Ventilatory Abnormalities During Exercise in Heart Failure: A Mini Review

Ross Arena[*,1], Marco Guazzi[2] and Jonathan Myers[3]

[1]*Department of Physical Therapy, Virginia Commonwealth University, Health Sciences Campus, Richmond, Virginia, USA*

[2]*University of Milano, San Paolo Hospital, Cardiopulmonary Laboratory, Cardiology Division, University of Milano, San Paolo Hospital, Milano, Italy*

[3]*VA Palo Alto Health Care System, Cardiology Division, Stanford University, Palo Alto, CA, USA*

Abstract: Heart Failure (HF) is a significant health care concern with in both the United States and Europe. While there are a number of mechanisms that lead to HF, a decline in the response to exercise is common amongst the various etiologies. Cardiopulmonary exercise testing (CPET) is a well established diagnostic and prognostic tool in the HF population. This exercise testing technique allows for the measurement of oxygen consumption (VO_2), carbon dioxide production (VCO_2) and minute ventilation (VE) across time. Cardiovascular and skeletal muscle dysfunction is considered central to the often abnormal exercise response observed in the HF population. As such, VO_2 at peak exercise is the most recognized CPET variable in patients with HF. In recent years however, the importance of assessing VE during exercise, either alone or in combination with expired gases, has been highlighted in a number of investigations. The VE-VCO_2 relationship, exercise periodic breathing (EPB) and the oxygen uptake efficiency slope (OUES) are, to this point, the most studied CPET measurements incorporating VE in the HF population. Of these, the VE-VCO_2 relationship has received the greatest amount of attention. This review will address the clinical significance of these CPET measurements in the HF population.

INTRODUCTION

Heart Failure (HF) is a significant health care concern with approximately five and ten million individuals diagnosed with this condition in the United States and Europe, respectively [1,2]. While there are a number of mechanisms that lead to HF, an impairment in the response to exercise is common amongst the various etiologies. Cardiopulmonary exercise testing (CPET) is a well established diagnostic and prognostic tool in the HF population and well respected American and European organizations have both put forth consensus statements supporting its use [3,4]. This exercise testing technique allows for the measurement of oxygen consumption (VO_2), carbon dioxide production (VCO_2) and minute ventilation (VE) across time. Cardiovascular and skeletal muscle dysfunction is considered central to the often abnormal exercise response observed in the HF population. As such, VO_2 at peak exercise (the product of cardiac output and the difference in oxygen content between the arterial and venous blood) is the most recognized CPET variable in patients with HF. In recent years, however, the importance of assessing VE during exercise, either alone or in combination with expired gases, has been highlighted in a number of investigations. The VE-VCO_2 relationship, exercise periodic breathing (EPB) and the oxygen uptake efficiency slope (OUES) are, to this point, the most studied CPET measurements incorporating VE in the HF population, of which, the VE-VCO_2 relationship has received the greatest amount of attention. This review will address the clinical significance of these CPET measurements in the HF population.

*Address correspondence to this author at the Department of Physical Therapy, P.O. Box 980224, Virginia Commonwealth University, Health Sciences Campus, Richmond, VA 23298-0224, USA; Tel: 804-828-0234; Fax: 804-828-8111; E-mail: raarena@.vcu.edu

The VE-VCO_2 Relationship

The rise in VE and VCO_2 with aerobic exercise is tightly coupled as increasing carbon dioxide levels as a consequence of increased metabolism and, at higher exercise intensities, lactic acid buffering drive the ventilatory response. This relationship is most commonly expressed as the VE/VCO_2 slope, although the ratio between VE and VCO_2 at maximal exercise has also been shown to provide prognostic value [5,6]. Furthermore, a change in VE/VCO_2 from rest to anaerobic threshold of less then 10% has been shown to effectively identify HF patients with a diminished aerobic capacity (<14 $mlO_2 \bullet kg^{-1} \bullet min^{-1}$, 96% positive predictive value and 88% negative predictive value) although the prognostic significance of this submaximal calculation has not been investigated [7]. The VE/VCO_2 slope is, however, the preferred expression since a greater amount of the exercise data is used for its calculation, thereby reducing the potential variability secondary to measurement error. During an incremental exercise test to maximal exertion, the VE/VCO_2 slope is generally linear although there is a notable and widely variable non-linear break point beyond the anaerobic threshold. The resultant second slope from the anaerobic threshold to maximal exertion has been shown to increase a mean of 2. 6 ±4. 1 units compared to the VE/VCO_2 slope measured from the onset of exercise to the point of anaerobic threshold, with a greater difference indicating worse prognosis [8]. Although submaximal VE/VCO_2 slope calculations provide valuable information, several investigations have demonstrated a VE/VCO_2 slope calculation incorporating all exercise data (onset of exercise to maximal exertion) produces clinically optimal information compared to submaximal calculations

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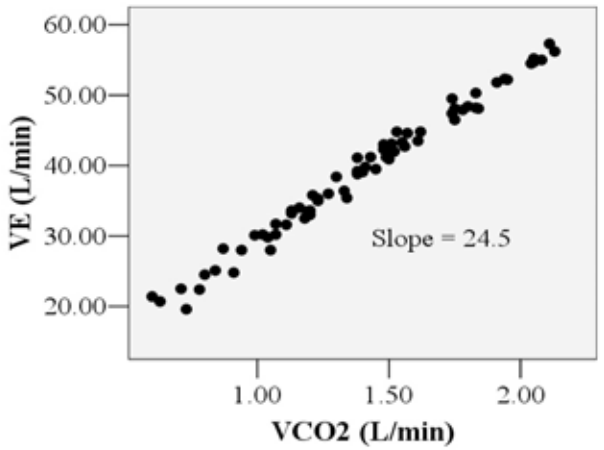
[8-11]. A normal VE/VCO_2 slope response to an incremental exercise test is less than 30, irrespective of how this variable is calculated (beginning of exercise to anaerobic threshold or maximal exertion). A VE/VCO_2 slope range between 17 and 69 has been reported in patients with HF [8]. Examples of a normal and abnormal VE/VCO_2 slope are illustrated in Fig. **1**.

1a. HF patient with normal VE/VCO_2 slope



1b. HF patient with abnormal VE/VCO_2 slope

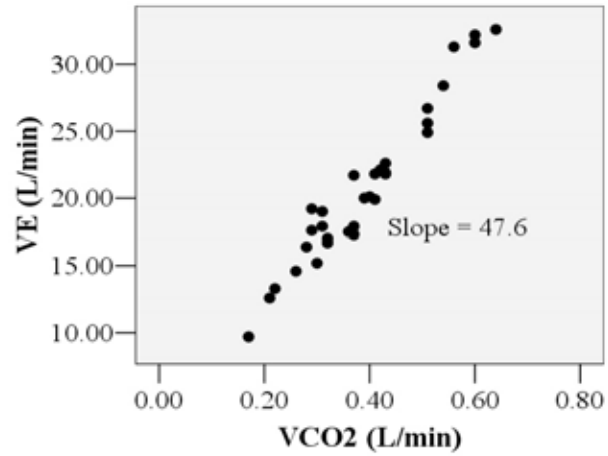


Fig. (1). The VE/VCO_2 slope*.

*Data points are 10-second averaged from initiation of exercise to peak.

PATHOPHYSIOLOGIC MECHANISMS BEHIND AN ABNORMAL VE-VCO_2 RELATIONSHIP IN HF

The pathophysiologic mechanisms accounting for an abnormally elevated VE/VCO_2 slope in patients with HF appear to be multifaceted with both central and peripheral contributions. A decrease in cardiac output, a hallmark consequence of HF, affects both left and right-sided circulation. A decline in pulmonary perfusion and carbon dioxide exchange, in the presence of normal alveolar ventilation, results in an elevated VE/VCO_2 slope. Previous studies have demonstrated a link between both ventilation-perfusion abnormalities [12-15] and declining cardiac output [16] and an abnormally high VE/VCO_2 slope in patients with HF. Reindl *et al.* [16] also demonstrated a correlation between resting pressures in the pulmonary vasculature and the VE/VCO_2 slope, indicating increased right sided pressure may also contribute to ventilation-perfusion mismatching. Adachi *et al.* [17] reported a link between an elevated VE/VCO_2 slope and depressed nitric oxide production in patients with HF, further supporting the mechanistic role of ventilation-perfusion mismatching, in this instance, *via* blunted vasodilation in the pulmonary vasculature during exercise. In addition to ventilation-perfusion mismatching, a heightened sensitivity to central and peripheral chemoreceptors as well as skeletal muscle ergoreceptors appear to influence the abnormal ventilatory response to exercise observed in HF [18-20]. Fig. **2** illustrates the pathophysiologic pathways that influence the VE-VCO_2 relationship.

PROGNOSTIC CHARACTERISTICS OF THE VE/VCO_2 SLOPE

A multitude of investigations have clearly demonstrated the prognostic value of CPET in the HF population. In 1991, Mancini *et al.* [21] published a seminal investigation in this area, demonstrating that a peak VO_2 threshold of ≤/>14 $mlO_2 \bullet kg^{-1} \bullet min^{-1}$ strongly discriminated between HF patients who survived versus those who died over a two year period. Other studies followed confirming the prognostic value of peak VO_2 [22-24]. As a result of these investigations, peak VO_2 is presently the most commonly assessed variable in clinical practice. More recently, the prognostic value of the VE/VCO_2 slope has been examined. A large body of evidence now exists demonstrating the prognostic robustness of the VE/VCO_2 slope. Furthermore, the majority of these investigations have shown the VE/VCO_2 slope is prognostically superior to peak VO_2 and other variables commonly used to stratify risk, such as left ventricular ejection fraction [25,26]. Table **1** summarizes several of the investigations examining the prognostic value of the VE/VCO_2 slope.

Most investigations have assessed the prognostic value of CPET exclusively in patients with systolic HF. Guazzi *et al.* [27], however, demonstrated the VE/VCO_2 slope is prognostically superior to peak VO_2 in a diastolic HF group as well, a finding which must be confirmed by additional investigations.

Most prognostic investigations have proposed a VE/VCO_2 slope threshold of approximately 34 to differentiate subjects at low and high risk for adverse events [28-30]. Other investigations have found prognosis becomes increasingly less favorable as the VE/VCO_2 slope increases from <28 to 28-35 to 35-42 to >42 [31]. Defining optimal prognostic threshold values and whether the VE/VCO_2 slope should be clinically reported dichotomously or through a multi-level classification system must be explored by additional research.

The VE/VCO_2 slope is independent from subject effort, which may be one of the primary reasons it is prognostically superior to peak VO_2. Mezzani *et al.* [32], for example, demonstrated a low peak VO_2 (≤ 10 $mlO_2 \bullet kg^{-1} \bullet min^{-1}$) no longer provided prognostic value in subjects with a peak respiratory exchange ratio below <1. 15. Conversely, the VE/VCO_2 slope remains prognostically significant with submaximal effort [5,8]. As previously mentioned, the VE/VCO_2 slope calculation with all of the exercise data points (beginning of exercise to peak) appears to be superior to submaximal calculations [8-11].

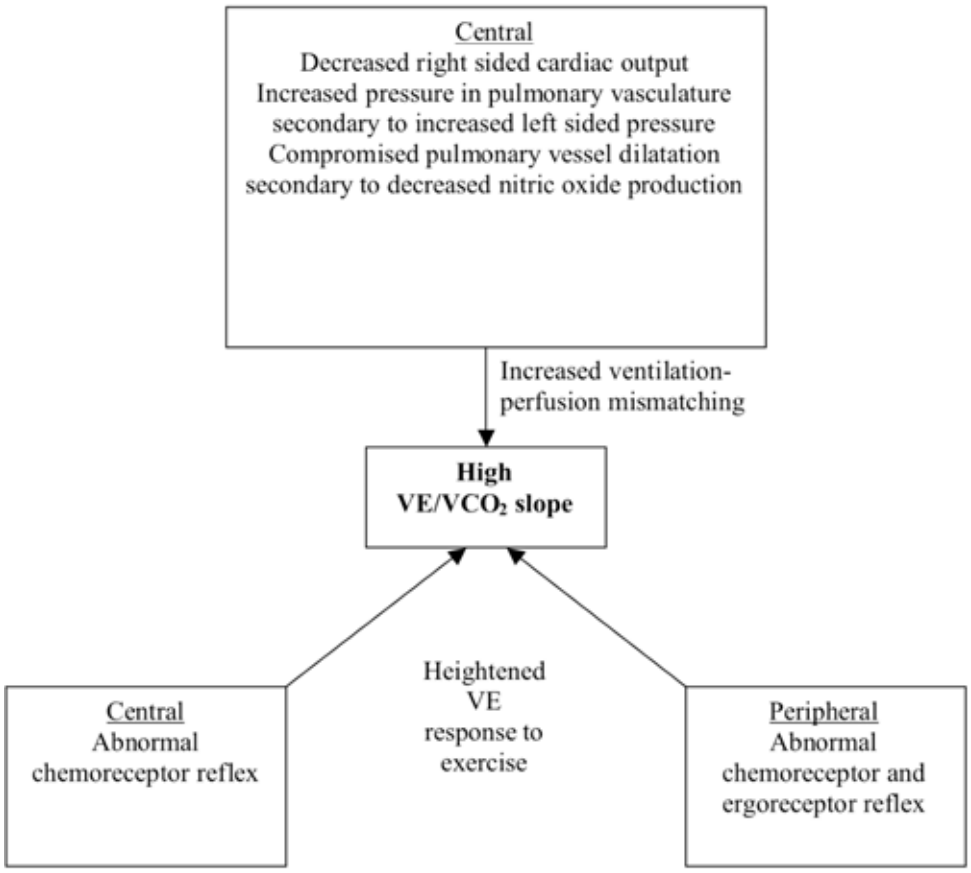


Fig. (2). Pathophysiologic mechanisms of an elevated VE/VCO_2 slope.

The impact of HF etiology, gender, mode of exercise, pharmacology and time past exercise testing on the prognostic value of the VE/VCO_2 slope has been previously examined. It appears the prognostic significance of the VE/VCO_2 slope is comparable in ischemic and non-ischemic HF [33], males and females [34], beta-blockade versus no beta-blockade [35] and exercise testing using a treadmill or lower extremity ergometer [36]. The time past exercise testing does, however, impact the prognostic characteristics of the VE/VCO_2 slope. The number of subjects with a favorable VE/VCO_2 slope who experience an adverse event substantially rises as time past exercise testing increases (decreased specificity) [37]. This latter finding indicates the VE/VCO_2 slope should not be used for prognostic assessment indefinitely, supporting the use of serial testing at yet to be determined time intervals.

IMPACT OF INTERVENTIONS ON THE VE/VCO_2 SLOPE

Several established interventions that improve central and/or peripheral function in the HF population have been shown to impact the VE/VCO_2 slope. Myers *et al.* [38] found two months of aerobic exercise training significantly lowered the mean VE/VCO_2 slope by 6 units ($p<0.01$) in male subjects with systolic dysfunction following myocardial infarction. Guazzi *et al.* [39] reported an ~5 unit reduction in the VE/VCO_2 slope following two months of exercise training in subjects with HF ($p<0.01$). Angiotensin converting enzyme inhibition [40,41], angiotensin II receptor antagonism [42] and beta-blockade [43,44] have all been shown to significantly reduce the VE/VCO_2 slope in patients with HF. Collectively, the reduction in the VE/VCO_2 slope in these pharmacological studies has ranged between 2 and 5 units. Malfatto *et al.* [45] reported the VE/VCO_2 slope decreased ~5 ($p=0.05$) units 10-15 months following cardiac resynchronization therapy. Abraham *et al.* [46] reported a mean decrease of ~2 units in the VE/VCO_2 slope 6 months after cardiac resynchronization therapy, which was significantly greater than placebo ($p=0.01$). Varma *et al.* [47] reported that the VE/VCO_2 slope was 4 units lower in an active pacing group compared to an inactive pacing group after 6 months of cardiac resynchronization therapy ($p=0.03$). Furthermore, normalization of the VE/VCO_2 slope (≤ 30) occurred in 59% of the subjects in the active pacing group ($p=0.002$). Lastly, Carter *et al.* [48] reported the VE/VCO_2 slope decreased a mean of >10 units one year post-heart transplant. These findings collectively support the serial assessment of the VE/VCO_2 slope to monitor the response to a number of clinically indicated interventions in patients with HF, and suggest that the VE/VCO2 slope may supplement established indices to help guide treatment (i. e. pharmacologic dosages, pacemaker settings, response to exercise training or other therapies). While peak VO_2 also positively responds to a number of these interventions, the VE/VCO_2 slope may be the preferred CPET variable to monitor because of its independence from subject effort. To date, no investigations have assessed whether prognosis is improved when the VE/VCO_2 slope is reduced as a result of the aforementioned interventions.

Table 1. Review of Studies Examining the Prognostic Value of the VE/VCO_2 Slope

Study	Type of HF and Number of Subjects	Events Tracked	Major Finding
Robbins *et al.* [25]	Systolic HF: 470	Death (71 events)	Multivariate regression: The VE/VCO_2 slope was the most powerful predictor of events, peak VO_2 did not add additional value
Kleber *et al.* [26]	Systolic HF: 142	Death, Cardiomyoplasty, Heart Transplant and Left ventricular assist device implantation (44 events)	Multivariate regression: The VE/VCO_2 slope was the most powerful predictor of events, peak VO_2 did not add additional value
Francis *et al.* [31]	Systolic HF: 303	Death (91 events)	Multivariate regression: The VE/VCO_2 slope was the most powerful predictor, peak VO_2 added prognostic value
Chua *et al.* [29]	Systolic HF: 173	Death and Heart Transplant (38 events)	Multivariate regression: The VE/VCO_2 slope and peak VO_2 retained with similar prognostic value
Ponikowski *et al.* [18]	Systolic HF: 123	Death (34 events)	The VE/VCO_2 slope was a significant predictor of events in subjects with a preserved exercise capacity ($\geq$18 $mlO_2 \bullet kg^{-1} \bullet min^{-1}$), peak VO_2 did not add prognostic value
Corra *et al.* [30]	Systolic HF: 600	Death and Heart transplant (87 events)	Multivariate regression: The VE/VCO_2 slope was the most powerful predictor, in subjects with an intermediate peak VO_2, superior to left ventricular ejection fraction
Arena *et al.* [28]	Systolic HF: 213	Death and Hospitalization (76 events at one year)	Multivariate regression: The VE/VCO_2 slope was the most powerful predictor, peak VO_2 added prognostic value in predicting hospitalization but not death
Guazzi *et al.* [27]	Systolic and Diastolic HF: 409	Death and Hospitalization (145 events)	Multivariate regression: The VE/VCO_2 slope was the most powerful predictor in both the systolic and diastolic HF groups, peak VO_2 added prognostic value in the systolic but not the diastolic HF group
Bard *et al.* [9]	Systolic HF: 355	Death and Heart Transplant (145 events)	Multivariate regression: The VE/VCO_2 slope was the most powerful predictor of events, peak VO_2 added prognostic value

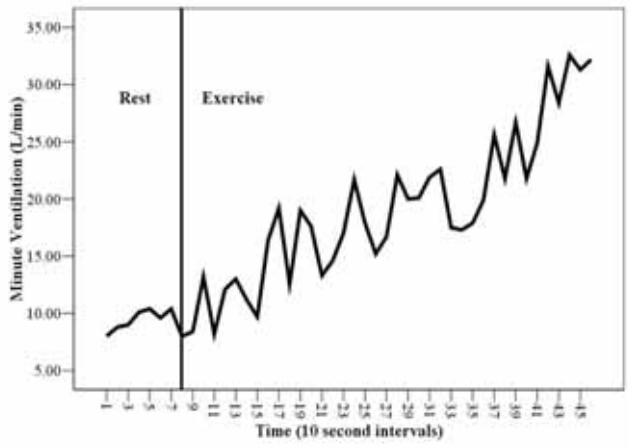
Exercise Periodic Breathing

In HF patients, oscillatory ventilation may occur during sleep (central sleep apnea, CSA) [49] or awake states both at rest (Cheyne-Stoke respiration, CSR)[50] and/or during exercise [51]. Although there is a tendency to describe these three breathing disorders under a common disease entity, they have been actually described and evaluated separately. Exercise periodic breathing (EPB) is a cyclic oscillation of ventilation consisting of hyperpnea and hypopnea associated with changes in arterial O_2 and CO_2 tensions, which may have different patterns throughout a maximal exercise test. Specifically, it may be transiently present during the initial portion of exercise and disappear at peak workload or persist for the entire exercise protocol. EPB is not characterized by apnea periods, which are, conversely, typical of both CSA and CSR. Nonetheless, ventilatory patterns may all share similar mechanistic explanations and EPB may reflect a less severe form of CSA and/or CSR. Interestingly, in a number of HF patients presenting with EPB, CSA is also present and their combination leads to a high burden of risk for adverse events [52].

Interest in the pathophysiological basis and clinical significance of EPB has recently increased in view of the central mechanisms sustaining oscillatory expired gas kinetics [53] and the emerging evidence of its prognostic significance [54]. However, definitive information and a precise phenomenon characterization across various populations with different HF severity are still under investigation. Patients with severe HF and very poor left ventricular systolic function are those who more likely show EPB [51,55], but it is uncertain whether the phenomenon may occur in the early stages of HF syndrome and whether this holds the same clinical significance.

Universally accepted criteria for EPB definition and classification (i. e. length and amplitude of oscillation, disappearance at early, intermediate or late exercise) are not yet established and several methods have been proposed. An initial report by Kremser *et al.* [56] identified cyclic variations in minute ventilation in 6 out of 31 CHF patients. EPB was defined as an oscillatory VE pattern >15% of the average value at rest lasting longer than 66% of the exercise test. In a larger sample of CHF patients, Leite *et al.* [57] defined EPB as the the following: 1) three or more regular oscillations detectable during exercise, which is clearly discernible from inherent noise; 2) regularity of the oscillatory pattern is confirmed if the standard deviation of three consecutive cycle lengths is within 20% of the average; and 3) a minimal average oscillatory amplitude of 5 liters. Using these criteria in a cohort of 84 HF patients, 30% presented with EPB. In two studies performed by Corrà *et al.* [52,58] using a definition of EPB as an oscillatory VE pattern at rest that persists for $\geq$60% of the exercise test at an amplitude $\geq$15% of the average resting value, the prevalence was 12 and 19% respectively. Fig. **3** illustrates a HF patient with (3a, meeting the definition proposed by Corra) and without (3b) EPB during incremental exercise testing. The graphs were generated using 10-second averaged VE data.

3a. Subject with EPB during exercise



3b. Subject with normal ventilatory response to exercise

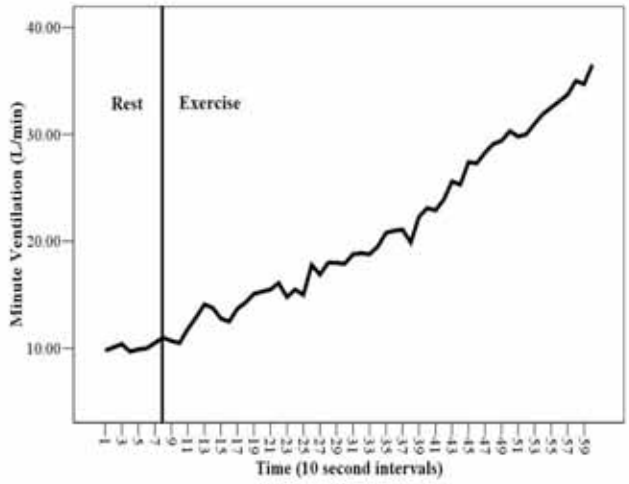


Fig. (3). Examples of an EPB and normal ventilatory response to exercise.

PATHOPHYSIOLOGIC MECHANISM BEHIND EPB IN HF

EPB appears to reflect the result of the deregulation of different physiologic systems that yields to the oscillatory pattern of ventilation and gas exchange. Although a firm understanding of pathways involved in respiratory oscillation is lacking, several pathogenetic theories have been formulated, which are described in the following.

In HF patients, the impairment in ventilatory drive results from abnormalities in several systems and redundancy of these systems may make it difficult to isolate the relative contribution of any single controller. With that said, oscillatory ventilation may be at least partially a consequence of abnormalities in feedback systems that control ventilation [59]. HF typically leads to a delay in information transfer (i. e. prolonged circulatory time), an increased gain in ventilatory controllers (i. e. overactivity of chemoreceptors and ergoreceptors) and a reduction in system damping (i. e. deregulation of cardiopulmonary and arterial baroreflex). Additional mechanisms that may contribute to an impaired ventilatory drive are pulmonary congestion and subclinical pulmonary edema that may stimulate interstitial J receptors and cause a reflexogenic excessive ventilatory response.

An enhanced central and peripheral chemosensitivity has been consistenly demonstrated in patients with HF [60,61]. Oscillatory ventilation also may be related to an increased chemoreflex gain. The presence of enhanced chemosensitivity has been associated with the presence of oscillatory breathing at rest. Suppression of the peripheral chemoreceptor system by hyperoxia or dyidrocodeina appears to ameliorate this abnormal respiratory pattern [50]. In particular, hypoxia seems to play a significant role in determining daytime breathing disorders in HF patients. The reduction in peripheral oxygen transport and consequent chronic mild hypoxemia of chemoreceptors may be a stimulus for hyperventilation [62]. In experimental conditions, an increase in chemoreceptor discharge induced oscillatory ventilation that was reversed by hyperoxia [63]. Activation of the peripheral chemoreflex may also contribute to impaired autonomic modulation and baroreflex sensitivity. An inverse correlation has actually been found between chemoreflex and baroreceptor activity and the lack of appropriate inhibition by baroreflex and cardiopulmonary receptors may be implicated in the occurrence of ventilatory oscillations [64].

The hypothesis that oscillations in cardiac output and fluctuations in pulmonary blood flow may directly induce EPB was originally advanced by Ben-Dov *et al.* [65]. Measurements of hemodynamic changes during exercise were however, not performed in this study. Simultaneous measurements of gas exchange and left ventricular ejection fraction was performed by Yajima *et al.* [66]. They found oscillatory changes both in ejection fraction and in ventilation during exercise, and postulated that these patients develop changes in pulmonary blood flow. However, no direct causal relationship between ventilation and changes in ejection fraction has been reported. The inability to separate the influence of breathing pattern on cardiac function due to respiratory variations in intrathoracic and abdominal pressure, the difficulties related to a precise measure of stroke volume on a beat-to beat basis during exercise and the mechanical interaction between the heart and lungs are limiting factors to clearly demonstrating a relationship between oscillations in cardiac output and ventilation. Francis *et al.* [59] however, performing a quantitative algebraic analysis of the dynamic cardiorespiratory physiology during EPB, found that the principal physiological factors that promote periodic oscillations are circulatory delay and an increased chemoreflex gain.

PROGNOSTIC CHARACTERISTICS AND THERAPEUTIC IMPLICATIONS OF EBP

Despite a paucity of large scale studies, there is initial compelling evidence that EPB is a strong independent prognosticator in HF patients. Corra *et al.* [58] found EPB was a significant multivariate predictor of cardiac mortality or transplantation in 323 patients with HF. In another investigation by the same group, Corra *et al.* [52] confirmed that EPB was a significant predictor of mortality in 133 patients with HF. Periodic breathing occurring only at rest prior to exercise testing does not appear to hold prognostic value [67]. The combination of sleep-related disorders and EPB however, may carry a particularly poor prognosis [52]. If rein-

forced by future investigations, the analysis of EPB in conjunction with other CPET variables, such as the VE/VCO_2 slope and peak VO_2 may be warranted. Related to this, Francis *et al.* [68] emphasized that the presence of EPB may cause artefactual elevations of peak VO_2, potentially impacting the prognostic validity of aerobic capacity. An assessment of the impact EPB has on the prognostic validity of peak VO_2 or the VE/VCO_2 slope has not been performed.

EPB quantification may be of importance when investigating the effects of therapeutic interventions. Ribeiro *et al.* [51] performed the only study that specifically explored the effects of pharmacological therapy on EPB. Administration of milrinone, a positive inotropic and vasodilatatory agent, reduced EPB in HF patients lending indirect support to the cardiac output oscillatory theory. In a more recent report by this group, a 12 week respiratory muscle exercise training program reduced EPB in patients with HF [69].

Other therapeutic approaches, such as application of continuous positive airway pressure, theophylline and oxygen supplementation, may also positively impact EPB given the effectiveness of these interventions on CSA [70-72]. Confirmation that EPB and CSA are clinical presentations of the same disorder and the potential that both may benefit from the same therapeutic approaches requires additional research.

The Oxygen Uptake Efficiency Slope

The oxygen uptake efficiency slope (OUES) is a comparatively new index that has been used to express ventilatory efficiency. Therefore, its analysis, particularly establishing a pathophysiologic mechanism in the HF population is limited. The OUES is derived by the slope of a semi-log plot of minute ventilation versus VO_2. As such, the OUES is an estimation of the efficiency of ventilation with respect to VO_2, with greater slopes indicating greater ventilatory efficiency (Fig. **4**).

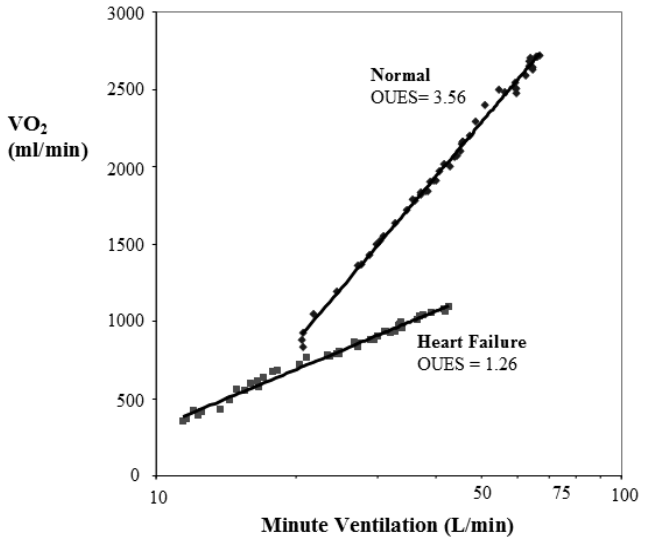


Fig. (4). Examples of OUES responses in a normal subject and a patient with heart failure.

The log function of ventilation is appropriate in theory because the ventilation to VO_2 relationship is curvilinear during exercise; the log transformation makes any two OUES values equally meaningful across a continuum. The OUES was initially applied to characterize the functional reserve among pediatric patients with congenital heart disease [73], later to functionally classify patients with HF [74-76], and more recently to predict risk of mortality in heterogeneous groups of patients with HF [77][*]. The OUES has been shown to correlate closely with peak VO_2 among healthy adults [76,78] patients with coronary artery disease (CAD) [78-80] and patients with HF [74,76].

There are several purported advantages to the OUES. First, like the VE/VCO_2 slope, the OUES does not require a determination of whether exercise was "maximal". In fact, Baba *et al.* [74,81] have shown that the OUES response is, in effect, equivalent regardless of whether patients achieved 75, 90, or 100% effort. Similarly, Davies *et al.* [77] observed that the OUES value changed only 1% when using only half *vs* all of the exercise test responses. Defoor *et al.* [80] reported that the OUES was marginally lower (5%) when calculated to a respiratory exchange ratio of 1. 0 *vs* using all data points during exercise. A second advantage of the OUES is, unlike the VT or peak VO_2, it is a mathematical construct, so subjectivity is removed. The OUES has also been shown to be reproducible [82], to be stable between different exercise protocols [73], and is highly correlated with peak VO_2 [74,76,78,80,81,83]; the latter finding suggests that the OUES may be a useful surrogate for peak VO_2 when estimating prognosis, particularly among patients who cannot achieve a good exercise effort. Finally, it is a comparatively simple reflection of the ventilatory requirement for a given the amount of physiologic work (VO_2), making it easily understandable for clinicians.

PROGNOSTIC CHARACTERISTICS AND THERAPEUTIC IMPLICATIONS OF OUES

Although data are sparse, there has been recent interest in the prognostic power of the OUES. Davies *et al.* [77] reported that the OUES, VT, and peak VO_2 were significant predictors of mortality in patients with HF. However, in a multivariate model, only the OUES was retained. Arena *et al.* [84] compared the prognostic power of the OUES with peak VO_2 and the VE/VCO_2 slope. The OUES, calculated using either 50 or 100% of the data during exercise, was similar to peak VO_2 in predicting combined cardiac related outcomes (ROC areas 0. 69, 0. 72, and 0. 68 for $OUES_{50}$, $OUES_{100}$ and peak VO_2, all $p<0.01$); however, the OUES was a weaker predictor than the VE/VCO_2 slope (ROC area 0. 80). McRae and colleagues followed 1,661 patients with CHF for a median of 2 years, and observed a strong association between the OUES and mortality; the adjusted hazard ratio comparing the lowest to the highest quartile for the OUES was 6. 5 (95% CI=4. 5-9. 3, $p<0.001$)[§]. In a multivariate model adjusted for potential confounders, the OUES significantly predicted mortality, while peak VO_2 was no longer predictive.

Recent studies have also applied the OUES to address the effects of exercise training. Defoor *et al.* [80] studied 425 patients with CAD who underwent 90 minutes of aerobic

[*]Ehrman JK, Brawner CA, Weaver D, Jacobsen G, Keteyian SJ. Oxygen Uptake Efficiency Slope and Survival in Patients with Systolic Heart Failure. Journal of the American College of Cardiology 2006; 47: 155A.

[§]McRae A, Young J, Alkotob M, Snader C, Blackstone EH, Lauer MS. The oxygen uptake efficiency slope as a predictor of mortality in chronic heart failure. Journal of the American College of Cardiology 2002; 39: 183.

exercise training for 3 months. The OUES correlated more closely with peak VO_2 (r=0. 84) than the VE/VCO_2 slope (r=0. 47). After exercise training, the OUES increased by 21%, an amount similar to the change in peak VO_2 (24%). Tsuyuki *et al*. [85] assessed the OUES and other cardiopulmonary responses to exercise training in patients undergoing hemodialysis. After 20 weeks of training, the OUES increased by 19%, and the change in OUES was strongly correlated with the change in peak VO_2 (r=0. 78) and the change in VT (r=0. 61). Although most patients with CAD or renal failure do not exhibit the inefficient ventilation typically seen among patients with HF, these studies suggest that the OUES may also be useful for quantifying exercise performance in these patients, and it appears to be sensitive to physical training.

CONCLUSIONS

Cardiopulmonary exercise testing provides a wealth of clinically valuable information in the HF population. While the assessment of aerobic capacity has long been considered the key piece of information ascertained from such testing, a number of investigations have demonstrated the ventilatory response to exercise provides robust diagnostic and prognostic information. To this point, the $VE\text{-}VCO_2$ relationship is the most established variable that incorporating the ventilatory response to exercise. Furthermore, there is compelling evidence that the $VE\text{-}VCO_2$ relationship is prognostically superior to peak VO_2. Other ventilatory variables, such as EPB and the OUES have also demonstrated clinical value but it is unclear if they provide superior or complimentary information to the $VE\text{-}VCO_2$ relationship. Additional research is required to better define the clinical utility of the ventilatory response to exercise in the HF population.

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