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ORIGINAL RESEARCH

Reliability and Physiological Interpretation of Pulmonary Gas Exchange by "Circulatory Equivalents" in Chronic Heart Failure

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***Background*—**Peak ratios of pulmonary gas-exchange to ventilation during exercise ($\dot{V}O_2/\dot{V}_E$ and $\dot{V}CO_2/\dot{V}_E$, termed "circulatory equivalents") are sensitive to heart failure (HF) severity, likely reflecting low and/or poorly distributed pulmonary perfusion. We tested whether peak $\dot{V}O_2/\dot{V}_E$ and $\dot{V}CO_2/\dot{V}_E$ would: (1) distinguish HF patients from controls; (2) be independent of incremental exercise protocol; and (3) correlate with lactate threshold (LT) and ventilatory compensation point (VCP), respectively.

***Methods and Results*—**Twenty-four HF patients (61±11 years) with reduced ejection fraction (31±8%) and 11 controls (63±7 years) performed ramp-incremental cycle ergometry. Eighteen HF patients also performed slow (5±1 W/min), medium (9±4 W/min), and fast (19±6 W/min) ramps. Peak $\dot{V}O_2/\dot{V}_E$ and $\dot{V}CO_2/\dot{V}_E$ from X-Y plot, and LT and VCP from 9-panel plot, were determined by 2 independent, blinded, assessors. Peak $\dot{V}O_2/\dot{V}_E$ (31.2±4.4 versus 41.8±4.8 mL/L; $P<0.0001$) and $\dot{V}CO_2/\dot{V}_E$ (29.3±3.0 versus 36.9±4.0 mL/L; $P<0.0001$) were lower in HF than controls. Within individuals, there was no difference across 3 ramp rates in peak $\dot{V}O_2/\dot{V}_E$ ($P=0.62$) or $\dot{V}CO_2/\dot{V}_E$ ($P=0.97$). Coefficient of variation (CV) in peak $\dot{V}O_2/\dot{V}_E$ was lower than for LT (5.1±2.1% versus 8.2±3.7%; $P=0.014$), and coefficient of variation in peak $\dot{V}CO_2/\dot{V}_E$ was lower than for VCP (3.3±1.8% versus 8.7±4.2%; $P<0.001$). In all participants, peak $\dot{V}O_2/\dot{V}_E$ was correlated with, but occurred earlier than, LT ($r^2=0.94$; mean bias, −0.11 L/min), and peak $\dot{V}CO_2/\dot{V}_E$ was correlated with, but occurred earlier than, VCP ($r^2=0.98$; mean bias −0.08 L/min).

***Conclusions*—**Peak circulatory equivalents during exercise are strongly associated with (but not identical to) LT and VCP. Peak circulatory equivalents are reliable, objective, effort-independent indices of gas-exchange abnormality in HF. **(*J Am Heart Assoc*. 2018;7:e008072. DOI: 10.1161/JAHA.117.008072.)**

Key Words: cycle ergometry • heart failure • incremental exercise • lactate threshold • ventilatory compensation

Chronic heart failure (HF) is characterized by dyspnea on exertion and exercise intolerance.[1] HF remains a progressive disease, and the associated exercise intolerance is the strongest correlate of morbidity and mortality.[2–4] Peak oxygen uptake ($\dot{V}O_{2peak}$),[5] end-tidal gas tensions,[6] and oscillatory breathing[7,8] measured by cardiopulmonary exercise testing (CPET) are prognostic of mortality in HF, and $\dot{V}O_{2peak}$ and lactate threshold (LT) are used for risk stratification, such as to guide suitability for transplant.[4,9–11] The relationship between ventilation ($\dot{V}_E$) and carbon dioxide output ($\dot{V}CO_2$) (either as the $\dot{V}_E/\dot{V}CO_2$ slope, or the value of $\dot{V}_E/\dot{V}CO_2$ at a specified submaximal metabolic rate; eg, at LT or the ventilatory compensation point [VCP]), typically provides one of the strongest prognosticators,[12–14] either independently or in combination with other CPET and non-CPET variables.[15,16]

Recently, the ratios of pulmonary gas exchange to ventilation ($\dot{V}O_2/\dot{V}_E$ and $\dot{V}CO_2/\dot{V}_E$, termed circulatory equivalents) have been added to the list of CPET-derived variables. By placing ventilation in the denominator, these "circulatory equivalents" (so called, because of the mechanistic dependence on pulmonary blood flow for O_2 and CO_2 exchange) reflect the rate of pulmonary gas exchange accomplished at a given level of ventilation. Hansen et al[17] demonstrated the sensitivity of circulatory equivalents to distinguish HF severity using a plot that presents $\dot{V}O_2/\dot{V}_E$ versus $\dot{V}CO_2/\dot{V}_E$ on equal X-Y axes. The response profiles of this graphical representation from rest, exercise, and recovery provide a simple

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Clinical Perspective

What Is New?

- The physiological basis, and sensitivity to exercise testing protocol, of peak ratios of pulmonary gas exchange to ventilation during exercise ($\dot{V}O_2/\dot{V}_E$ and $\dot{V}CO_2/\dot{V}_E$)—termed "circulatory equivalents"—were investigated in heart failure and controls.

What Are the Clinical Implications?

- Peak circulatory equivalents are reliable, objective, effort-independent indices of gas-exchange abnormality in heart failure, which may help to simplify interpretation of cardiopulmonary exercise testing results.

visualization of the normalcy (or otherwise) of gas exchange: a large "open" curve with greater peak values represents greater aerobic capacity and greater ventilatory efficiency than a "narrow" curve with lower peak values (eg, see Figure 1B and 1D). The peak values of the $\dot{V}O_2/\dot{V}_E$ and $\dot{V}CO_2/\dot{V}_E$ ratios are effort-independent quotients that occur submaximally and therefore do not depend on maximal effort during a symptom limited test. Objectively measured peak circulatory equivalents stratify severity in HF.[17]

The physiological processes that determine peak circulatory equivalents, however, have not been established. Break points in ventilatory equivalents (the inverse of circulatory equivalents) are used to inform the noninvasive estimation of LT and VCP.[9,18,19] We therefore aimed to establish the association between peak $\dot{V}O_2/\dot{V}_E$ and LT and peak $\dot{V}CO_2/\dot{V}_E$ and VCP during ramp-incremental exercise in HF. Association among these variables would support the physiological constructs underpinning the profile of the circulatory equivalent X-Y plot.[17]

It is well established that peak $\dot{V}CO_2$ and $\dot{V}_E$ responses to incremental exercise differs in response to fast, medium, and slow ramp-incremental tests in HF, whereas LT and peak $\dot{V}O_2$ do not.[20,21] Therefore, to assess the robustness of peak circulatory equivalents, we measured these variables using fast (lasting ≈5 minutes before intolerance), medium (≈10 minutes), and slow (≈15 minutes) ramp-incremental tests. We reasoned that should peak $\dot{V}O_2/\dot{V}_E$ and $\dot{V}CO_2/\dot{V}_E$ represent LT and VCP (epoch events in an individual's aerobic range), then they should be unaffected by different ramp-incremental protocols: A low variability would support the reliability of circulatory equivalents to detect abnormality, where it occurs, independently of the exercise testing protocol.

We therefore tested the hypotheses that the peak $\dot{V}O_2/\dot{V}_E$ and $\dot{V}CO_2/\dot{V}_E$ values during ramp-incremental exercise would: (1) distinguish HF patients from age-matched controls, as previously shown; (2) be independent of incremental exercise protocol within the same patients; and (3) correlate with LT and VCP, respectively.

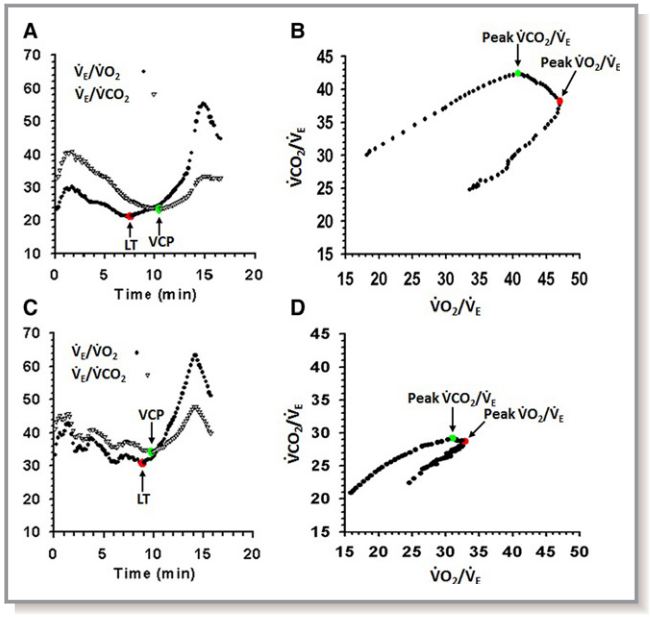

Figure 1. Ratios of ventilation and pulmonary gas exchange during ramp-incremental exercise in heart failure and controls. A, Ventilatory equivalents ($\dot{V}_E/\dot{V}O_2$ and $\dot{V}_E/\dot{V}CO_2$) in a healthy subject plotted against time using a 90-second rolling average. B, Circulatory equivalents ($\dot{V}O_2/\dot{V}_E$ and $\dot{V}CO_2/\dot{V}_E$) in a healthy subject, using the same data as in (A), plotted in an X-Y plot arrangement. C, Ventilatory equivalents ($\dot{V}_E/\dot{V}O_2$ and $\dot{V}_E/\dot{V}CO_2$) in a heart failure patient plotted against time using a 90-second rolling average. D, Circulatory equivalents ($\dot{V}O_2/\dot{V}_E$ and $\dot{V}CO_2/\dot{V}_E$) in a heart failure patient, using the same data as in (C), plotted in an X-Y plot arrangement. Red dots indicate the point of identification of the lactate threshold or peak $\dot{V}_E/\dot{V}O_2$. Green dots indicate the point of identification of the ventilatory compensation point or peak $\dot{V}_E/\dot{V}CO_2$. LT indicates lactate threshold; $\dot{V}CO_2$, carbon dioxide output; VCP, ventilatory compensation point; $\dot{V}_E$, expired ventilation; $\dot{V}O_2$, oxygen uptake.

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Participants

Retrospective analysis was conducted on de-identified data from 24 male HF patients (Weber class[22] A/B/C/D n=1/6/15/2) and 11 age-matched controls (Table 1). LT and peak exercise physiological responses of the HF group[21] and some (n=9) of the control group[23] were published previously. Data were chosen on the basis that participants had performed 3 different ramp-incremental protocols resulting in intolerance in ≈5, 10, and 15 minutes, or were age- and sex-matched

Table 1. Participant Characteristics

	Heart Failure (n=24)	Controls (n=11)
Age, y	64±11	63±7
Sex, M/F	24/0	9/2
Height, cm	172±7	170±8
Weight, kg	88±16	80±12
Peak $\dot{V}O_2$, mL/min per kg	14.2±3.0	31.8±8.3
NYHA functional class, I/II/III/IV	4/19/1/0	…
Etiology of CHF, IHD/DCM	16/8	…
LVEF, %	31±8	…

Data are presented as mean±SD. CHF indicates congestive heart failure; DCM, dilated cardiomyopathy; IHD, ischemic heart disease; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

controls. HF participants were in a stable condition and on optimized therapy (angiotensin-converting enzyme inhibitors [n=22], aspirin [n=17], β-blocker [n=22], digoxin [n=4], furosemide [n=19], spironolactone [n=18], and statin [n=18]). None showed evidence of exercise oscillatory ventilation. Control participants were recruited for previous studies in our lab to be free of pulmonary, neuromuscular, metabolic, and skeletal disorders or significant anemia. All participants gave written informed consent to participate in the original research studies at the Faculty of Biological Sciences, University of Leeds, or at Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center. Institutional ethical or review boards approved all studies.

Exercise Testing

Participants undertook ramp-incremental exercise on a cycle ergometer (Excalibur Sport; Lode BV, Groningen, The Netherlands). Eighteen HF patients each performed 3 tests using slow (5±1 W/min), medium (9±4 W/min), and fast (19±6 W/min) ramps resulting in endurance times of ≈5, 10, and 15 minutes. An additional 6 HF patients and 11 controls underwent a ramp-incremental exercise test to intolerance in ≈10 minutes (7±3 and 22±6 W/min, respectively). Breath-by-breath gas exchange, ventilatory, and cardiac variables were measured by metabolic cart (MSX; nSpire Health, Hertford, UK or Vmax; Carefusion, Yorba Linda, CA). During exercise tests, participants initially sat at rest on the cycle ergometer for ≈3 minutes, followed by ≈3 minutes of unloaded cycling, ramp-incremental exercise to symptom-limited peak, and unloaded active recovery for ≈5 minutes.

Data Processing

Data were processed and displayed in 3 different ways using Sigma Plot (version 13.0; Systat Software Inc., Chicago, IL). Initially, breath-by-breath data were averaged into 30 bins and plotted in a standard "9-panel" CPET report format for estimation of LT and VCP by standard gas exchange and ventilatory criteria.[24] LT and VCP were identified by 2 reviewers independently. $\dot{V}O_{2peak}$ is reported as the peak 30-second average during exercise. Second, breath-by-breath data were subject to 90-second rolling average and were assessed again using the 9-panel report, in a blinded fashion, for verification that the longer averaging window (that was subsequently used for circulatory equivalent analyses) had no influence on the LT and VCP estimation. Finally, 90-second rolling average plots of $\dot{V}O_2/\dot{V}_E$-versus-$\dot{V}CO_2/\dot{V}_E$ (the X-Y plot) were produced. LT and VCP (from 9-panel) and peak $\dot{V}O_2/\dot{V}_E$ and $\dot{V}CO_2/\dot{V}_E$ (from X-Y plot) were assessed by the same 2 assessors blinded to the group and condition. The $\dot{V}O_2$ at each of the 4 discrete points was identified for direct comparison among graphical analysis methods.

Statistical Analysis

Comparison of variables (LT, VCP, $\dot{V}O_{2peak}$, $\dot{V}O_2/\dot{V}_E$, and $\dot{V}CO_2/\dot{V}_E$) between patients and controls was made using the Mann–Whitney *U* test. The Kruskal–Wallis test was used to compare the effect of protocol (ramp-incrementation rate) on LT, VCP, $\dot{V}O_{2peak}$, peak $\dot{V}O_2/\dot{V}_E$, and peak $\dot{V}CO_2/\dot{V}_E$ in 18 congestive heart failure patients. Agreement between the 9-panel and X-Y graphical methods to identify physiological thresholds (LT and VCP) was assessed in 24 patients and 11 controls using Bland-Altman analysis. All analyses were performed using IBM SPSS Statistics software (version 20.0; SPSS 20; IBM Corp., Armonk, NY). Data are presented as mean±SD. Statistical significance was accepted at $P<0.05$.

Results

Participant Characteristics

Characteristics of HF patients and controls are summarized in Table 1. No significant difference was found in age, height, or weight between 24 HF patients and 11 controls.

LT, VCP, and $\dot{V}O_{2peak}$ in HF and Controls

We found no significant difference in LT (0.03±0.05 L/min; $P=0.172$) or in VCP (0.01±0.04 L/min; $P=0.398$) between 30- and 90-second averaging methods, hence the values using the 90-second rolling average are reported for consistency of comparison with circulatory equivalents. Figure 1 shows examples of LT and VCP detection for a representative control (Figure 1A) and HF patient (Figure 1C). As expected LT, VCP, and $\dot{V}O_{2peak}$ were significantly lower in HF than controls (Table 2). However, within HF patients, there was no

Table 2. LT, VCP and Peak Oxygen Uptake (VO_{2peak}) in HF Patients and Controls Determined Noninvasively Using the 9-Panel Plot

	LT (L/min)	VCP (L/min)	$\dot{V}O_{2peak}$ (L/min)
Control (n=11, medium ramp)	1.55±0.56	2.06±0.71	2.58±0.84
HF (n=24, medium ramp)	0.81±0.18*	1.01±0.26*	1.28±0.34*
HF (n=18, different ramp protocols)			
Slow ramp	0.83±0.16	1.04±0.18	1.29±0.30
Medium ramp	0.82±0.15	1.02±0.20	1.28±0.30
Fast ramp	0.84±0.14	1.04±0.18	1.32±0.26

Data are presented as mean±SD.
*P<0.001 HF vs control for the same ramp protocol (medium).
HF indicates heart failure; LT, lactate threshold; VCP, ventilatory compensation point.

significant effect of protocol (ramp-incrementation rate) on the estimates of LT (P=0.816), VCP (P=0.894), and $\dot{V}O_{2peak}$ (P=0.476).

Circulatory Equivalents in HF and Controls

Figure 1 shows examples of peak $\dot{V}O_2/\dot{V}_E$ and peak $\dot{V}CO_2/\dot{V}_E$ detection for a representative control participant (Figure 1B) and HF patient (Figure 1D). The peak $\dot{V}O_2/\dot{V}_E$ (31.2±4.4 versus 41.8±4.8 mL/L; P<0.0001) and peak $\dot{V}CO_2/\dot{V}_E$

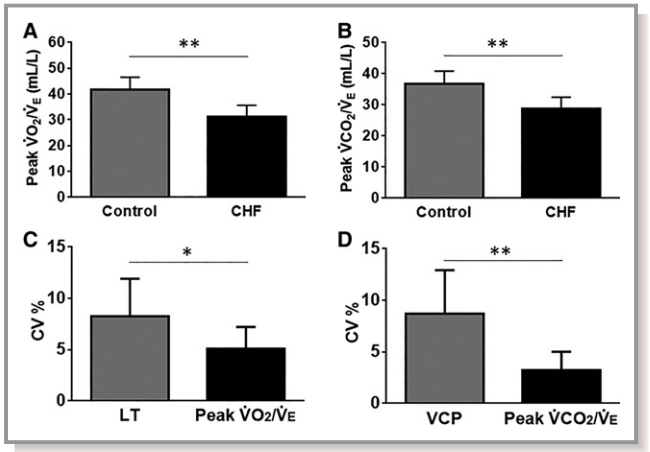

Figure 2. Values and reliability of peak $\dot{V}O_2/\dot{V}_E$ and peak $\dot{V}CO_2/\dot{V}_E$ (circulatory equivalents) in heart failure patients and healthy controls. A, Peak $\dot{V}O_2/\dot{V}_E$ in heart failure patients and healthy controls. B, Peak $\dot{V}CO_2/\dot{V}_E$ in heart failure patients and healthy controls. C, CV% of peak $\dot{V}O_2/\dot{V}_E$ and LT during slow, medium, and fast ramp-incremental exercise tests in heart failure patients. D, CV% of peak $\dot{V}CO_2/\dot{V}_E$ and VCP during slow, medium and fast ramp-incremental exercise tests in heart failure patients. CHF indicates congestive heart failure; CV%, coefficient of variation; LT, lactate threshold; $\dot{V}CO_2$, carbon dioxide output; VCP, ventilatory compensation point; $\dot{V}_E$, exhaled ventilation; $\dot{V}O_2$, oxygen uptake. *P<0.05; **P<0.0001.

Table 3. Peak Circulatory Equivalents ($\dot{V}O_2/\dot{V}_E$ and $\dot{V}CO_2/\dot{V}_E$) in HF Patients and Controls Determined Using the X-Y Plot

	Peak $\dot{V}O_2/\dot{V}_E$ (mL/L)	Peak $\dot{V}CO_2/\dot{V}_E$ (mL/L)
Control (n=11, medium)	41.8±4.8	36.9±4.0
HF (n=24, medium ramp)	31.2±4.4*	28.7±3.8*
HF (n=18, different ramp protocols)		
Slow ramp	31.9±4.2	29.2±3.5
Medium ramp	31.8±3.7	29.3±3.0
Fast ramp	31.0±3.7	29.0±3.1

Data are presented as mean±SD.
*P<0.01 HF vs control for the same ramp protocol (medium).
HF indicates heart failure.

(29.3±3.0 versus 36.9±4.0 mL/L; P<0.0001) were lower in HF than controls (Figure 2A and 2B). Within individuals, there was no significant effect of protocol on peak $\dot{V}O_2/\dot{V}_E$ (P=0.62) or $\dot{V}CO_2/\dot{V}_E$ (P=0.97; Table 3). However, among different ramp-incrementation rates in HF, the coefficient of variation (%) for estimation of peak $\dot{V}O_2/\dot{V}_E$ by X-Y plot was significantly lower than the coefficient of variation for LT estimation using the 9-panel plot (5.1±2.1% versus 8.2±3.7%; P=0.014; Figure 2C). Similarly, peak $\dot{V}CO_2/\dot{V}_E$ from the X-Y plot was

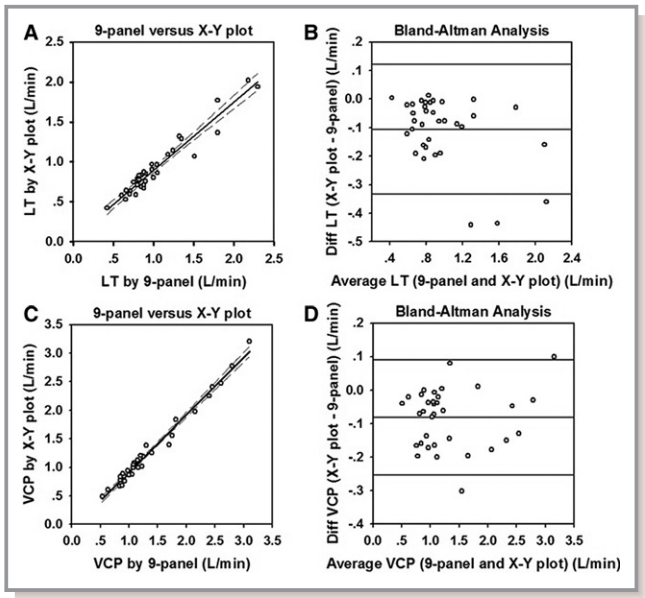

Figure 3. Regression and agreement analysis (Bland-Altman) for LT and VCP estimation using X-Y plot and 9-panel plot. A, Regression between $\dot{V}O_2$ at LT (9-panel) and $\dot{V}O_2$ at peak $\dot{V}O_2/\dot{V}_E$ (X-Y plot): r^2=0.94; P<0.0001. B, Agreement plot of $\dot{V}O_2$ at LT (9-panel) and $\dot{V}O_2$ at peak $\dot{V}O_2/\dot{V}_E$ (X-Y plot): mean bias, −0.11 L/min; 95% confidence interval, −0.15, −0.07 L/min. C, Regression between $\dot{V}O_2$ at VCP (9-panel) and $\dot{V}O_2$ at peak $\dot{V}CO_2/\dot{V}_E$ (X-Y plot): r^2=0.98, P<0.0001. D, Agreement plot of $\dot{V}O_2$ at VCP (9-panel) and $\dot{V}O_2$ at peak $\dot{V}CO_2/\dot{V}_E$ (X-Y plot): mean bias, −0.08 L/min; 95% confidence interval, −0.11, −0.05 L/min. LT indicates lactate threshold; VCP, ventilatory compensation point.

significantly less variable than VCP from the 9-panel (3.3±1.8% versus 8.7±4.2%; $P<0.001$; Figure 2D).

Agreement of Threshold Detection Between Circulatory Equivalents and 9-Panel Methods

In all 35 participants, the $\dot{V}O_2$ at which peak $\dot{V}O_2/\dot{V}_E$ occurred was very strongly correlated with, but was lower than, LT ($r^2=0.94$; $P<0.0001$; mean bias, −0.11 L/min; 95% confidence interval, −0.15, −0.07; Figure 3A and 3B). Similarly, the $\dot{V}O_2$ at which peak $\dot{V}CO_2/\dot{V}_E$ occurred was very strongly correlated with, but was lower than, VCP ($r^2=0.98$; $P<0.0001$; mean bias, −0.08 L/min; 95% confidence interval, −0.11, −0.05; Figure 3C and 3D).

Discussion

CPET provides valuable information for the diagnosis, disease severity, and prognosis of patients with HF.[25–27] The strong prognostic value of several CPET-derived variables for evaluation of HF patients is well established, including LT, $\dot{V}_E/\dot{V}CO_2$ at LT or nadir, $\dot{V}_E/\dot{V}CO_2$ slope, $\dot{V}O_{2peak}$, oscillatory breathing, and end-tidal PO_2 or PCO_2. The value of peak $\dot{V}O_2/\dot{V}_E$ and peak $\dot{V}CO_2/\dot{V}_E$, however, is less well explored.[17] In this study, we confirmed previous findings that peak circulatory equivalents distinguish between patients with HF and controls.[17] We went on to establish that peak $\dot{V}O_2/\dot{V}_E$ and peak $\dot{V}CO_2/\dot{V}_E$ values are strongly associated with (although not identical to) LT and VCP, respectively. We also demonstrated that these circulatory equivalents are less sensitive to different ramp-incremental protocols in HF than noninvasive estimates of LT and VCP using traditional criteria.[9] Together, these data provide a physiological interpretation of peak circulatory equivalents and demonstrate stronger reliability of these quantities across repeated exercise tests in the same patients than physiological thresholds determined by traditional methods. Circulatory equivalents therefore provide highly robust, effort-independent, variables that reflect physiological events known to hold very strong prognostic value in HF. Circulatory equivalents may be a useful approach to simplify the measurement, display, and interpretation of cardiopulmonary exercise testing data.

Physiological Interpretation

Gas exchange during exercise assesses severity in HF better than several other procedures.[7,28,29] Variables relating pulmonary gas exchange to ventilation independently discriminate HF severity better than echocardiography, resting hemodynamics, and other exercise measurements.[30,31] The peak values of $\dot{V}O_2/\dot{V}_E$ and $\dot{V}CO_2/\dot{V}_E$ also hold the advantage that they occur (in a large majority) during submaximal aerobic exercise and therefore provide an effort-independent, objective, assessment of disease severity. The dynamics and peak values of circulatory equivalents are proposed to be strongly reflective of the rate of pulmonary perfusion for a given rate of ventilation, attributed to their dependence on the product of pulmonary blood flow and arteriovenous O_2 and CO_2 concentration differences. In health and HF, both C(a−v)O_2 and C(v−a)CO_2 differences widen progressively soon after exercise onset.[32,33] Hence, abnormality in $\dot{V}O_2/\dot{V}_E$ or $\dot{V}CO_2/\dot{V}_E$ is likely to reflect abnormality in the ability to increase and distribute pulmonary perfusion. Although these variables cannot distinguish between hyperventilation that reduces P_aCO_2, or deranged pulmonary perfusion that causes high rates of ventilation with eucapnia (eg, high $\dot{V}_A/\dot{Q}$ and/or V_D/V_T), the latter more commonly predominates; at least when peak circulatory equivalents are >25% below normal.[34] For these reasons, the peak values of $\dot{V}O_2/\dot{V}_E$ and $\dot{V}CO_2/\dot{V}_E$ that occur during submaximal exercise are sensitive indices of gas-exchange abnormality in HF that are likely to reflect a low and/or poorly distributed pulmonary perfusion, rather than excessive pulmonary ventilation per se, for example, $\dot{V}CO_2/\dot{V}_E = k \times P_aCO_2 \times (1 - V_D/V_T)$.

In this study, we demonstrated strong associations between peak $\dot{V}O_2/\dot{V}_E$ and LT ($r^2=0.94$) and between peak $\dot{V}CO_2/\dot{V}_E$ and VCP ($r^2=0.98$). Although there was a small, but significant, negative bias in these relationships (circulatory equivalents detected LT and VCP slightly earlier in the metabolic rate range), conceptually these variables should be closely associated. The very strong association between $\dot{V}CO_2$ and $\dot{V}_E$ over all metabolic rates preceding ventilatory compensation means that, at LT, where metabolic CO_2 output is supplemented by CO_2 evolved from buffering the associated acidosis, $\dot{V}_E$ begins to increase out of proportion to $\dot{V}O_2$. That is, unlike $\dot{V}_E/\dot{V}CO_2$, $\dot{V}_E/\dot{V}O_2$ increases more rapidly immediately after LT than before it. The sub-LT relation between $\dot{V}_E$ and $\dot{V}O_2$ is hyperbolic. On the other hand, the peak $\dot{V}O_2/\dot{V}_E$ occurs at a point in the circulatory equivalent plot where $\dot{V}O_2/\dot{V}_E$ is approaching a vertical asymptote (Figure 1B and 1D). Therefore, small deviations in data measurement or sampling methods may influence the measurements of the single peak value. This may be why peak $\dot{V}O_2/\dot{V}_E$ was consistently, by a small margin, lower in the metabolic range than LT, and the 95% confidence interval spanned ≈125 mL/min (≈10% of $\dot{V}O_{2peak}$) either side of this mean. Peak $\dot{V}O_2/\dot{V}_E$ is an objectively determined maximum, whereas LT estimation by 9-panel requires interpretation of several variables.[24] As such, it is likely that LT estimation by 9-panel has greater internal validity and accuracy because more variables are considered for its estimation. Nevertheless, it is currently unknown whether the differences between peak $\dot{V}O_2/\dot{V}_E$ and LT reflects the ability for more-accurate noninvasive estimation of LT by circulatory equivalent or by 9-

panel. Similarly, the onset of ventilatory compensation (defined as an increase in ventilation out of proportion to CO_2 output and a reduction in end-tidal PCO_2) was typically identified earlier by peak $\dot{V}CO_2/\dot{V}_E$ in the X-Y plot than by 2 independent reviewers using the 9-panel report. Despite these concerns, the greater reliability (lower coefficient of variation) of peak $\dot{V}O_2/\dot{V}_E$ and peak $\dot{V}CO_2/\dot{V}_E$ measurement is encouraging.

Reliability of Circulatory Equivalents

Different ramp-incremental exercise protocols may influence the ability to detect or alter the values of CPET-derived variables, particularly LT, $\dot{V}_E$ peak, and $\dot{V}CO_2$ peak. In this study, however, altering the ramp-incrementation rate did not influence peak $\dot{V}O_2$ and $\dot{V}_E/\dot{V}CO_2$ at LT[21,35] or circulatory equivalents in HF patients. During exercise, breath-by-breath measurement of ventilation is less variable than gas exchange. As such, using $\dot{V}_E$ as the denominator (circulatory equivalents) tends to reduce variability compared with their inverse ratios (ventilatory equivalents). Plotting circulatory equivalents against one another, displayed on X-Y plot (rather than against time, $\dot{V}O_2$ or work rate), amplifies abrupt changes in response patterns, making the submaximally occurring peak $\dot{V}O_2/\dot{V}_E$ and $\dot{V}CO_2/\dot{V}_E$ more readily identifiable. This may be another reason why peak circulatory equivalents were less variable than LT and VCP detection in this study, because they are less influenced by subjective user assessment. Our data suggest that identification of physiological variables using peak circulatory equivalents were more reliable than traditional methods of LT and VCP assessment across a wide range of ramp-incremental exercise test durations in HF patients and therefore may provide the basis for an improved assessment method.

It is important to note, however, that break points in ventilatory equivalents observed at LT and VCP do not, by necessity, have to be coincident with their minima (and thus maxima in circulatory equivalents). Typically, breakpoints and minima in ventilatory equivalents occur at the same metabolic rate (eg, see Figure 1A and 1C). However, in patients with very large V_D/V_T or $\dot{V}_A/\dot{Q}$ inequality, it is possible for ventilatory equivalents to increase (not decrease) early in exercise where the slope of the relationship between $\dot{V}_E$ and $\dot{V}CO_2$ has a negative intercept. Therefore, the association between peak circulatory equivalents and LT or VCP that we have identified here should be tested in a larger heterogeneous cohort.

Practical Implication

Whereas most modern metabolic carts measure the variables required to calculate $\dot{V}O_2/\dot{V}_E$ and $\dot{V}CO_2/\dot{V}_E$ on a breath-by breath basis, these ratios mathematically reduce to $1-F_{\bar{E}}O_2$ and $F_{\bar{E}}CO_2$, respectively (where $F_{\bar{E}}$, is the mixed expired gas fractional concentration). Conceptually, the determinants of mixed expired gas fractions are related to the balance between delivery and clearance of each gas to the pulmonary compartment: greater anatomic dead space, greater un- or underperfused lung regions, and/or a greater ventilation of gas-exchanging regions will each lower $1-F_{\bar{E}}O_2$ and $F_{\bar{E}}CO_2$. Practically, $1-F_{\bar{E}}O_2$ and $F_{\bar{E}}CO_2$ have the advantage of being simpler to measure than breath-by-breath gas exchange, because only gas analyzers and a mixing chamber are required. Therefore, using a mixing chamber system and online X-Y plot of circulatory equivalents to monitor the normalcy or otherwise of gas exchange during exercise[18] may simplify both the measurement and interpretation of the normalcy or impairment of gas-exchange responses in HF patients.

Limitations

We showed that noninvasive measurement of peak $\dot{V}O_2/\dot{V}_E$ was less variable in repeated testing that noninvasive estimation of LT by 9-panel plot. However, we did not conduct invasive measurements of the time course of blood lactate to determine which threshold estimate (9-panel versus X-Y plot) was more accurate. In addition, invasive measurements of P_aCO_2 would allow us to distinguish the contributions of pulmonary ventilation and/or pulmonary perfusion to the peak $\dot{V}O_2/\dot{V}_E$ and $\dot{V}CO_2/\dot{V}_E$ values.

Plotting 2 "noisy" ratios such as $\dot{V}O_2/\dot{V}_E$ and $\dot{V}CO_2/\dot{V}_E$ against each other exaggerates the influence of breath-by-breath fluctuations. Therefore, signal averaging is required (we used a 90-second rolling average as previously identified[17]) to discern the underlying patterns within the variables. This influences the absolute values of the peak circulatory equivalents, but improves the ability to identify them. Nevertheless, we found no effect of this averaging procedure on the values for LT and VCP, whereas the peak circulatory equivalents remained a more-reliable assessment, suggesting that this averaging procedure did not bias our conclusions.

Our experiments were performed only in HF patients with a reduced EF. Therefore, whether our data are also applicable to HF patients with a preserved EF is unclear.

It is possible that, the modest sample size influenced our ability to detect differences in circulatory equivalents among ramp protocols. However, using estimates of a clinically meaningful difference in peak $\dot{V}O_2$ of 1 mL/kg/min, or ≈6% (based on a relative risk reduction of 5% from the HF-ACTION cohort[36]), we estimate a statistical power (1-β) in this study ranging 0.79 to 0.90 to identify a significant difference in circulatory equivalents among ramp-incrementation rates. On balance, we think that a type II error is therefore unlikely.

We did not assess the dynamics of circulatory equivalents in this article. Characteristics such as falling $\dot{V}O_2/\dot{V}_E$

immediately at onset, rising $\dot{V}O_2/\dot{V}_E$ and $\dot{V}CO_2/\dot{V}_E$ at cessation, or "narrow loops" in the X-Y plot may have prognostic value. A fall in $\dot{V}O_2/\dot{V}_E$ and $\dot{V}CO_2/\dot{V}_E$ at exercise onset is sometimes observed in pulmonary hypertension, the opposite to healthy participants, which might reflect a paradoxical increase in $\dot{V}_A/\dot{Q}$ and/or V_D/V_T at exercise onset in these patients. A rise in both $\dot{V}O_2/\dot{V}_E$ and $\dot{V}CO_2/\dot{V}_E$ at cessation is characteristic of HF,[17] which might reflect a sudden increase in pulmonary perfusion given that thoracic pressure falls and venous return is able to increase during active recovery. In an attempt to quantify the entire profile, we calculated the area enclosed by the $\dot{V}O_2/\dot{V}_E$ versus $\dot{V}CO_2/\dot{V}_E$ loop as a potential index of impaired circulatory equivalent dynamics, but the variably incomplete recovery of these data among subjects rendered this analysis unreliable. The dynamic profile of the circulatory equivalent plot, and not only peak values, deserve further consideration for their utility in interpretation of CPET data.

Conclusion

The circulatory equivalents, $\dot{V}O_2/\dot{V}_E$ and $\dot{V}CO_2/\dot{V}_E$, by X-Y plot are sensitive indices of gas-exchange abnormality during submaximal exercise and can distinguish HF patients from controls. The circulatory equivalents are likely to reflect a low and/or poorly distributed pulmonary perfusion, rather than excessive pulmonary ventilation per se. The $\dot{V}O_2$ at which peak $\dot{V}O_2/\dot{V}_E$ and peak $\dot{V}CO_2/\dot{V}_E$ values occurred were strongly associated with (although not identical to), and were more reliable than, LT and VCP, respectively, using traditional noninvasive assessment methods. In addition, peak $\dot{V}O_2/\dot{V}_E$ and peak $\dot{V}CO_2/\dot{V}_E$ values were not affected by ramp-incrementation rate. Overall therefore, peak circulatory equivalents are strongly related to LT and VCP during exercise; they are reliable, sensitive, effort independent, and uninfluenced by different exercise testing protocols, making them useful objective cardiopulmonary exercise testing indices for diagnosis and prognosis in HF patients.

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Disclosures

None.

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