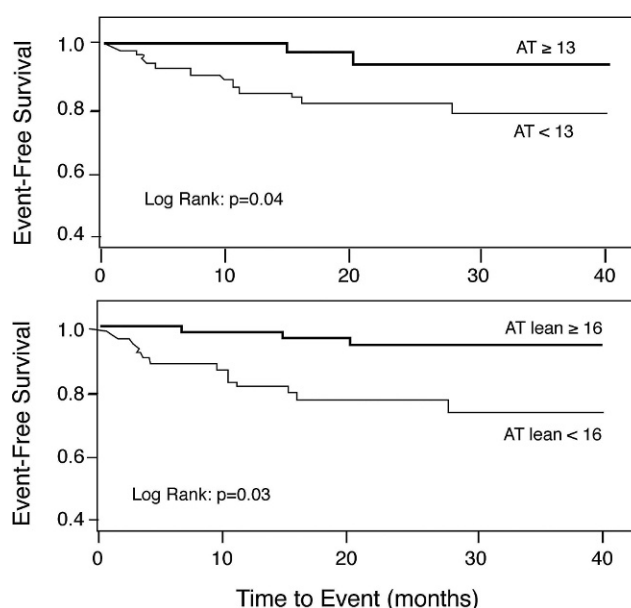
Osman et al<sup>15</sup> demonstrated superior diagnostic characteristics using the peak  $\dot{V}O_2$  lean cutoff of 19 mL/kg per minute (Figure 1). During the follow-up period, 29 cardiac events (14 cardiovascular deaths and 15 urgent HTs) were observed. Diagnostic test analysis was used to calculate sensitivity, specificity, likelihood ratios, and positive and negative predictive values for peak  $\dot{V}O_2$  and for peak  $\dot{V}O_2$  lean, with the latter being superior to unadjusted peak  $\dot{V}O_2$  in all diagnostic parameters. Peak  $\dot{V}O_2$  lean demonstrated better sensitivity and specificity compared with peak  $\dot{V}O_2$ , with values of 72.3% vs 63.6% and 59.3% vs 56%, respectively. Likelihood ratios were also superior using peak  $\dot{V}O_2$  lean, with 1.78 (95% confidence interval [CI], 1.30–2.45) vs 1.45 (95% CI, 1.01–2.08) for a positive test result and 0.46 (95% CI, 0.23–0.92) vs 0.65 (95% CI, 0.37–1.15) for a negative test result. In addition, positive predictive value and negative predictive value were higher using the LBM-adjusted value, with 20.1% vs 16.9% and 93.9% vs 91.7%, respectively. Other parameters were observed; although cutoffs of percentage predicted  $\dot{V}O_2$  not exceeding 50% and of peak  $\dot{V}O_2$  not exceeding



**Figure 1.** Kaplan-Meier survival curves using both peak oxygen consumption ( $\text{VO}_2$ ) of 14 mL/kg per minute and peak  $\text{VO}_2$  lean of 19 mL/kg per minute as cutoffs show stronger prognostic value for the fat-adjusted peak  $\text{VO}_2$  by log-rank testing. Reproduced with permission from Osman et al.<sup>15</sup>

14 mL/kg per minute showed a trend toward significance in the studied population, a peak  $\text{VO}_2$  lean not exceeding 19 mg/kg per minute correlated best with the combined end point ( $P = .0006$ ). At 12 months, patients with peak  $\text{VO}_2$  lean not exceeding 19 mg/kg per minute had a survival of 80% compared with 98% for those with values exceeding 19 mL/kg per minute ( $P = .001$ ).<sup>15</sup>

In addition, discordant variable analysis of data by Osman et al<sup>15</sup> revealed that none of 8 patients having peak  $\text{VO}_2$  not exceeding 14 mL/kg per minute and having peak  $\text{VO}_2$  lean of at least 19 mL/kg per minute reached any of the outcomes. Most of these patients were obese (6 of 8) and female (5 of 8). Conversely, 4 of 10 patients having peak  $\text{VO}_2$  of at least 14 mL/kg per minute and having peak  $\text{VO}_2$  lean not exceeding 19 mL/kg per minute had major events (2 required urgent HT and 2 died of progressive HF). These data further elucidate the incremental prognostic value of body fat-adjusted peak  $\text{VO}_2$  vs the standard unadjusted value. Furthermore, by subgroup analysis, women had lower total body weight ( $P = .02$ ), had higher percentage body fat ( $P < .0001$ ), and achieved lower mean (SD) unadjusted peak  $\text{VO}_2$  (13.5 [5.2] vs 16.2 [5.8] mL/kg per minute,  $P = .0002$ ), but no statistical difference was observed when peak  $\text{VO}_2$  lean was used (18.8 [7.6] vs 20.4 [7.5] mL/kg per minute,  $P = .11$ ), and no difference in outcome was observed (13.2% of women reached an outcome compared with 18.8% of men,  $P = .4$ ). Obese patients showed lower mean (SD) AT (11.5 [3.5] vs 12.7 [4.2] mL/kg per minute,  $P = .03$ ) and unadjusted peak  $\text{VO}_2$  (14.4 [4.7] vs 16.5 [6.1] mL/kg per minute,  $P = .04$ ) but similar peak  $\text{VO}_2$  lean (19.3 [6.7] vs 20.5 [7.9] mL/kg per minute,  $P = .2$ ), and there was no statistical difference in outcome (10% of obese patients



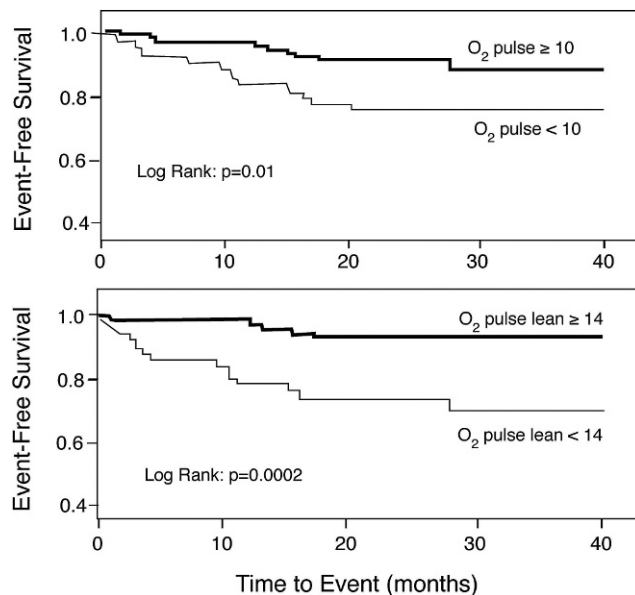
**Figure 2.** Kaplan-Meier survival curves using both anaerobic threshold (AT) of 13 mL/kg per minute and AT lean of 16 mL/kg per minute as cutoffs for predicting event-free survival. Reproduced with permission from Lavie et al.<sup>18</sup>

reached an end point vs 17.8% of nonobese individuals,  $P = .1$ ).<sup>15</sup>

The study by Lavie et al<sup>18</sup> revealed that patients with clinical events (28 of 209) had a statistically significant lower percentage predicted peak  $\text{VO}_2$ , peak  $\text{VO}_2$ , peak  $\text{VO}_2$  lean,  $\text{O}_2$  pulse, and  $\text{O}_2$  pulse lean and a higher  $\text{VE}/\text{VCO}_2$  ratio. As previously noted by Osman et al,<sup>15</sup> LBM-adjusted values provided more accurate discrimination between patients with events and patients without events. Peak  $\text{VO}_2$  was lower in patients with events ( $P = .01$ ), as was peak  $\text{VO}_2$  lean ( $P < .0001$ ). A cutoff for peak  $\text{VO}_2$  lean of 19 mL/kg per minute was a better predictor of prognosis than the classic peak  $\text{VO}_2$  cutoff of 14 mL/kg per minute ( $P = .0003$ ). The same held true for AT ( $P < .01$ ) and for AT lean ( $P < .001$ ). The best AT cutoff to differentiate patients with and without events was 13 mL/kg per minute ( $P = .04$ ). Its prognostic value further improved after adjusting the AT to LBM with a cutoff value of 16 mL/kg per minute. Last, peak  $\text{O}_2$  pulse and peak  $\text{O}_2$  pulse lean were significantly lower in patients with clinical outcomes compared with event-free patients ( $P < .0001$  for both); however,  $\text{O}_2$  pulse lean cutoff of 14 mL/beat improved prediction of event-free survival compared with the unadjusted value cutoff of 10 mL/beat ( $P = .0002$  and  $P = .01$ , respectively). Figure 2 and Figure 3 show event-free survival when applying cutoffs for AT and  $\text{O}_2$  pulse vs their respective LBM-adjusted values.

Lavie et al<sup>18</sup> also compared peak  $\text{VO}_2$  and  $\text{O}_2$  pulse. Both parameters predicted prognosis, partic-





**Figure 3.** Kaplan-Meier survival curves using both oxygen ( $O_2$ ) pulse of 10 mL/beat and  $O_2$  pulse lean of 14 mL/beat as cutoffs for predicting event-free survival. Reproduced with permission from Lavie et al.<sup>18</sup>

ularly when corrected for LBM. Although a cutoff of 19 mL/kg per minute for peak  $VO_2$  lean was superior to unadjusted peak  $VO_2$  (cutoff, 14 mL/kg per minute), peak  $O_2$  pulse lean was similar to or superior to peak  $VO_2$  lean in predicting major clinical events, particularly in subgroups with increased body fat (eg, obese individuals and women). This was suggested by the study data; however, clinical events were too few (4 and 8 for obese and female patients, respectively) for meaningful analysis. The  $VE/VCO_2$  ratio was significant in univariate analysis, but it did not add significantly to the  $VO_2$  data in the multivariate models. Direct comparison of LBM-adjusted values and  $VE/VCO_2$  slope was not performed.

The effect of  $\beta$ -blocker use was also explored. There was no difference in clinical events among patients receiving and not receiving  $\beta$ -blockers. However, patients receiving  $\beta$ -blockers had higher  $O_2$  pulse and  $O_2$  pulse lean. All parameters seemed to provide considerably better prognostic stratification in patients not taking  $\beta$ -blockers, although the number of patients receiving  $\beta$ -blockers and the number of events in this group may have been too few for a meaningful analysis.

## DISCUSSION

CPX testing is considered the “gold standard” for assessment of functional capacity and for establishment of prognosis in patients with HF.<sup>1,7,19,20</sup> Studies by Weber and Janicki<sup>7</sup> and later by Szlachcic et al<sup>8</sup> initially proposed the prognostic utility of CPX in

patients with HF.<sup>11</sup> Subsequent studies by Cohn et al<sup>9</sup> and by Mancini et al<sup>10</sup> led to the standard peak  $VO_2$  cutoff of 14 mL/kg per minute for good prognosis and safe deferral of HT in the near term.<sup>15</sup> Richards et al<sup>11</sup> attempted to identify if sex-specific differences exist in the ability of peak  $VO_2$  to risk stratify ambulatory patients with HF. They analyzed an age- and sex-adjusted variable (percentage predicted  $VO_2$ ) and assessed its potential as a better discriminatory value. Their findings revealed decreased peak  $VO_2$  in women compared with men, increased percentage predicted peak  $VO_2$ , and improved survival. Women have a higher percentage of non- $O_2$ -consuming body fat than men, and this may lead to a pseudoreduction of peak  $VO_2$  in women.<sup>11</sup> Furthermore, percentage predicted peak  $VO_2$  has been suggested as an additional prognostic variable, particularly for patients who have peak  $VO_2$  less than 14 mL/kg per minute.<sup>21,22</sup> This discrepancy across the sex line, as well as the known contribution of body fat changes in  $VO_2$ , led to examination of the effect of LBM-adjusted values such as peak  $VO_2$ , AT, and  $O_2$  pulse.<sup>15</sup>

CPX testing parameters used to predict prognosis in patients with HF (including the already mentioned peak  $VO_2$ ) are corrected for total body weight as opposed to LBM. For practical purposes, fat consumes virtually no  $O_2$  and receives minimal perfusion.<sup>11,15,23,24</sup> In addition, body fat composition varies greatly across populations.<sup>15,24,25</sup> It has been previously proposed that CPX may lose prognostic power in certain subgroups with high percentages of body fat such as women and obese patients.<sup>1,7,19,20</sup> All studies reviewed herein demonstrated that simple adjustment of metabolic parameters to LBM provides much greater prognostic strength than the traditionally reported unadjusted peak  $VO_2$ , with peak  $VO_2$  lean (cutoff, 19 mL/kg per minute) and peak  $O_2$  pulse lean (cutoff, 14 mL/kg per minute) being the strongest predictors. The study by Osman et al<sup>15</sup> confirmed the hypothesis that peak  $VO_2$  lean is superior to unadjusted peak  $VO_2$  when risk stratifying patients with systolic HF (Figure 1). Lavie et al<sup>18</sup> subsequently obtained similar results in regard to peak  $VO_2$  lean, further supporting better prognostication with the LBM-adjusted value. Additional analysis of data by Lavie et al<sup>18</sup> revealed stronger prognostic power for other LBM-adjusted parameters as well, including AT and peak  $O_2$  pulse (Figures 2 and 3). As obesity reaches epidemic proportions in westernized society, with almost 70% of adults classified as overweight or obese,<sup>19,25,26</sup> correction of these values to LBM may prove to be mandatory when evaluating patients with chronic systolic HF who are being considered for HT.

Other centers have studied additional parameters for prognostication in patients with HF. Values that

incorporate VE have proven to be clinically valuable.<sup>27</sup> The prognostic value of the VE/VCO<sub>2</sub> slope has been proposed as being superior or equal to the standard peak V<sub>O<sub>2</sub></sub>.<sup>27-37</sup> Arena et al<sup>27</sup> suggested that the VE/VCO<sub>2</sub> slope may be the single most clinically valuable CPX variable (cutoff, 34 [values  $\geq 34$  represent poor prognosis]). The oxygen uptake efficiency slope (OUES), which represents the logarithmic relationship between VE and V<sub>O<sub>2</sub></sub>, is another variable that has reported prognostic superiority compared with the standard peak V<sub>O<sub>2</sub></sub>.<sup>38</sup> Initially, Baba et al<sup>39</sup> reported a significant correlation between OUES and peak V<sub>O<sub>2</sub></sub> in patients with HF. This correlation was later confirmed by Van Laethem et al,<sup>40</sup> and Davies et al<sup>38</sup> more recently found that OUES (cutoff, 1.47 [values  $< 1.47$  represent poor prognosis]) was a significant predictor of mortality in patients with HF and was superior to other parameters, including VE/VCO<sub>2</sub> slope and peak V<sub>O<sub>2</sub></sub>. Additional investigations by Arena et al<sup>27</sup> produced discrepant findings, with both VE/VCO<sub>2</sub> slope and OUES being superior to peak V<sub>O<sub>2</sub></sub> but with the former being superior to the latter. This discrepancy may be explained by the length of follow-up in the studies (3 years<sup>27</sup> vs 9 years<sup>38</sup>) and/or by the assessment of OUES as log OUES in the study by Davies et al.<sup>27,38</sup> Despite increasing evidence that supports the prognostic utility of these parameters, no single study (to our knowledge) has compared the prognostic value of VE/VCO<sub>2</sub> slope or OUES with peak V<sub>O<sub>2</sub></sub> lean or O<sub>2</sub> pulse lean, and further investigation is warranted.

A known limitation of peak V<sub>O<sub>2</sub></sub> and O<sub>2</sub> pulse is underestimation of these values due to early cessation of the exercise test before maximal physiologic effort<sup>41</sup> (typically defined as a respiratory exchange ratio  $< 1.0$ ). The VE/VCO<sub>2</sub> slope has been demonstrated to retain prognostic power even when calculated with suboptimal effort test data.<sup>27,36,41</sup> This finding may be explained by the relatively linear relationship between VE and VCO<sub>2</sub>. Although VE/VCO<sub>2</sub> slope retains prognostic value despite suboptimal patient effort, it is a stronger predictor of mortality when calculated from data obtained during the entire duration of the test.<sup>27,42</sup> This is due to its bilinear relationship in a significant number of patients, one representing the initial minutes of exercise and one after the ventilatory compensation phase or AT.<sup>42</sup> The OUES has also been proposed as having prognostic utility when calculated during submaximal exercise. Van Laethem et al<sup>40</sup> found that OUES varies by less than 3% when calculated at different stages of exercise. Similarly, Davies et al<sup>38</sup> found variability of only 1% in OUES when calculated with data from half of the exercise duration and with full exercise data. Arena et al<sup>27</sup> compared the prognostic ability of VE/

VCO<sub>2</sub> slope and OUES when calculated using data collected during the first half of the exercise test; VE/VCO<sub>2</sub> slope was found to be superior in their study, although the difference was not statistically significant. Increasing evidence suggests that assessment of these parameters may in fact provide the best prognosis stratification in patients who are unable to reach maximal physiologic effort during CPX.

To our knowledge, no specific variable has been proven to be significantly superior in predicting hospitalization. However, Arena et al found strong correlation between cardiac-related hospitalization and several of the studied parameters, specifically VE/VCO<sub>2</sub> slope, exercise partial pressure of end-tidal carbon dioxide<sup>43</sup> (P<sub>ET</sub>CO<sub>2</sub>), and resting P<sub>ET</sub>CO<sub>2</sub>.<sup>44</sup> A later study<sup>45</sup> by the same group of investigators found that resting P<sub>ET</sub>CO<sub>2</sub> (cutoff, 33 mm Hg [values  $\leq 33$  mm Hg indicate poor prognosis]) also has prognostic value when applied to major cardiac events or death, especially in combination with other variables (New York Heart Association class, left ventricular ejection fraction, and VE/VCO<sub>2</sub> slope). Furthermore, in that study, resting P<sub>ET</sub>CO<sub>2</sub> added prognostic power to VE/VCO<sub>2</sub> slope.

The increasing number of parameters shown to provide significant prognostic value demonstrates a need for a simplified method to integrate these data. An attempt to develop a simplified multivariate score for CPX-derived metabolic parameters was recently published by Myers et al.<sup>46</sup> Assignment of a weighted score to CPX response (peak V<sub>O<sub>2</sub></sub>), ventilatory efficiency (VE/VCO<sub>2</sub> slope, P<sub>ET</sub>CO<sub>2</sub>, and OUES), and hemodynamic responses (heart rate recovery<sup>47</sup>) produced a graded score (CPX score). The score had stronger prognostic power for major and minor cardiac events (cardiac-related hospitalization, HT, left ventricular assist device implantation, or cardiac-related death) than any single parameter. However, the data were not sufficient to validate the score.

The prognostic ability of CPX parameters in patients taking  $\beta$ -blockers is also under question. Although findings at the OCF suggest that parameters derived from CPX provide better prognostic stratification in patients not taking  $\beta$ -blockers,<sup>18</sup> other results have shown that peak V<sub>O<sub>2</sub></sub> and VE/VCO<sub>2</sub> slope provide better stratification for patients being treated with these medications.<sup>48</sup> In investigations performed at the OCF, peak V<sub>O<sub>2</sub></sub> provided particularly poor prognostic stratification, and peak O<sub>2</sub> pulse lean provided the best prognostic stratification in patients taking  $\beta$ -blockers. However, in the study by Lavie et al<sup>18</sup> that evaluated the effect of  $\beta$ -blocker use on CPX data, the number of patients taking  $\beta$ -blockers and the number of events in this subgroup were too few to provide meaningful analysis. The use of peak O<sub>2</sub> pulse

(a value that is more dependent on cardiac pump reserve) seems promising for prognostic stratification in patients treated with  $\beta$ -blockers. Larger patient populations with optimal medical therapy during this era of  $\beta$ -blocker use may be necessary to provide more accurate stratification.

## CONCLUSION

Studies at OCF have consistently demonstrated the superior prognostic value of LBM-adjusted parameters over the standard peak  $\text{VO}_2$ . Correction of these parameters should be strongly considered when evaluating patients with HF, especially those being considered for HT. Other parameters, including but not limited to  $\text{VE}/\text{VCO}_2$  slope, OUES, and resting and exercise  $\text{P}_{\text{ET}}\text{CO}_2$ , have proven superiority over the standard peak  $\text{VO}_2$  and are especially valuable when evaluating data obtained from submaximal exercise. To our knowledge, no study has compared the prognostic power of these parameters versus that of peak  $\text{VO}_2$  lean or  $\text{O}_2$  pulse lean. Future studies are needed to assess the prognostic value of various CPX parameters (including  $\text{VE}/\text{VCO}_2$  slope) using body fat-adjusted peak  $\text{VO}_2$  in patients with HF.<sup>49</sup> Sex, age, obesity, and (more recently) race/ethnicity<sup>49,50</sup> have been shown to affect exercise capacitance and CPX-derived parameters. A composite of several CPX parameters, including  $\text{VE}/\text{VCO}_2$  slope, peak  $\text{VO}_2$  (especially if adjusted for percent body fat), OUES, resting  $\text{P}_{\text{ET}}\text{CO}_2$ , and heart rate recovery, as has been recently suggested,<sup>46</sup> may best predict HF prognosis.<sup>49</sup>

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