Ventilatory Power

A Novel Index That Enhances Prognostic Assessment of Patients With Heart Failure

Daniel E. Forman, MD; Marco Guazzi, MD, PhD; Jonathan Myers, PhD; Paul Chase, MEd; Daniel Bensimhon, MD; Lawrence P. Cahalin, PhD, PT; Mary Ann Peberdy, MD; Euan Ashley, MD; Erin West, MS; Karla M. Daniels, MS; Ross Arena, PhD, PT

Background—Minute ventilation/CO_2 production (VE/V_{CO_2}) slope is an index determined by cardiopulmonary exercise testing, which incorporates pertinent cardiac, pulmonary, and skeletal muscle physiology into a substantive composite assessment. The VE/V_{CO_2} slope has many applications, including utility as a well-validated prognostic gauge for patients with heart failure (HF). In this study, we combine VE/V_{CO_2} slope with systolic blood pressure, creating a novel index that we labeled ventilatory power. Ventilatory power links the combined physiology inherent in the VE/V_{CO_2} slope to peripheral pressure, adding an additional dimension pertinent to HF assessment. Whereas the related concept of circulatory power links peak oxygen consumption with peak systolic blood pressure as a prognostic index, we hypothesized that ventilatory power would provide greater prognostic discrimination than VE/V_{CO_2} slope, peak oxygen consumption, and circulatory power for patients with systolic HF.

Methods and Results—Patients with systolic HF (left ventricular ejection fraction ≤35%) underwent symptom-limited cardiopulmonary exercise testing as part of routine management and were followed for up to 4 years for major cardiac events (mortality, left ventricular assist device implantation, and heart transplantation). Eight hundred seventy-five patients with HF (left ventricular ejection fraction, 26±9%; mean age, 55±14) were studied. Cardiopulmonary exercise testing indices peak oxygen consumption, VE/V_{CO_2} 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—Although circulatory power and traditional cardiopulmonary exercise testing parameters can be used to predict prognosis among patients with HF, ventilatory power provides relatively greater prognostic discrimination and may constitute a relatively more useful composite tool. **(*Circ Heart Fail*. 2012;5:621-626.)**

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 (V_{O_2}) and the minute ventilation/CO_2 production (VE/V_{CO_2}) slope are 2 well-validated CPX ventilatory indices used to assess prognosis of patients with heart failure (HF).[1–8]

Clinical Perspective on p 626

In a seminal study, Williams et al[9] combined peak V_{O_2} with a novel index, cardiac power, the product of cardiac output and mean arterial pressure (MAP), to characterize the relationship between cardiac-generated blood flow and peripheral perfusion pressure. Patients with HF with both low peak V_{O_2} and low cardiac power have worse outcomes than those with low peak V_{O_2} 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 noninvasively. Applying peak V_{O_2} as a surrogate for cardiac output and systolic blood pressure (SBP) for MAP, circulatory power is calculated as the product of peak V_{O_2} and SBP.

In this study, we analyzed the VE/V_{CO_2} slope in combination with SBP to form a new index that we labeled ventilatory power. Although peak V_{O_2} is thought to primarily reflect

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From the Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston, MA (D.E.F., E.W., K.M.D.); Heart Failure Unit, I.R.C.C.S Policlinico San Donato, University of Milano, Department of Biomedical Sciences for Health, Milano, Italy (M.G.); Division of Cardiology, VA Palo Alto Healthcare System, Palo Alto, CA (J.M.); Lebauer Cardiovascular Research Foundation, Greensboro, NC (P.C., D.B.); Department of Physical Therapy, University of Miami, Miami, FL (L.P.C.); Department of Internal Medicine, Virginia Commonwealth University, Richmond, VA (M.A.P.); Cardiovascular Medicine, Stanford University, Palo Alto, CA (A.S.); and Division of Physical Therapy, Department of Orthopaedics and Rehabilitation and Division of Cardiology, Department of Internal Medicine, University of New Mexico School of Medicine, Albuquerque, NM (R.A.).

Correspondence to Daniel E. Forman, MD, Division of Cardiovascular Medicine, 75 Francis St, Boston, MA 02115. Email deforman@partners.org

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central cardiac performance, the VE/V_{CO_2} slope manifests both peripheral (eg, peripheral perfusion and skeletal muscle chemoreflex and afferent reflex) and central and pulmonary hemodynamics (cardiac output, alveolar perfusion).[11,12] In this analysis, we compared ventilatory power with other ventilatory and hemodynamic indices derived from CPX to evaluate their prognostic use both individually and in combination with one another.

Methods

This study was a multicenter analysis including patients with HF from the exercise testing laboratories at LeBauer Cardiovascular Research Foundation, Greensboro, NC; Stanford University, Palo Alto, CA; VA Palo Alto Health Care System, Palo Alto, CA; Brigham and Women's Hospital, Boston, MA; Virginia Commonwealth University, Richmond, VA; 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 (ie, transplant candidacy/mechanical device implantation assessment and 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 <35% by 2-dimensional echocardiography obtained within 1 month of data collection. Institutional review board approval was obtained at LeBauer Cardiovascular Research Foundation Stanford University, VA Palo Alto Health Care System, Brigham and Women's Hospital, Virginia Commonwealth University, and San Paolo Hospital. All subjects provided written informed consent.

CPX Procedures

Symptom-limited CPX was performed on all subjects, and pharmacological therapy was maintained during exercise testing. Progressive exercise testing protocols using treadmill (93% of tests) or cycle ergometry (7% of tests) were used 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 True One 2400, Sandy, UT). We have previously found that 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. VE, V_{O_2}, and V_{CO_2} were acquired breath-by-breath and averaged over 10-second intervals. Peak V_{O_2} and peak respiratory exchange ratio were expressed as the highest 10-second averaged sample obtained during the last 20 seconds of testing. The VE and V_{CO_2} values, acquired from the initiation of exercise to peak, were entered into spreadsheet software (Microsoft Excel; Microsoft Corp, Bellevue, WA) to calculate the VE/V_{CO_2} slope via least squares linear regression ($y=mx+b$, m=slope). SBP, diastolic blood pressure, and MAP were assessed at rest, immediately before CPX and at peak exercise. MAP was approximated using the formula MAP=diastolic blood pressure+1/3(SBP−diastolic blood pressure). Circulatory power was defined as the product of peak V_{O_2} and peak SBP. Ventilatory power was defined as peak SBP divided by VE/V_{CO_2} 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/V_{CO_2} slope.

End Points

In the overall cohort, subjects were followed for major cardiac events (mortality, left ventricular assist device implantation, and urgent heart transplantation) via medical chart review for up to 4 years after 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 used in the present study. Any death with a cardiac-related discharge diagnosis was considered an event.

Statistical Analysis

Statistical software packages (SPSS 19.0; SPSS, Chicago, IL, and R, http://www.r-project.org/) were used to perform all analyses. Continuous and categorical data are reported as mean±SD 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 left ventricular ejection fraction and all CPX variables, 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 New York Heart Association class according to event status. χ^2 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 was compared using the concordance index.[14] For variables retained in the multivariate regression, receiver operating characteristic 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 Kaplan-Meier analyses. A 2-sided $P<0.05$ was considered statistically significant for all tests.

Results

A total of 875 patients were assessed. Their mean age was 55±14 years; 76% were men. The mean left ventricular ejection fraction was 26±9%, and the mean New York Heart Association Class was 2.5±0.08. The cause of HF was ischemic in 37% of the subjects and nonischemic in the remaining 63%.

There were 149 major cardiac events (82 deaths, 26 left ventricular assist device implantations, and 41 transplantations) during the 4-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 New York Heart Association class, a significantly higher left ventricular ejection fraction (after controlling for sex and age), and were more frequently prescribed an angiotensin converting enzyme inhibitor. Respiratory exchange ratio 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 (χ^2=0.27; P=0.61) nor sex (χ^2=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

Table 1. Differences in Baseline and CPX Variables According to Major Cardiac Event Status

	Event Free (n=726)	Major Cardiac Event (n=149)	*P* Value
Age, y	54.3±13.8	56.1±13.6	0.14
Sex (% male)	75	82	0.05
HF cause (% ischemic)	37	44	0.12
NYHA class	2.4±0.77	3.0±0.79	<0.001
LVEF, %	27.1±9.6	22.3±8.3	<0.001
Prescribed β-blocker, %	86	80	0.06
Prescribed ACE inhibitor, %	70	61	0.03
CPX variables			
Peak V_{O_2}, $mL_{O_2} \cdot kg^{-1} \cdot min^{-1}$	16.7±6.0	12.6±4.6	<0.001
Peak RER	1.13±0.13	1.12±0.17	0.06
VE/V_{CO_2} slope	34.1±8.8	40.7±11.3	<0.001
Resting SBP, mm Hg	116.9±20.7	106.3±21.7	<0.001
Resting DBP, mm Hg	72.8±13.0	68.2±12.4	<0.001
Resting MAP, mm Hg	87.4±13.7	80.9±13.6	<0.001
Peak SBP, mm Hg	147.2±29.6	123.9±27.9	<0.001
SBP increase, mm Hg	30.3±22.9	17.7±19.4	<0.001
Peak DBP, mm Hg	76.8±14.7	72.3±13.9	0.005
Peak MAP, mm Hg	100.3±16.9	89.5±16.7	<0.001
Circulatory power, $mm\ Hg \cdot mL_{O_2} \cdot kg^{-1} \cdot min^{-1}$	2498.7±1138.6	1600.8±820.0	<0.001
Ventilatory power, mm Hg	4.6±1.6	3.3±1.2	<0.001

CPX indicates cardiopulmonary exercise testing; HF, heart failure; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; ACE, angiotensin converting enzyme; V_{O_2}, oxygen consumption; RER, respiratory exchange ratio; VE/V_{CO_2}, minute ventilation/CO_2 production; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure.

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, whereas circulatory power was also retained in the regression (Table 3). The concordance index of the multivariate analysis listed in Table 3 improved in comparison with values for univariate predictors listed in Table 2. All other variables listed in Table 2 were removed from the multivariate predictive model (residual $\chi^2 \leq 3.8$; $P \geq 0.05$).

Table 2. Survival Analysis for Key Resting and CPX Variables: Univariate Predictors

	Univariate Analysis			
	χ^2	Hazard Ratio (95% CI)*	Concordance Index	*P* Value
Peak V_{O_2}	60.3	0.85 (0.82–0.89)	0.75	<0.001
VE/V_{CO_2} slope	107.4	1.07 (1.05–1.08)	0.76	<0.001
Resting SBP	44.0	0.97 (0.96–0.98)	0.68	<0.001
Resting DBP	23.2	0.97 (0.95–0.98)	0.63	<0.001
Resting MAP	38.7	0.96 (0.95–0.97)	0.67	<0.001
Peak SBP	91.3	0.97 (0.96–0.98)	0.76	<0.001
SBP increase	39.9	0.98 (0.97–0.98)	0.69	<0.001
Peak DBP	14.4	0.98 (0.97–0.99)	0.62	<0.001
Peak MAP	59.0	0.96 (0.95–0.97)	0.71	<0.001
Circulatory power	82.8	0.99 (0.99–0.99)	0.80	<0.001
Ventilatory power	110.8	0.43 (0.37–0.50)	0.80	<0.001

CPX indicates cardiopulmonary exercise testing; V_{O_2}, oxygen consumption; RER, respiratory exchange ratio; VE/V_{CO_2}, minute ventilation/CO_2 production; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure.

*Hazard ratio reflects per 1 unit increase (for VE/V_{CO_2} slope) or decrease (all other variables) for each variable listed. Units for each variable are listed in Table 1.

Receiver operating characteristic curve analysis identified ≤/>3.5 mm Hg (area under the curve: 0.70; $P<0.001$) and ≤/>1750 $mm\ Hg \cdot mL_{O_2} \cdot kg^{-1} \cdot min^{-1}$ (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 1 and 2 values below the defined thresholds demonstrated progressively worse event-free survival.

Discussion

This study introduces and evaluates the prognostic use of the novel concept of ventilatory power, a CPX-derived index that links the VE/V_{CO_2} slope and peak SBP. We demonstrated that ventilatory power is a strong predictor of cardiac events, ie, stronger than standard CPX indices (peak V_{O_2} and VE/V_{CO_2} slope) and even stronger than the enhanced prognostic index circulatory power, in which hemodynamics are linked to

Table 3. Survival Analysis for Key Resting and CPX Variables: Multivariate Predictors Retained in the Regression

	Multivariate Analysis			
	Hazard Ratio (95% CI)*	χ^2	Combined Concordance Index	*P* Value
Ventilatory power	0.57 (0.45–0.68)	110.8		<0.001
		Residual χ^2	0.82	
Circulatory power	0.99 (0.99–1.00)	13.8		<0.001

CPX indicates cardiopulmonary exercise testing.

*Hazard ratio reflects per 1 unit increase (for VE/V_{CO_2} slope) or decrease (all other variables) for each variable listed. Units for each variable are listed in Table 1.

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 use of CPX indices to assess prognosis of patients with HF.[1–8,11] It is novel in its reliance on the VE/V_{CO_2} slope, in combination with hemodynamics as a pivotal gauge of HF prognosis. Combining hemodynamics into the assessment is important because it incorporates manifestations of peripheral perfusion physiology into a composite quantification.

Arena et al[11] and others[7,8,15] have demonstrated the relatively greater use of the VE/V_{CO_2} slope over peak V_{O_2} to gauge HF pathophysiology and prognosis. The VE/V_{CO_2} slope is thought to better reflect the complex interplay of pulmonary, cardiac, and peripheral manifestations of the disease. Although Cohen-Solal et al[10] combined a CPX index with blood pressure to increase prognostic discrimination in their seminal study, they relied on peak V_{O_2}, which has several inherent limitations. The assumption that peak V_{O_2} provides a reliable proxy to cardiac output presumes that arteriovenous O_2 differences are fixed and overlook many of the pertinent physiological dynamics that also contribute to HF pathophysiology (eg, pulmonary function, skeletal muscle function, endothelial function).[16] Furthermore, although peak V_{O_2} depends on patient motivation, the VE/V_{CO_2} slope is relatively less likely to fluctuate, irrespective of a patient's level of exertional effort (and limitations because of noncardiac comorbidities).[17]

Although all CPX variables were significant univariate predictors of survival among patients with HF 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, diastolic blood pressure, and MAP) were substantially lower before, during, and after exercise in patients who experienced a major cardiac event compared with those who remained event free. These data attest to the broad relevance of hemodynamics in HF management[18–20] 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 and common medications

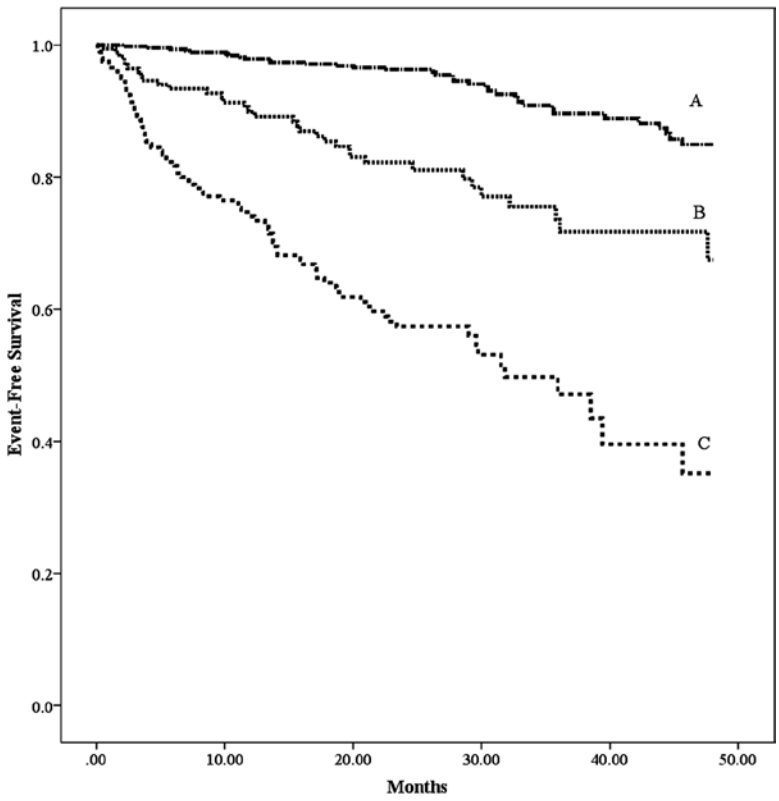

Figure. Applying specific cut points for ventilatory and circulatory power, gradations of risk were identified. **A**, Four hundred ninety-six subjects had ventilatory power >3.5 mm Hg and circulatory power >1750 mm $Hg \cdot mL_{O_2} \cdot kg^{-1} \cdot min^{-1}$. They experienced 34 events consistent with 93.1% event-free survival. **B**, One hundred seventy-six subjects had ventilatory power ≤3.5 mm Hg or circulatory power ≤1750 mm $Hg \cdot mL_{O_2} \cdot kg^{-1} \cdot min^{-1}$. They experienced 34 events, consistent with 80.7% event-free survival. **C**, Two hundred three subjects had ventilatory power ≤3.5 mm Hg and circulatory power ≤1750 mm $Hg \cdot mL_{O_2} \cdot kg^{-1} \cdot min^{-1}$. They had 81 events, consistent with 60.1% event-free survival. Overall, heart failure patients with the combination of both ventilatory power ≤3.5 mm Hg and circulatory power ≤1750 mm $Hg \cdot mL_{O_2} \cdot kg^{-1} \cdot min^{-1}$ were at highest risk for the composite cardiovascular end points.

used for this condition can both lead to hemodynamic lability,[21] especially in patients prone to chronotropic incompetence.[22] Whereas hypotension is common among patients with HF receiving guideline-based therapies, the consequences are presumed to be relatively benign among asymptomatic patients.[21] 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 with respect to ventilatory power (ie, ≥/< 3.5 mm Hg) or circulatory power (≤/> 1750 mm $Hg \cdot mL_{O_2} \cdot kg^{-1} \cdot min^{-1}$). 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 on a retrospective analysis of patients with HF. Prospective evaluations are needed to fully evaluate the use of ventilatory power as a marker of prognosis. Although the current study recognized common HF medications (β-blockers and angiotensin converting enzyme inhibitors), it did not systematically assess all cardiac and noncardiac medications, many of which might also have affected test results (eg, diuretics, statins, aldosterone antagonists). Similarly, comprehensive assessment of comorbidities was not completed (eg, hypertension, chronic obstructive pulmonary disease, 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 that the data obtained are comparable between treadmill and cycle ergometer tests.[22] Last, 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 the CPX laboratories included in the current analysis are very experienced, giving us high confidence in the validity and reliability of data. Furthermore, 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/V_{CO_2} slope by linking this ventilatory index to peripheral blood pressure. We demonstrated that ventilatory power provides excellent prognostic discrimination in a large population of patients with HF, exceeding that provided by traditional CPX indices and even by circulatory power.

Disclosures

None.

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CLINICAL PERSPECTIVE

This study introduces and evaluates the prognostic use of a novel cardiopulmonary exercise testing (CPX) index ventilatory power that links the minute ventilation/CO_2 (VE/V_{CO_2}) slope and peak systolic blood pressure. VE/V_{CO_2} slope manifests components of both peripheral (eg, peripheral perfusion and skeletal muscle chemoreflex and afferent reflex) and central (cardiac output, alveolar perfusion) indices that have been validated previously as a prognostic gauge for patients with heart failure. In this study, we demonstrate that the prognostic efficacy of VE/V_{CO_2} slope is enhanced by linking it to hemodynamics. Ventilatory power, defined as systolic blood pressure divided by VE/V_{CO_2} slope, is a strong predictor of cardiac events for patients with systolic HF, ie, stronger than standard CPX indices (peak V_{O_2} and VE/V_{CO_2} slope) and even stronger than circulatory power, another innovative CPX index in which peak V_{O_2} is linked to hemodynamics. Ventilatory power is independently predictive of cardiac events. Furthermore, when ventilatory power is analyzed in combination with circulatory power, the prognostic discrimination is synergistic. Overall, this study demonstrates growing sophistication regarding functional assessment by CPX and progressive refinements of CPX prognostic applications for HF. In particular, we show significant value in linking CPX-based ventilatory parameters to exercise hemodynamics as a composite index that identifies patients with systolic HF at greatest risk. Ventilatory power <3.5 mm Hg is an effective cut point to distinguish patients with systolic HF who may benefit most from added therapeutic measures.