Ventilatory Power: A Novel Index that Enhances Prognostic Assessment of Patients with Heart Failure

Forman et al: Ventilation and Hemodynamics in Heart Failure

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Abstract

Background—Ventilatory efficiency (VE/VCO₂ slope) is an index determined by cardiopulmonary exercise testing (CPX) which incorporates pertinent cardiac, pulmonary, and skeletal muscle physiology into a substantive composite assessment. The VE/VCO₂ slope has many applications, including utility as a well-validated prognostic gauge for heart failure (HF) patients. In this study, we combine VE/VCO₂ slope with systolic blood pressure (SBP), creating a novel index that we labeled “ventilatory power.” Ventilatory power links the combined physiology inherent in the VE/VCO₂ slope to peripheral pressure, adding an additional dimension pertinent to HF assessment. Whereas the related concept of circulatory power links peak oxygen consumption (VO₂) with peak SBP as a prognostic index, we hypothesized that ventilatory power would provide greater prognostic discrimination than VE/VO₂ slope, peak VO₂, and/or circulatory power for systolic heart failure (HF) patients.

Methods and Results—Systolic HF patients (left ventricular ejection fraction [LVEF] ≤35%) underwent symptom-limited CPX as part of routine management and were followed for up to four years for major cardiac events (mortality, left ventricular assist device [LVAD] implantation, and heart transplantation). 875 HF patients (LVEF 26±9%; mean age 55 ±14) were studied. CPX indices peak VO₂, VE/VCO₂ slope, circulatory power and ventilatory power were all predictive of cardiac events (p <0.001). Multivariate analysis demonstrated that ventilatory power was the strongest indicator of prognosis.

Conclusions—While circulatory power and traditional CPX parameters can be used to predict prognosis among HF patients, ventilatory power provides relatively greater prognostic discrimination and may constitute a relatively more useful composite tool.

Key Words: cardiopulmonary exercise testing; prognosis; heart failure; hemodynamics
Cardiopulmonary exercise testing (CPX) combines breath-by-breath ventilatory gas exchange assessments with standard exercise testing procedures. Peak oxygen consumption (VO₂) and the minute ventilation/carbon dioxide production (VE/VCO₂) slope are two well-validated CPX ventilatory indices used to assess prognosis of heart failure (HF) patients. (1-8)

In a seminal study Williams et al. combined peak VO₂ with a novel index, “cardiac power,” (9) the product of cardiac output and mean arterial pressure (MAP), to characterize the relationship between cardiac-generated blood flow and peripheral perfusion pressure. HF patients with both low peak VO₂ and low cardiac power have worse outcomes than those with low peak VO₂ and preserved cardiac power. Yet while cardiac power has compelling conceptual appeal, its application is limited by reliance on invasive cardiac assessments.

The index “circulatory power” subsequently introduced by Cohen-Solal et al. (10) is related to cardiac power, but relies on CPX to achieve equivalent assessments non-invasively. Applying peak VO₂ as a surrogate for cardiac output and systolic blood pressure (SBP) for MAP, circulatory power is calculated as the product of peak VO₂ and SBP.

In this study, we analyzed the VE/VCO₂ slope in combination with SBP to form a new index that we labeled “ventilatory power.” While peak VO₂ is thought to primarily reflect central cardiac performance, the VE/VCO₂ slope manifests both peripheral (e.g., peripheral perfusion and skeletal muscle chemo- and afferent-reflexes) as well as central and pulmonary hemodynamics (cardiac output, alveolar perfusion). (11, 12) In this analysis, we compared ventilatory power to other ventilatory and hemodynamic indices derived from CPX to evaluate their prognostic utility both individually and in combination with one another.
Methods

This study was a multi-center analysis including HF patients from the exercise testing laboratories at LeBauer Cardiovascular Research Foundation, Greensboro, North Carolina, Stanford University, Palo Alto, CA, VA Palo Alto Health Care System, Palo Alto, California, Brigham and Women’s Hospital, Boston, MA, and Virginia Commonwealth University, Richmond, Virginia, and San Paolo Hospital, Milan, Italy. The centers, well-experienced in CPX, combined to form a clinical registry with outcomes data. All patients included in the current analysis underwent CPX as part of their clinical management/standard of care (i.e. transplant candidacy/mechanical device implantation assessment and/or assessment of exertional symptoms). A total of 875 patients with systolic HF, clinically referred for CPX, and who underwent testing between April 1993 and May 2011, were included in the current analysis. The inclusion criteria consisted of a diagnosis of HF and evidence of left ventricular ejection fraction (LVEF < 35%) by two-dimensional echocardiography obtained within one month of data collection. All subjects completed a written informed consent and institutional review board approval was obtained at each institution.

CPX Procedures

Symptom-limited CPX was performed on all subjects and pharmacologic therapy was maintained during exercise testing. Progressive exercise testing protocols using treadmill (93% of tests) or cycle ergometry (7% of tests) were employed at all centers and ventilatory expired gas analysis was performed using a metabolic cart (Medgraphics CPX-D and Ultima, Minneapolis, MN, Sensormedics Vmax29, Yorba Linda, CA or Parvomedics TrueOne 2400, Sandy, UT). We have previously found these exercise modes do not alter the prognostic
characteristics of CPX variables in patients with HF. (13) Before each test, the equipment was calibrated in standard fashion using reference gases. Minute ventilation (VE), VO₂, and carbon dioxide output (VCO₂) were acquired breath-by-breath and averaged over 10-second intervals. Peak VO₂ and peak respiratory exchange ratio (RER) were expressed as the highest 10-second averaged sample obtained during the last 20 seconds of testing. The VE and VCO₂ values, acquired from the initiation of exercise to peak, were entered into spreadsheet software (Microsoft Excel, Microsoft Corp., Bellevue, WA) to calculate the VE/VCO₂ slope via least squares linear regression (y = mx + b, m=slope). SBP, diastolic blood pressure (DBP) and MAP were assessed at rest, immediately prior to CPX and at peak exercise. MAP was approximated using the formula MAP = DBP+1/3(SBP-DBP). Circulatory power was defined as the product of peak VO₂ and peak SBP. Ventilatory power was defined as peak SBP divided by the VE/VCO₂ slope. Ventilatory power was assessed as a ratio rather than a product (as with circulatory power) with the rationale that a good prognosis is reflected by a greater SBP and lower VE/VCO₂ slope.

Endpoints

In the overall cohort, subjects were followed for major cardiac events (mortality, left ventricular assist device [LVAD] implantation, and urgent heart transplantation) via medical chart review for up to four years post CPX. Subjects were followed by the HF programs at their respective institution providing a high likelihood that all events were thoroughly tracked and captured. External means of tracking events, such as the Social Security Death Index, were not utilized in the present study. Any death with a cardiac-related discharge diagnosis was considered an event.
Statistical Analysis

Statistical software packages (SPSS 19.0, Chicago, IL and R, http://www.r-project.org/) were used to perform all analyses. Continuous and categorical data are reported as mean ± standard deviation and percentages, respectively. An independent t-test was used to assess differences in age between subgroups of patients who remained event free or suffered a major cardiac event during the tracking period. For LVEF and all CPX variables, Analysis of Covariance (ANCOVA), adjusting for age and sex, was used to assess differences between subgroups of patients who remained event free or suffered a major cardiac event during the tracking period. The Mann-Whitney U test was used to compare differences in NYHA class according to event status. Chi-square analysis compared categorical baseline variables between subgroups of patients who remained event free or suffered a major cardiac event during the tracking period. Univariate and multivariate (Forward stepwise method; entry and removal value 0.05 and 0.10, respectively) Cox regression analysis, adjusted for age and sex, was used to assess the prognostic value of key hemodynamic and CPX variables. The strength of univariate and multivariate predictors were compared using the concordance index (14). For variables retained in the multivariate regression, receiver operating characteristic (ROC) curve analysis was used to identify optimal threshold values. Kaplan-Meier analysis was used to estimate the cumulative incidence of cardiac events for each group separately, according to dichotomous classification of variables retained in the Cox multivariate regression analysis. The log-rank test determined statistical significance among the groups for the Kaplan-Meier analyses. A two-sided p-value <0.05 was considered statistically significant for all tests.
Results

A total of 875 patients were assessed. Their mean age was 55 ±14 years; 76% were male. The mean left LVEF was 26 ±9% and the mean New York Heart Association (NYHA) Class was 2.5 ±0.08. Etiology of HF was ischemic in 37% of the subjects and non-ischemic in the remaining 63%.

There were 149 major cardiac events (82 deaths, 26 LVAD implantations, and 41 transplantations) over the four year tracking period. The median length of follow-up was 24 months (quartiles: 25% = 11 months, 50% = 24 months, 75% = 35 months). The average yearly event rate was 7.6%. Table 1 lists the observed baseline, CPX and hemodynamic parameters relative to major cardiac events. With respect to baseline characteristics, subjects who remained event free had a significantly lower NYHA class, a significantly higher LVEF (after controlling for sex and age), and were more frequently prescribed an ACE inhibitor. RER was similar in both groups, indicating similarly high exertion during CPX; however, after controlling for age and sex, there were significant differences in all the other functional and hemodynamic variables relative to the occurrence or absence of events.

Neither age (chi-square=0.27, p=0.61) nor sex (chi-square=0.04, p=0.84) were predictors of adverse events. Tables 2 and 3 list the univariate and multivariate Cox regression analyses respectively, for hemodynamic and CPX variables, all of which adjusted for age and sex. All the variables were significant univariate predictors of survival (Table 2). The multivariate analysis revealed that the ventilatory power was the strongest predictor of adverse events, while circulatory power was also retained in the regression (Table 3). The concordance index of the multivariate analysis listed in Table 3 improved in comparison to values for univariate predictors.
listed in Table 2. All other variables listed in Table 2 were removed from the multivariate predictive model (residual chi-square $\leq 3.8$, $p \geq 0.05$).

ROC curve analysis identified $\leq/> 3.5$ mmHg (area under the curve: 0.70, $p<0.001$) and $\leq/> 1750$ mmHg $\cdot$ mlO$_2$$\cdot$kg$^{-1}$$\cdot$min$^{-1}$ (area under the curve: 0.69, $p<0.001$) as optimal prognostic threshold values for peak ventilatory power and circulatory power, respectively. Using these thresholds, Kaplan-Meier analysis results are illustrated in the Figure. Subjects with both peak ventilatory power and circulatory power values above these thresholds demonstrated a high level of event-free survival. Subjects with one and two values below the defined thresholds demonstrated progressively worse event free survival.

**Discussion**

This study introduces and evaluates the prognostic utility of the novel concept of “ventilatory power”, a CPX-derived index that links the VE/VCO$_2$ slope and peak SBP. We demonstrated that ventilatory power is a strong predictor of cardiac events, i.e., stronger than standard CPX indices (peak VO$_2$ and VE/VCO$_2$ slope), and even stronger than the enhanced prognostic index circulatory power, in which hemodynamics are linked to oxygen uptake. Ventilatory power is independently predictive of cardiac events and, when analyzed in combination with circulatory power, the prognostic discrimination is synergistic.

This study extends the extensive literature demonstrating the utility of CPX indices to assess prognosis of HF patients.(1-8,11) It is novel in its reliance on the VE/VCO$_2$ slope in combination with hemodynamics as a pivotal gauge of HF prognosis. Combining hemodynamics into the assessment is important as it incorporates manifestations of peripheral perfusion physiology into a composite quantification.
Arena et al (11) and others (7, 8, 15-16) have demonstrated the relatively greater utility of the VE/VCO₂ slope over peak VO₂ to gauge HF pathophysiology and prognosis. The VE/VCO₂ slope is thought to better reflect the complex interplay of pulmonary, cardiac, and peripheral manifestations of the disease. While Cohen-Solal et al. (10) combined a CPX index with blood pressure to increase prognostic discrimination in their seminal study, they relied on peak VO₂ which has several inherent limitations. The assumption that peak VO₂ provides a reliable proxy to cardiac output presumes arterio-venous O₂ differences are fixed and overlooks many of the pertinent physiological dynamics that also contribute to HF pathophysiology (e.g., pulmonary function, skeletal muscle function, endothelial function). (17) Furthermore, while peak VO₂ depends on patient motivation, the VE/VCO₂ slope is relatively less likely to fluctuate irrespective of a patient’s level of exertional effort (and/or limitations due to non-cardiac comorbidities). (18)

While all CPX variables were significant univariate predictors of survival among HF patients in this study, the strongest predictors of major events in multivariate analyses were ventilatory power and, to a lesser extent, circulatory power. Blood pressure (SBP, DBP, and MAP) were substantially lower before, during, and following exercise in patients who experienced a major cardiac event when compared to those who remained event free. These data attest to the broad relevance of hemodynamics in HF management (19-21), and to the particular benefit of combining hemodynamics with ventilatory efficiency.

The hemodynamic differences among patients who experienced major cardiac events have important clinical implications. HF itself as well as common medications used for this condition can both lead to hemodynamic lability (22), especially in patients prone to chronotropic incompetence. (23) Whereas hypotension is common among HF patients receiving
guideline-based therapies, the consequences are presumed to be relatively benign among asymptomatic patients. The current study suggests that blood pressure dynamics during exercise may provide a critical perspective by which prognostic implications can be better assessed.

Our data also indicate specific thresholds that demarcate better or worse prognosis in respect to ventilatory power (i.e. ≥/≤ 3.5mmHg) or circulatory power (≥/≤ 1750 mmHg•mlO₂•kg⁻¹•min⁻¹). Use of this novel measure should therefore be encouraged as a simple means of assessment when CPX has been performed to provide more appropriate preventive measures.

**Limitations**

This study was based upon a retrospective analysis of HF patients. Prospective evaluations are needed in order to fully evaluate the utility of ventilatory power as a marker of prognosis. While the current study recognized common HF medications (beta blockers and ACE inhibitors), it did not systematically assess all cardiac and non-cardiac medications, many of which might also have affected test results (e.g., diuretics, statins, aldosterone antagonists). Likewise, comprehensive assessment of comorbidities was not completed (e.g., hypertension, COPD, renal disease). Future studies may aim to better clarify the impact of medications and comorbidities on ventilatory power as a prognostic index. Patients in this study underwent CPX testing using either a treadmill or a cycle ergometer protocol. Future studies need to further clarify the effect of exercise mode on prognostic assessment, although initial studies indicate the data obtained is comparable between treadmill and cycle ergometer tests. Lastly, we were unable to perform meaningful subgroup analyses according to the individual centers included in the current study. Dividing subjects by center would diminish the number of subjects and events.
in such a way that multivariate analyses including all variables of interest would be
underpowered. All of the CPX laboratories included in the current analysis are very
experienced, giving us high confidence in the data’s validity and reliability. Moreover, testing
procedures (equipment calibration, implantation of conservative testing protocols, etc.) were
similar across centers. Even so, future studies conducting a similar analysis at a single center in a
large cohort would be a valuable endeavor.

Conclusion

The novel concept of ventilatory power extends the value of the VE/VCO₂ slope by
linking this ventilatory index to peripheral blood pressure. We demonstrated that ventilatory
power provides excellent prognostic discrimination in a large population of HF patients,
exceeding that provided by traditional CPX indices, and even by circulatory power.

Disclosures

None.

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Table 1. Differences in Baseline and CPX variables according to major cardiac event status

<table>
<thead>
<tr>
<th></th>
<th>Event-Free (n=726)</th>
<th>Major Cardiac Event (n=149)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>54.3 ±13.8</td>
<td>56.1 ±13.6</td>
<td>0.14</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>75</td>
<td>82</td>
<td>0.05</td>
</tr>
<tr>
<td>HF etiology (% ischemic)</td>
<td>37</td>
<td>44</td>
<td>0.12</td>
</tr>
<tr>
<td>NYHA class</td>
<td>2.4 ± 0.77</td>
<td>3.0 ±0.79</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>27.1 ±9.6</td>
<td>22.3 ±8.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prescribed beta-blocker (%)</td>
<td>86</td>
<td>80</td>
<td>0.06</td>
</tr>
<tr>
<td>Prescribed ACE inhibitor (%)</td>
<td>70</td>
<td>61</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>CPX Variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak VO\textsubscript{2} (mlO\textsubscript{2}•kg\textsuperscript{-1}•min\textsuperscript{-1})</td>
<td>16.7 ±6.0</td>
<td>12.6 ±4.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak RER</td>
<td>1.13 ±0.13</td>
<td>1.12 ±0.17</td>
<td>0.06</td>
</tr>
<tr>
<td>VE/VCO\textsubscript{2} slope</td>
<td>34.1 ±8.8</td>
<td>40.7 ±11.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Resting SBP (mmHg)</td>
<td>116.9 ±20.7</td>
<td>106.3 ±21.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Resting DBP (mmHg)</td>
<td>72.8 ±13.0</td>
<td>68.2 ±12.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Resting MAP (mmHg)</td>
<td>87.4 ±13.7</td>
<td>80.9 ±13.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak SBP (mmHg)</td>
<td>147.2 ±29.6</td>
<td>123.9 ±27.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBP increase (mmHg)</td>
<td>30.3 ±22.9</td>
<td>17.7 ±19.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak DBP (mmHg)</td>
<td>76.8 ±14.7</td>
<td>72.3 ±13.9</td>
<td>0.005</td>
</tr>
<tr>
<td>Peak MAP (mmHg)</td>
<td>100.3 ±16.9</td>
<td>89.5 ±16.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Circulatory Power (mmHg • mlO\textsubscript{2}•kg\textsuperscript{-1}•min\textsuperscript{-1})</td>
<td>2498.7 ±1138.6</td>
<td>1600.8 ±820.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ventilatory Power (mmHg)</td>
<td>4.6 ±1.6</td>
<td>3.3 ±1.2</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CPX, cardiopulmonary exercise testing; HF, heart failure; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; ACE, angiotensin converting enzyme inhibitor; VO\textsubscript{2} = oxygen consumption; RER = respiratory exchange ratio; VE/VCO\textsubscript{2} = minute ventilation/carbon dioxide production; SBP = systolic blood pressure; DBP = diastolic blood pressure; MAP = mean arterial pressure
Table 2. Survival analysis for key resting and CPX variables: Univariate predictors

<table>
<thead>
<tr>
<th>Variable</th>
<th>Chi-Square</th>
<th>Hazard Ratio (95% CI)*</th>
<th>Concordance Index</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak VO₂</td>
<td>60.3</td>
<td>0.85 (0.82-0.89)</td>
<td>0.75</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VE/VCO₂ slope</td>
<td>107.4</td>
<td>1.07 (1.05-1.08)</td>
<td>0.76</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Resting SBP</td>
<td>44.0</td>
<td>0.97 (0.96-0.98)</td>
<td>0.68</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Resting DBP</td>
<td>23.2</td>
<td>0.97 (0.95-0.98)</td>
<td>0.63</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Resting MAP</td>
<td>38.7</td>
<td>0.96 (0.95-0.97)</td>
<td>0.67</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak SBP</td>
<td>91.3</td>
<td>0.97 (0.96-0.98)</td>
<td>0.76</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBP increase</td>
<td>39.9</td>
<td>0.98 (0.97-0.98)</td>
<td>0.69</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak DBP</td>
<td>14.4</td>
<td>0.98 (0.97-0.99)</td>
<td>0.62</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak MAP</td>
<td>59.0</td>
<td>0.96 (0.95-0.97)</td>
<td>0.71</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Circulatory</td>
<td>82.8</td>
<td>0.99 (0.99-0.99)</td>
<td>0.80</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ventilatory</td>
<td>110.8</td>
<td>0.43 (0.37-0.50)</td>
<td>0.80</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 3. Survival analysis for key resting and CPX variables: Multivariate predictors retained in the regression

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio (95% CI)*</th>
<th>Chi-Square</th>
<th>Combined Concordance Index</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventilatory</td>
<td>0.57 (0.45-0.68)</td>
<td>110.8</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Circulatory</td>
<td>0.99 (0.99-1.00)</td>
<td>13.8</td>
<td></td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

VO₂ = oxygen consumption; RER = respiratory exchange ratio; VE/VCO₂ = minute ventilation/carbon dioxide production; SBP = systolic blood pressure; DBP = diastolic blood pressure; MAP = mean arterial pressure

Hazard ratio reflects per 1 unit increase (for VE/VCO₂ slope) or decrease (all other variables) for each variable listed. Units for each variable are listed in Table 1.
Figure Legend

Figure. Applying specific cutpoints for ventilatory and circulatory power, gradations of risk were identified:

A—496 subjects had Ventilatory Power >3.5 mmHg and Circulatory Power >1750 mmHg • mlO₂•kg⁻¹•min⁻¹. They experienced 34 events consistent with 93.1% event-free survival.

B—176 subjects had Ventilatory Power ≤3.5 mmHg or Circulatory Power ≤1750 mmHg • mlO₂•kg⁻¹•min⁻¹. They experienced 34 events, consistent with 80.7% event-free survival.

C—203 subjects had Ventilatory Power ≤3.5 mmHg and Circulatory Power ≤1750 mmHg • mlO₂•kg⁻¹•min⁻¹. They had 81 events, consistent with 60.1% event-free survival.

Overall, HF patients with the combination of both ventilatory power ≤3.5 mmHg and circulatory power ≤1750 mmHg • mlO₂•kg⁻¹•min⁻¹ were at highest risk for the composite cardiovascular endpoints.
Figure: Kaplan-Meier Analysis

Log-rank: 159.9, p<0.001
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