End-Tidal CO_2 Pressure and Cardiac Performance during Exercise in Heart Failure

JONATHAN MYERS[1], PRADEEP GUJJA[2], SURESH NEELAGARU[3], LEON HSU[1], TIMOTHY VITTORIO[4], TAMIKA JACKSON-NELSON[4], and DANIEL BURKHOFF[5]

[1]Cardiology Division, Veterans Affairs Palo Alto Health Care System, Stanford University, Palo Alto, CA; [2]Texas Tech University of Health Sciences, Amarillo, TX; [3]Lonestar Arrhythmia and Heart Failure Center, Amarillo, TX; [4]Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY; and [5]Columbia University, New York, NY

ABSTRACT

MYERS, J., P. GUJJA, S. NEELAGARU, L. HSU, T. VITTORIO, T. JACKSON-NELSON, and D. BURKHOFF. End-Tidal CO_2 Pressure and Cardiac Performance during Exercise in Heart Failure. *Med. Sci. Sports Exerc.*, Vol. 41, No. 1, pp. 18–24, 2009. **Introduction:** In patients with heart failure (HF), end-tidal CO_2 pressure ($PetCO_2$) is related to ventricular function at rest and has been shown to predict prognosis. However, little is known about the association between ventricular performance and $PetCO_2$ responses to exercise. **Methods:** Forty-eight patients with HF and 13 normal subjects underwent cardiopulmonary exercise testing (CPX), while cardiac output and other hemodynamic measurements at rest and during exercise were obtained using a novel, noninvasive, bioreactance device based on assessment of relative phase shifts of electric currents injected across the thorax, heart rate, and ventricular ejection time. CPX responses and indices of cardiac performance were compared between normal subjects and HF patients achieving above and below a $PetCO_2$ of 36 mm Hg at the ventilatory threshold ($PetCO_2$@VT). **Results:** HF patients with an abnormal $PetCO_2$@VT (<36 mm Hg) had a lower exercise capacity, a lower $\dot{V}O_2$@VT, a higher $\dot{V}_E/\dot{V}CO_2$ slope, and lower oxygen uptake efficiency slope (OUES) values compared with normal subjects and patients achieving a normal $PetCO_2$@VT. Patients with reduced $PetCO_2$@VT had lower peak cardiac output responses to exercise (20.0 ± 10, 17.8 ± 6, and 13.7 ± 7 $L \cdot min^{-1}$ for normal subjects and HF patients with normal and abnormal $PetCO_2$ responses to exercise, respectively, $P = 0.04$). $PetCO_2$@VT was inversely related to the $\dot{V}_E/\dot{V}CO_2$ slope ($r = -0.78$, $P < 0.001$) and directly related to the OUES ($r = 0.55$, $P < 0.001$). **Conclusion:** Reduced $PetCO_2$ reflects impairments in the functional, ventilatory, and cardiac performance response to exercise in patients with HF. $PetCO_2$ can supplement other clinical and CPX indices in the functional and prognostic evaluation of patients with HF. **Key Words:** CARDIAC OUTPUT, OXYGEN UPTAKE, EXERCISE TESTING, VENTRICULAR FUNCTION, EXERCISE CAPACITY

Over the last two decades, the cardiopulmonary exercise test (CPX) has been widely used to help establish the severity of disease and to estimate prognosis in patients with chronic heart failure (CHF). The most commonly applied CPX response has been $\dot{V}O_2$ peak; specific $\dot{V}O_2$ peak values achieved have been used to stratify the degree of risk and have thus been recommended in consensus reports and guidelines on heart failure management (11,30,39). However, limitations to the use of $\dot{V}O_2$ peak for predicting prognosis have been widely described; these include an inability to determine "maximal" effort in some patients, its dependence on motivation, its questionable prognostic utility among patients who fall into an intermediate range ($10–18$ $mL \cdot kg^{-1} \cdot min^{-1}$) (7,9,23,25), and a discordance between $\dot{V}O_2$ peak, ventricular performance, and disease severity (24,36–38).

More recently, CPX responses reflecting ventilatory inefficiency during exercise have generated a great deal of interest. These indices include the ventilation to carbon dioxide production ($\dot{V}_E/\dot{V}CO_2$) slope, $\dot{V}O_2$ kinetics at exercise onset or in recovery, the oxygen uptake efficiency slope (OUES), an oscillatory breathing pattern, and a reduced end-tidal CO_2 pressure ($PetCO_2$) (1,3,13,20). Although the mechanisms underlying abnormal $\dot{V}_E/\dot{V}CO_2$ slope and OUES responses to exercise and their prognostic value have been extensively studied (1,3,13,20), little is known regarding clinical applications of $PetCO_2$. Based on studies performed in the intensive care unit (ICU) setting in a variety of disease states at rest, reduced $PetCO_2$ has been related to impaired cardiac output (5,12,14,27,31). Because an impaired cardiac output response to exercise underlies ventilation/perfusion mismatching leading to ventilatory inefficiency, there has been interest in $PetCO_2$ as a

Address for correspondence: Jonathan Myers, Ph.D., Cardiology Division-111C, Veterans Affairs Palo Alto Health Care System, 3801 Miranda Ave, Palo Alto, CA 94304; E-mail: drj993@aol.com.
Submitted for publication May 2008.
Accepted for publication June 2008.

0195-9131/09/4101-0018/0
MEDICINE & SCIENCE IN SPORTS & EXERCISE®

DOI: 10.1249/MSS.0b013e318184c945

prognostic marker. Indeed, both resting and exercise $PetCO_2$ have recently been demonstrated to be strong predictors of risk for adverse events in CHF (2,5); it has been reported that reduced $PetCO_2$ is an even more powerful predictor of risk than $\dot{V}O_2$ peak (5).

Studies describing the association between $PetCO_2$ and cardiac performance have largely done so using only cardiac performance measures at rest. Given the strong association between $PetCO_2$ and outcomes in patients with CHF, it would be useful to further explore the mechanisms underlying abnormalities in $PetCO_2$ at rest and during exercise. Historically, accurately acquiring cardiac output during exercise was a cumbersome process requiring right heart catheterization, which is costly and carries an inherent risk. The development of new technologies using transthoracic electrical properties offers the possibility of reasonably accurate, easy to perform, noninvasive measurements of cardiac output during exercise (17). One such approach is based on analysis of blood-flow–dependent changes in the phase shift of electrical currents applied across the chest. In contrast to the bioimpedance approach, which relies on detection of flow-dependent changes in electrical signal amplitude, phase shifts are inherently more accurately detectable and less subject to noise. Accordingly, this approach (termed *bioreactance*) has an improved signal-to-noise ratio and is less susceptible to physical factors such as body habitus, body motion, and ambient conditions. This approach has recently been reported to have acceptable precision and responsiveness for monitoring cardiac output in the catheterization laboratory and in the ICU among patients with a wide range of circulatory dysfunction (15,26) and during exercise among patients with CHF (22).

In light of recent studies demonstrating $PetCO_2$ to be a strong prognostic marker and the ability to measure cardiac performance noninvasively, we performed the current study. Our objectives were 1) to evaluate the association between $PetCO_2$ at rest and during exercise, other CPX responses, and the severity of CHF; and 2) to determine the ability of $PetCO_2$ to identify CHF patients with impaired cardiac output responses to exercise.

METHODS

Subjects. This was a retrospective analysis of clinical data obtained from 61 consecutive subjects referred to two private cardiology clinics for CPX testing for evaluation of dyspnea. All subjects provided written consent for the use of their data in the analysis; Investigational Review Board approval for the study was obtained from each institution. Forty-eight of the subjects had HF (31 with low ejection fraction [EF], 17 with normal EF) and 13 were ultimately diagnosed as normal (normal EF and $\dot{V}O_2$ peak, dyspnea based on noncardiac factors). Demographic and clinical characteristics of the subjects are summarized in Table 1. In the overall population, there was a broad range of EF, $\dot{V}O_2$ peak, and peak cardiac output values. All subjects were limited during exercise by fatigue or dyspnea, and none had clinical evidence of pulmonary disease or ischemic changes on the ECG.

TABLE 1. Demographic and clinical characteristics.

Patient Characteristics	CHF	Normals	*P* value
N	48	13	
Age (yr)	63 ± 12	51 ± 11	0.002
Height (cm)	170.8 ± 10	171.8 ± 10	0.76
Weight (kg)	84.3 ± 16	76.1 ± 14	0.10
Ejection fraction (%)	41.7 ± 16	56.5 ± 9	0.007
$\dot{V}O_2$ peak ($mL \cdot kg^{-1} \cdot min^{-1}$)	16.1 ± 5.7	24.8 ± 6.2	0.003
CHF etiology, no. subjects (%)		—	—
Ischemic cardiomyopathy	35 (74)	—	—
Idiopathic dilated cardiomyopathy	2 (4)	—	—
CHF with normal EF[a]	17 (35)	—	—
NYHA classification, *n* (%)			
Class I	12 (25)	—	—
Class II	9 (19)	—	—
Class III	21 (44)	—	—
Class IV	6 (12)	—	—
Medications, no. subjects (%)			
Digoxin	4 (9)	—	—
Beta blocker	36 (75)	6 (46)	—
ACE/ARB	38 (79)	—	—

CHF, chronic heart failure; EF, ejection fraction; NYHA, New York Heart Association; ACE/ARB, ACE inhibitor/angiotensin receptor blocker.
[a] >45%.

Exercise testing. Symptom-limited maximal exercise tests were performed on a treadmill using a ramp protocol (21). All subjects were requested to abstain from eating or smoking at least 3 h before the test. Ventilatory oxygen uptake was measured using a CPX-D (Medical Graphics Corporation, St. Paul, MN). Gas exchange data were acquired breath by breath and expressed in 10-s intervals of rolling 30-s averages. Oxygen uptake, carbon dioxide production, minute ventilation, and respiratory exchange ratio were calculated online. The percentage of age-predicted normal $\dot{V}O_2$ peak was determined for each subject using the equation of Wasserman et al. (33). A 12-lead electrocardiogram was monitored continuously and recorded every minute. Blood pressure was recorded manually every 2 min throughout the test. All subjects were encouraged to provide a maximal effort; among patients with CHF, the Borg 0 to 10 perceived exertion scale was used to quantify effort.

The ventilatory threshold was determined by two experienced, independent reviewers using the V-slope method (33) and was confirmed by ventilatory criteria. $PetCO_2$ represents the partial pressure of CO_2 at the end of an exhalation; the value was taken at the point of the ventilatory threshold (2), which typically represents the highest value of $PetCO_2$, after which it declines toward peak exercise (16,29) (termed $PetCO_2$@VT). A value of ≤36 mm Hg was used to define an abnormal response based on our previous observation that this represented an optimal cutpoint to define high-risk patient (2). In addition, a resting $PetCO_2$ value of ≤33 mm Hg was used to define abnormal based on previous findings that this value represents an optimal high-risk cutpoint (5). $\dot{V}_E$ and $\dot{V}CO_2$ responses, acquired from the initiation of exercise to peak, were used to calculate the $\dot{V}_E/\dot{V}CO_2$ slope via least squares linear regression

($y = mx + b$, where m = slope) (1). The oxygen uptake efficiency slope (OUES) was derived by the slope of a semi-log plot of minute ventilation versus $\dot{V}O_2$. As such, the OUES is an estimation of the efficiency of ventilation with respect to $\dot{V}O_2$, with greater slopes indicating greater ventilatory efficiency (1,3).

Cardiac output. The NICOM bioreactance-based system (Cheetah Medical, Wilmington, DE) is based on an analysis of relative phase shifts of an oscillating current that occur when traversing the thoracic cavity. This contrasts with the traditional bioimpedance-based systems that rely only on measured changes in signal amplitude. The NICOM system is comprised of a radiofrequency generator for creating a high-frequency current that is injected across the thorax, four dual surface electrodes that are used to establish electrical contact with the body, a receiving amplifier for recording the transthoracic voltage in response to the injected current, and circuitry for determining the relative phase shift between the injected current and the recorded voltage. Within each of the dual electrodes, one electrode is used by the high-frequency current generator whereas the other is used by the input voltage amplifier. Signals are applied to and recorded from the left and the right sides of the thorax; these signals are processed separately and averaged after digital processing. During exercise testing, the electrodes can be placed on the subject's back so that the cables do not interfere with upper body motion.

The signal processing unit of the system determines the relative phase shift ($\Delta\Phi$) between the input signal relative to the output signal. $\Delta\Phi$ in turn is due to changes in blood flow in the aorta. It has been shown that stroke volume (SV) is estimated by

$$SV = C \cdot VET \frac{d\Phi}{dt_{max}} \quad [1]$$

where C is a constant of proportionality and VET is the ventricular ejection time that is determined from the NICOM and the ECG signal. The value of C has been optimized in prior studies and accounts for patient age, gender, and body size (28). Cardiac output (CO) is then calculated using the relation

$$CO = SV \times HR, \quad [2]$$

where HR is the heart rate.

The NICOM system has conformité europeené (CE) mark in Europe and 510(k) clearance from the US Food and Drug Administration and is available for clinical use in both Europe and United States.

Statistical analysis. Differences in demographic and clinical characteristics between normal subjects and patients with CHF were assessed using unpaired *t*-tests for continuous data and chi-square tests for categorical data. Differences in CPX responses and indices of cardiac performance were compared between normal subjects and CHF patients achieving a $PetCO_2$@VT <36 and ≥36 mm Hg; these comparisons were performed using one-way ANOVA. *Post hoc* testing was performed using the Bonferroni method. The associations between noninvasive cardiac performance indices, clinical variables, and other exercise test responses were assessed using linear regression.

RESULTS

Among patients with CHF, 28 had a normal $PetCO_2$@VT response and 20 had an abnormal response. Table 2 presents exercise test responses between normal subjects and CHF patients with normal and abnormal $PetCO_2$ responses. Normal subjects were younger (51 ± 11 yr), but

TABLE 2. Exercise test responses in normal subjects and CHF patients with normal and abnormal $PetCO_2$ at the ventilatory threshold (mean ± SD).

	Normals	CHF and $PetCO_2$@VT ≥ 36	CHF and $PetCO_2$@VT < 36	*P* value[a]
Rest				
Standing heart rate (beats·min^{-1})	75 ± 13	72 ± 10	77 ± 13	0.26
Systolic blood pressure (mm Hg)	125 ± 9	120 ± 12	117 ± 7	0.09
Ventilatory threshold				
Heart rate (beats·min^{-1})	130 ± 22	100 ± 31*	97 ± 20*	0.002
Systolic blood pressure (mm Hg)	140 ± 7	137 ± 11	124 ± 13*†	0.006
Oxygen uptake (mL·min^{-1})	1487 ± 483	1190 ± 433	799 ± 295*†	<0.001
Oxygen uptake (mL·kg^{-1}·min^{-1})	19.8 ± 6	12.6 ± 4.2*	9.6 ± 2.7*	<0.001
Minute ventilation (L·min^{-1})	38.2 ± 15	30.8 ± 11.8	27.5 ± 9.7	0.05
CO_2 production (mL·min^{-1})	1445 ± 580	1089 ± 454	725 ± 284*†	<0.001
$PetCO_2$	42.7 ± 4.1	41.2 ± 4.2	32.3 ± 3.6*†	<0.001
Perceived exertion	—	4.1 ± 3	4.6 ± 3	0.78
Maximal exercise				
Heart rate (beats·min^{-1})	139 ± 24	121 ± 26	106 ± 21*	<0.001
Systolic blood pressure (mm Hg)	143 ± 12	146 ± 19	131 ± 15	0.02
Oxygen uptake (mL·min^{-1})	1857 ± 464	1614 ± 508	1044 ± 452*†	<0.001
Oxygen uptake (mL·kg^{-1}·min^{-1})	24.8 ± 6.2	18.4 ± 5.7*	13.0 ± 4.1*†	<0.001
Minute ventilation (L·min^{-1})	63.7 ± 16	55.0 ± 18	45.1 ± 17*	0.01
$\dot{V}_E/\dot{V}CO_2$ slope	0.28 ± 0.03	0.30 ± 0.04	0.41 ± 0.08*†	<0.001
OUES	2.1 ± 0.59	1.9 ± 0.60	1.2 ± 0.49*†	<0.001
CO_2 production	2173 ± 577	1784 ± 615	1099 ± 488*†	<0.001
Respiratory exchange ratio	1.15 ± 0.09	1.10 ± 0.11	1.08 ± 0.09	0.20
Perceived exertion	—	7.6 ± 2	8.0 ± 1	0.64

OUES, oxygen uptake efficiency slope.
[a] *P* value represents ANOVA main effect between groups.
* $P < 0.05$ versus normal subjects.
† $P < 0.05$ versus CHF and normal $PetCO_2$.

TABLE 3. Noninvasive cardiac output data at rest and peak exercise in normal subjects and CHF patients with normal and elevated $PetCO_2$ at the ventilatory threshold.

	Normals	CHF and $PetCO_2$@VT ≥ 36	CHF and $PetCO_2$@VT < 36	*P* value[a]
Rest				
Cardiac output ($L \cdot min^{-1}$)	5.45 ± 1.7	4.84 ± 1.4	4.77 ± 1.5	0.39
Cardiac index ($L \cdot min^{-1} \cdot M^{-2}$)	2.89 ± 0.78	2.40 ± 0.56	2.54 ± 0.76	0.12
dx/dt ($\Omega \cdot s^{-1}$)	171.3 ± 107	100.2 ± 64	148.3 ± 119	0.09
VET (ms)	174.3 ± 36	166.8 ± 25	157.4 ± 16	0.21
Ejection fraction	56.5 ± 9	45.0 ± 15	36.9 ± 17*	0.03
Peak exercise				
Cardiac output ($L \cdot min^{-1}$)	20.0 ± 10.0	17.8 ± 5.9	13.7 ± 6.6	0.04
Cardiac index ($L \cdot min^{-1} \cdot M^{-2}$)	10.6 ± 4.7	9.0 ± 3.3	7.2 ± 3.2*	0.04
dx/dt ($\Omega \cdot s^{-1}$)	557.8 ± 239	395.2 ± 203	362.7 ± 140*†	0.04
VET (ms)	143.6 ± 17	143.6 ± 12	149.3 ± 22	0.52

VT, ventilatory threshold; VET, ventricular ejection time.
[a] P value represents ANOVA main effect between groups.
* $P < 0.05$ versus normal subjects.
† $P < 0.05$ versus CHF and $PetCO_2 \geq 36$.

the two groups of CHF patients did not differ (61 ± 12 and 66 ± 12 yr, respectively). For the overall group, the mean maximal perceived exertion was 7.8 ± 1.7 (range = 5–10), and the mean peak respiratory exchange ratio was 1.12 ± 0.09 (range = 0.87–1.28), suggesting that maximal effort was achieved by most patients. Normal subjects generally achieved higher exercise test responses than both groups of patients with CHF, and patients with an abnormal $PetCO_2$ response achieved lower values compared to patients with a normal response. Mean maximal oxygen uptake values for normal subjects and patients with a normal and an abnormal $PetCO_2$ response were 24.8 ± 6, 18.4 ± 6, and 13.0 ± 4 $mL \cdot kg^{-1} \cdot min^{-1}$, respectively ($P < 0.001$). Similarly, oxygen uptake at the ventilatory threshold and other CPX responses were highest among normal subjects and lowest among CHF patients with an abnormal $PetCO_2$ response to exercise. CHF patients with an abnormal $PetCO_2$@VT also had a higher $\dot{V}_E/\dot{V}CO_2$ slope and a lower OUES versus patients with a normal $PetCO_2$ response.

Although CPX and cardiac output responses tended to be highest among normal subjects and lowest among patients with an abnormal $PetCO_2$ at rest, the differences were not as striking as those for $PetCO_2$ during exercise ($PetCO_2$@VT). The $\dot{V}_E/\dot{V}CO_2$ slope, however, was notably different between the three groups (0.28 ± 0.03, 0.31 ± 0.06, and 0.38 ± 0.09 for normal subjects and CHF patients with a normal and abnormal resting $PetCO_2$, respectively, $P < 0.001$)

Table 3 shows resting and peak exercise cardiac output, cardiac index, index of peak aortic flow (*dx/dt*), and ventricular ejection time (VET) between normal subjects and CHF patients with normal and abnormal $PetCO_2$ responses to exercise. Resting EF was lower in CHF patients with an abnormal $PetCO_2$ response to exercise versus normal subjects. No other differences were observed in measures of cardiac performance at rest between groups. CHF patients with an abnormal $PetCO_2$@VT had reduced cardiac output and cardiac index responses to exercise (cardiac output = 20.0 ± 10, 17.8 ± 5.9, and 13.7 ± 6.6 $L \cdot min^{-1}$ for normal subjects and CHF patients with normal and abnormal $PetCO_2$@VT responses, respectively, $P = 0.04$). Similar results were observed for cardiac output responses at the VT (Fig. 1). When CHF patients were separated by high and low EF (<45% or ≥45%), no differences were observed in exercise test or cardiac performance measures between groups.

Table 4 presents correlation coefficients between CPX responses and indices of cardiac performance. Peak cardiac output was significantly correlated to the OUES ($r = 0.57$, $P < 0.001$) and inversely related to the $\dot{V}_E/\dot{V}CO_2$ slope ($r = -0.36$, $P < 0.01$). $PetCO_2$@VT was significantly but

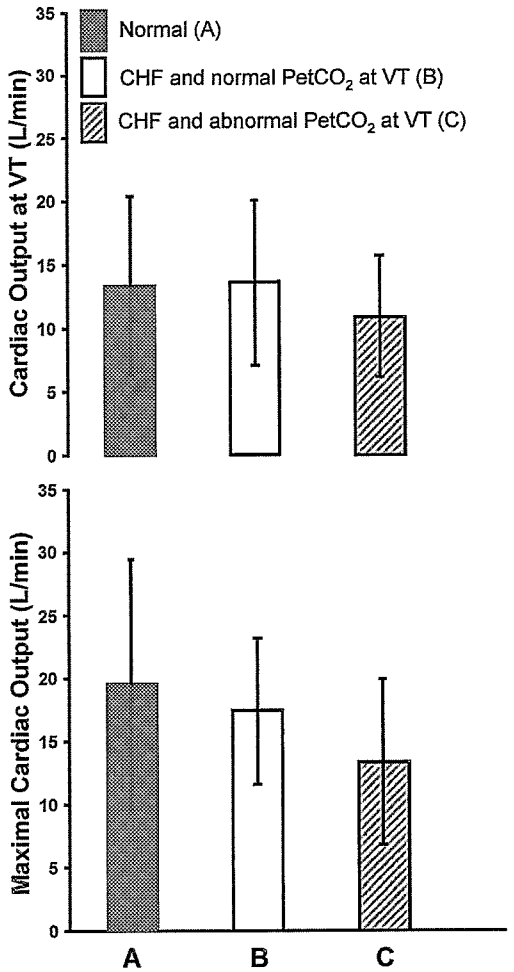

FIGURE 1—Cardiac output among normal subjects and CHF patients with normal and abnormal $PetCO_2$ responses to exercise at the ventilatory threshold (VT, *top*) and maximal exercise (*bottom*; ANOVA main effect $P = 0.03$). Error bars represent the SD.

TABLE 4. Correlation coefficients between CPX responses and measures of cardiac performance.

	Peak Cardiac Output	Cardiac Output at VT	$\dot{V}O_2$ Peak	$PetCO_2$@VT	$\dot{V}_E/\dot{V}CO_2$ Slope	OUES
Peak cardiac output	—					
Cardiac output at VT	0.58*	—				
$\dot{V}O_2$ peak	0.45*	0.23	—			
$PetTCO_2$@VT	0.28†	0.25	0.78*	—		
$\dot{V}_E/\dot{V}CO_2$ slope	−0.36*	−0.27†	−0.57*	−0.78*	—	
OUES	0.57*	0.38*	0.73*	0.55*	−0.67*	—

VT, ventilatory threshold; $PetCO_2$, end-tidal CO_2 pressure; OUES, oxygen uptake efficiency slope.
*$P < 0.01$.
†$P < 0.05$.

weakly related to peak cardiac output ($r = 0.28$, $P < 0.05$) but strongly related to markers of ventilatory inefficiency ($r = -0.78$, $P < 0.001$, and $r = 0.55$, $P < 0.001$, for the relation between $PetCO_2$@VT and $\dot{V}_E/\dot{V}CO_2$ slope and OUES, respectively; Fig. 2).

DISCUSSION

$PetCO_2$ has been associated with cardiac output in a variety of experimental and clinical settings, including the ICU, in cardiogenic shock, and during surgery. Idris et al. (12), for example, observed that $PetCO_2$, at a constant ventilation, paralleled cardiac output over a wide range of flow rates in an animal model. Sibutani et al. (27) reported that across a range of cardiac output responses and at a constant ventilation among subjects undergoing abdominal aortic aneurysm repair, $PetCO_2$ correlated closely with changes in cardiac output. Using dye dilution measurements of cardiac output, Matsumoto et al. (18) reported that the sensitivity and the specificity of a low $PetCO_2$ during exercise to predict an impaired cardiac output response to exercise were 77% and 75%, respectively, in a heterogeneous group of patients with cardiovascular disease. Over the last decade, numerous other studies have proposed the application of $PetCO_2$ as a surrogate marker of cardiac impairment in various disease states (2,4,5,8,14,32), but few data are available during exercise. Moreover, despite recent interest in $PetCO_2$ at rest and during exercise as a prognostic marker (2,5), little is known regarding the relationship between $PetCO_2$ and cardiac performance during exercise in patients with CHF.

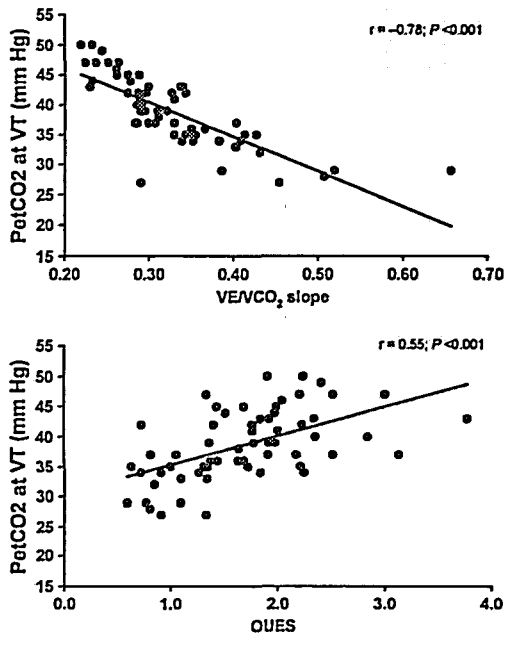

FIGURE 2—The relationships between the $PetCO_2$@VT and the $\dot{V}_E/\dot{V}CO_2$ slope (*top*) and the oxygen uptake efficiency slope (OUES, *bottom*).

The current results. Using a $PetCO_2$ response to exercise that has previously identified CHF patients at high risk for adverse outcomes (2), we observed that $PetCO_2$ identified patients with a reduced exercise capacity, a ventilatory inefficiency, an earlier onset of the ventilatory threshold, and reduced cardiac performance during exercise. The mean $\dot{V}O_2$ peak among patients with an abnormal $PetCO_2$ response to exercise was 13.0 $mL \cdot kg^{-1} \cdot min^{-1}$, a value below the cut point that has long been recognized in CHF guidelines as a marker for high risk (11,30,39). This suggests that that $PetCO_2$, a variable that is readily available from a typical metabolic system, can be used as a rough surrogate for the degree of cardiac impairment in response to exercise. The clinical implications of these results include the fact that $PetCO_2$ can complement other clinical and exercise test responses in the evaluation of patients with CHF. The observations that $PetCO_2$ reflects cardiac impairment during exercise (Fig. 1), is a marker of ventilatory inefficiency (Fig. 2), and strongly predicts prognosis (2,5) suggest that $PetCO_2$ should be routinely measured and included in the CPX test report when evaluating patients with CHF.

The current findings extend previously demonstrated associations between $PetCO_2$ and cardiac output at rest (4,5,8,12,14,27,31,32) by observing an association between $PetCO_2$ during exercise and the severity of CHF, the degree of exercise intolerance, and the degree of ventilatory inefficiency. The associations between $PetCO_2$@VT and indices of ventilatory inefficiency ($\dot{V}_E/\dot{V}CO_2$ slope and OUES, $r = -0.78$ and 0.55, respectively; Fig. 2) underscore the link between low $PetCO_2$ and an impaired cardiac output response to exercise, leading to ventilation/perfusion mismatching, heightened dead space ventilation, and exercise intolerance. Our results are similar to those of Tanabe et al. (29), who reported a correlation coefficient of −0.84 between the peak exercise $PetCO_2$ and the $\dot{V}_E/\dot{V}CO_2$ slope, and those of Matsumoto et al. (18), who observed a

correlation of −0.78 between the $\dot{V}_E/\dot{V}CO_2$ slope and $PetCO_2$ at the respiratory compensation point. Both these previous studies also observed that $PetCO_2$ during exercise was strongly and inversely related to V_D/V_T during exercise. The relation we observed between exercise $PetCO_2$ and $\dot{V}O_2$ peak was more modest ($r = 0.53$), similar to that observed by Wasserman et al. (34) ($r = 0.36$). Although numerous previous studies have reported that *resting* $PetCO_2$ reflects cardiac output changes among hospitalized patients (e.g., ICU settings) and has been shown to be prognostic (4,5,8,12,14,18,27,31,32), resting $PetCO_2$ in the current study was somewhat less effective in identifying patients with an impaired exercise response. This is likely because unlike hospitalized patients, our subjects were ambulatory and generally did not exhibit overtly reduced cardiac output at rest.

Mechanism for impaired $PetCO_2$. In normal subjects, $PetCO_2$ increases during exercise due to a higher rate of CO_2 production and thus CO_2 delivery to the lungs by venous return. Although $PetCO_2$ is similar to arterial CO_2 pressure ($PaCO_2$) in normally perfused alveoli, it is generally lower than $PaCO_2$ in patients with ventilation/perfusion (V_D/V_T) mismatching, such as that commonly present in patients with CHF (33,34). Thus, when the rise in cardiac output with exercise is impaired, $PetCO_2$ is reduced due both to the reduction in delivery of CO_2 to the lung and to the mismatching of ventilation and perfusion caused by impaired cardiac output. $PetCO_2$ during exercise is reduced when the V_D/V_T ratio is high, as has been reported in patients with chronic obstructive pulmonary disease and pulmonary hypertension (10), and is reduced in accordance with the impairment in $\dot{V}O_2$ peak in patients with CHF (18,29,34).

Noninvasive estimation of cardiac output. The noninvasive estimation of cardiac output using the NICOM device provided a useful and an easily applied tool to gain insight into cardiac performance during exercise. An impaired cardiac output response to exercise is a widely recognized hallmark of CHF (3,13,22,33,34,39), and direct measurements of the cardiac output response to exercise have been demonstrated to predict outcomes in CHF (6,17,19,35). Data on the direct measurement of the impaired cardiac output response to exercise are limited, however, due to the difficulties associated with performing this procedure (including the fact that it is invasive, costly, and associated with higher risk). The ability to routinely quantify cardiac output during exercise easily and noninvasively potentially has a great deal of value, both in terms of quantifying the degree of cardiac impairment as well as for risk stratification. Although both the $PetCO_2$ (2,15) and the cardiac output response to exercise (6,17,19,35) have been shown to be strong markers of prognosis in patients with CHF, the extent to which these two measures provide independent or additive prognostic value requires further study.

Limitations. We did not have direct measurements of cardiac output with which to compare those of the noninvasive device, although the device has recently undergone validation in both experimental and clinical conditions (15,22,26,28). We did not measure direct arterial blood gases with which to quantify V_D/V_T; however, numerous prior studies have documented ventilation/perfusion mismatching with exercise in CHF. In addition, both $PetCO_2$ and noninvasive estimates of cardiac performance require further study as determinants of prognosis.

Summary. Reduced $PetCO_2$ during exercise reflects the severity of HF and the impaired cardiac output response to exercise in patients with CHF. $PetCO_2$ is a marker of ventilatory inefficiency and cardiac performance that should be routinely reported when performing CPX to evaluate patients with CHF.

This study was supported in part by a grant from the Cheetah Medical Inc., Wilmington, DE. The results of the present study do not constitute endorsement by ACSM.

REFERENCES

1. Arena R, Guazzi M, Myers J. Ventilatory abnormalities during exercise in heart failure: a mini review. *Curr Respir Med Rev.* 2007;3:179–87.
2. Arena R, Guazzi M, Myers J. Prognostic value of end-tidal carbon dioxide during exercise testing in heart failure. *Int J Cardiol.* 2007; 117:103–8.
3. Arena R, Myers J, Guazzi M. The clinical and research applications of aerobic capacity and ventilatory efficiency in heart failure: an evidenced-based review. *Heart Fail Rev.* 2008; 13:245–69.
4. Arena R, Peberdy MA. Reliability of resting end-tidal carbon dioxide in chronic heart failure. *J Cardiopulm Rehabil Prev.* 2005;25:177–80.
5. Arena R, Peberdy MA, Myers J, Guazzi M, Tevald M. Prognostic value of resting end-tidal carbon dioxide in patients with heart failure. *Int J Cardiol.* 2006:109;351–8.
6. Chomsky DB, Lang CC, Rayos GH, et al. Hemodynamic exercise testing: a valuable tool in the selection of cardiac transplantation candidates. *Circulation.* 1996;94:3176–83.
7. Corra U, Mezzani A, Bosimini E, Scapellato F, Imparato A, Giannuzzi P. Ventilatory response to exercise improves risk stratification in patients with chronic heart failure and intermediate functional capacity. *Am Heart J.* 2002;143:418–26.
8. Deakin CD, Sado DM, Coats TJ, Davies G. Prehospital end-tidal carbon dioxide concentration and outcome in major trauma. *J Trauma.* 2004;57:65–8.
9. Francis DP, Shamin W, Ceri Davies L, et al. Cardiopulmonary exercise testing for prognosis in chronic heart failure: continuous and independent prognostic value from $\dot{V}_E/\dot{V}CO_2$ slope and peak $\dot{V}O_2$. *Eur Heart J.* 2000;21:154–61.
10. Hansen J, Ulubay G, Chow B, Sun X, Wasserman K. Mixed-expired and end-tidal CO_2 distinguish between ventilation and

perfusion defects during exercise testing in patients with lung and heart diseases. *Chest.* 2007;132:977–83.
11. Hunt SA. American College of Cardiology, American Heart Association Task Force on Practice Guidelines. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to update the 2001 Guidelines for the Evaluation and Management of Heart Failure). *J Am Coll Cardiol.* 2005;46:e1–82.
12. Idris AH, Staples ED, O'Brien DJ, et al. End-tidal carbon dioxide during extremely low cardiac output. *Ann Emerg Med.* 1994;23: 568–72.
13. Ingle L. Theoretical rational and practical recommendations for cardiopulmonary exercise testing in patients with chronic heart failure. *Heart Fail Rev.* 2007;12:12–22.
14. Jin X, Weil MH, Tang W, et al. End-tidal carbon dioxide as a noninvasive indicator of cardiac index during circulatory shock. *Crit Care Med.* 2000;28:2415–9.
15. Keren H, Burkhoff D, Squara P. Evaluatin of a non-invasive cardiac output monitoring system based on thoracic bioreactance. *Am J Physiol.* 2007;293:H583–9.
16. Koike A, Wasserman K, Armon Y, Weiler-Ravell D. The work-rate dependent effect of carbon monoxide on ventilatory control during exercise. *Respir Physiol.* 1991;85:169–83.
17. Lang CC, Agostoni P, Mancini DM. Prognostic significance and measurement of exercise-derived hemodynamic variables in patients with heart failure. *J Card Fail.* 2007;13:672–9.
18. Matsumoto A, Itoh H, Eto Y, et al. End-tidal CO_2 pressure decreases during exercise in cardiac patients: association with severity of heart failure and cardiac output reserve. *J Am Coll Cardiol.* 2000;36:242–9.
19. Metra M, Faggiano P, D'Aloia A, et al. Use of cardiopulmonary exercise testing with hemodynamic monitoring in the prognostic assessment of ambulatory patients with chronic heart failure. *J Am Coll Cardiol.* 1999;33:943–50.
20. Myers J. Applications of cardiopulmonary exercise testing in the management of cardiovascular and pulmonary disease. *Int J Sports Med.* 2005;26:s490–55.
21. Myers J, Buchanan N, Walsh D, et al. Comparison of the ramp versus standard exercise protocols. *J Am Coll Cardiol.* 1991;17: 1334–42.
22. Myers J, Gujja P, Neelagaru S, Burkhoff D. Cardiac output and cardiopulmonary responses to exercise in heart failure: application of a new bio-reactance device. *J Cardiac Fail.* 2007;13; 629–36.
23. Myers J, Gullestad L, Vagelos R, et al. Cardiopulmonary exercise testing and prognosis in severe heart failure: 14 mL/kg/min revisited. *Am Heart J.* 2000;139:78–84.
24. Myers J, Zaheer N, Quaglietti S, Madhavan R, Froelicher V, Heidenreich P. Association of functional and health status measures in heart failure. *J Card Fail.* 2006;12;439–45.
25. Opasich C, Pinna GD, Bobbio M, et al. Peak oxygen consumption in chronic heart failure: toward efficient use in the individual patient. *J Am Coll Cardiol.* 1998;31:766–75.
26. Raval NY, Squara P, Cleman M, Yalamanchili K, Winkmaier M, Burkhoff D. Multicenter evaluation of non-invasive cardiac output measurement by bioreactance technique. *J Clin Monit Comput.* 2008;22:113–9.
27. Shibutani K, Muraoka M, Shirasaki S, Kubal K, Sanchala VT, Gupte P. Do changes in end-tidal PCO_2 quantitatively reflect changes in cardiac output? *Anesth Analg.* 1994;79:829–33.
28. Squara P, Denjean D, Estagnasie P, Brusset A, Dubois C. Non-invasive cardiac output monitoring. (NICOM); clinical evaluation. *Intensive Care Med.* 2007;33:1191–4.
29. Tanabe Y, Hosaka Y, Ito M, Ito E, Suzuki K. Significance of end-tidal PCO_2 response to exercise and its relation to functional capacity in patients with chronic heart failure. *Chest.* 2001;119: 811–7.
30. Task Force of the Italian Working Group on Cardiac Rehabilitation and Prevention, Working Group on Cardiac Rehabilitation and Exercise Physiology of the European Society of Cardiology. Statement on cardiopulmonary exercise testing in chronic heart failure due to left ventricular dysfunction: recommendations for performance and interpretation. Part III: interpretation of cardiopulmonary exercise testing in chronic heart failure and future applications. *Eur J Cardiovasc Prev Rehabil.* 2006;13(4);485–95.
31. Wahba RW, Tessler MJ, Beique F, Kleiman SJ. Changes in PCO_2 with acute changes in cardiac index. *Can J Anaesth.* 1996; 43:243–5.
32. Ward KR, Yealy DM. End-tidal carbon dioxide monitoring in emergency medicine. Part 2: Clinical applications. *Acad Emerg Med.* 1998;5:637–46.
33. Wasserman K, Hansen JE, Sue DY, Casaburi R, Whipp BJ. Principles of exercise testing and interpretation, 4th ed. Baltimore: Lippincott, Williams & Wilkins; 2004, p. 160–7.
34. Wasserman K, Zhang YY, Gitt A, et al. Lung function and exercise gas exchange in chronic heart failure. *Circulation.* 1997;96:2221–7.
35. Williams SG, Cooke GA, Wright DJ, et al. Peak exercise cardiac power output; a direct indicator of cardiac function strongly predictive of prognosis in chronic heart failure. *Eur Heart J.* 2001; 16:1496–503.
36. Wilson JR, Hanamanthu S, Chomsky DB, Davis SF. Relationship between exertional symptoms and functional capacity in patients with heart failure. *J Am Coll Cardiol.* 1999;33: 1943–7.
37. Wilson JR, Rayos G, Yeoh TK, Gothard P. Dissociation between peak exercise oxygen consumption and hemodynamic dysfunction in potential heart transplant candidates. *J Am Coll Cardiol.* 1995; 26:429–35.
38. Wilson JR, Rayos G, Yeoh TK, Gothard P, Bak K. Dissociation between exertional symptoms and circulatory function in patients with heart failure. *Circu.* 1995;92:47–53.
39. Working Group on Cardiac Rehabilitation & Exercise Physiology and Working Group on Heart Failure of the European Society of Cardiology. Recommendations for exercise testing in chronic heart failure patients. *Eur Heart J.* 2001;22: 37–45.