Published in final edited form as:

Int J Cardiol. 2012 February 09; 154(3): 384–385. doi:10.1016/j.ijcard.2011.11.038.

The relationship between minute ventilation and oxygen consumption in heart failure: Comparing peak VE/VO_2 and the oxygen uptake efficiency slope

Ross Arena^{a,*}, Marco Guazzi^b, Jonathan Myers^c, Paul Chase^d, Daniel Bensimhon^d, Lawrence P. Cahalin^e, Mary Ann Peberdy^f, Euan Ashley^g, Erin West^h, Daniel E. Forman^h

^aDepartment of Orthopaedics and Rehabilitation, Physical Therapy Program and Department of Internal Medicine, Division of Cardiology, University of New Mexico School of Medicine, Albuquerque, NM, United States

^bDivision of Cardiology, University of Milano, Milano, Italy

^cDivision of Cardiology, VA Palo Alto Healthcare System, Palo Alto, CA, United States

^dLebauer Cardiovascular Research Foundation, Greensboro, NC, United States

^eDepartment of Physical Therapy, Leonard M. Miller School of Medicine, University of Miami, Miami, FL, United States

^fDepartment of Internal Medicine, Virginia Commonwealth University, Richmond, VA, United States

^gCardiovascular Medicine, Stanford University, Palo Alto, CA, United States

^hDivision of Cardiovascular Medicine, Brigham and Women's Hospital, Boston, MA, United States

Keywords

Expired gas analysis; Prognosis; Ventilatory efficiency

The assessment of ventilatory efficiency during cardiopulmonary exercise testing (CPX) is now widely recognized for its prognostic value in patients with systolic heart failure (HF) [1]. Of the various ways to quantify ventilatory efficiency, the relationship between minute ventilation (VE) and carbon dioxide production (VCO_2), commonly expressed as the VE/VCO_2 slope, is perhaps the most widely utilized CPX variable for this purpose. While the general linearity of the $VE-VCO_2$ relationship allows for a slope calculation, the relationship between VE and oxygen consumption (VO_2) does not follow a similar pattern. Thus, the $VE-VO_2$ relationship has historically been expressed as a peak exercise ratio, which also demonstrates prognostic value [2]. To accommodate for this dislinearity, the oxygen uptake efficiency slope (OUES), which is derived from the strongly linear relationship between VO_2 on the y-axis and the log transformation of VE on the x-axis, was

*Corresponding author at: Physical Therapy Program, Department of Orthopaedics, University of New Mexico Health Sciences Center, HSSB Rm 204, MSC09 5230, Albuquerque, NM 87131-0001, United States. Tel.: +1 505 272 6956; fax: +1 505 272 8079. R.Arena@salud.unm.edu (R. Arena).

developed [3]. Previous studies have also found the OUES to portend prognostic value in systolic HF patients [4]. However, we are unaware of any previous investigation which has compared the relationship or the prognostic strength of the OUES and peak VE/VO_2 , which is the purpose of the present investigation.

This study was a multi-center analysis including systolic HF patients from four U.S. exercise testing laboratories; LeBauer Cardiovascular Research Foundation, Greensboro, North Carolina, Stanford University, Palo Alto, CA, VA Palo Alto Health Care System, Palo Alto, California, and Virginia Commonwealth University, Richmond, Virginia. A total of 398 patients with systolic HF (age: 55.0 ± 14.2 years, ejection fraction: $27.2 \pm 10.1\%$, 72% males, 41% ischemic HF) underwent CPX using a conservative treadmill protocol. Minute ventilation, VO_2 and VCO_2 were acquired breath-by-breath, and averaged over 10-second intervals. Peak VO_2 was defined as the highest 10-second averaged value during CPX. Minute ventilation and VCO_2 values, acquired from the initiation of exercise to peak, were input into spreadsheet software (Microsoft Excel, Microsoft Corp., Bellevue, WA) to calculate the VE/VCO_2 slope via least squares linear regression ($y=mx+b$, m =slope). For the OUES, VE , averaged over 10-second intervals, was transformed into its logarithmic equivalent. The OUES was determined via least squares linear regression ($VO_2 = a \log_{10} VE + b$; VO_2 and VE are expressed in L/min) by spreadsheet software (Microsoft Excel, Microsoft Corp., Bellevue, WA) [3]. The peak VE/VO_2 ratio was defined as the ten-second averaged value at maximal exercise. Subjects were followed by the HF programs at their respective institution. Major cardiac events (mortality, LVAD implantation, urgent heart transplantation) were tracked via medical chart review for up to four years post CPX. Institutional board approval was obtained and all subjects signed a written informed consent prior to study initiation. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

Statistical analysis was performed using SPSS 19.0 (SPSS, Chicago, IL). Pearson product moment correlation was used to assess the relationship between the OUES and peak VE/VO_2 . Univariate and multivariate (forward stepwise method; entry and removal values 0.05 and 0.10, respectively) Cox regression analysis was used to assess the prognostic value of peak VO_2 , the VE/VCO_2 slope, the OUES and peak VE/VO_2 . A p-value ≤ 0.05 was considered statistically significant for all tests.

The mean peak VO_2 , VE/VCO_2 slope, OUES and peak VE/VO_2 were $16.5 (\pm 5.7) \text{ mL O}_2 \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, $35.4 (\pm 9.9)$, $1.7 (\pm 0.74)$ and $38.2 (9.9 \pm)$, respectively. The correlation between the OUES and peak VE/VO_2 was modest, which is illustrated in Fig. 1. There were 66 major cardiac events (51 deaths, 5 left ventricular assist device implantations and 10 transplantations) during the four year tracking period, equating to an average yearly event rate of 6.7%. Univariate and multivariate Cox regression analysis results are listed in Table 1. All CPX variables were significant univariate prognostic markers. In the multivariate regression, the VE/VCO_2 slope was the strongest prognostic marker with the OUES adding predictive value and being retained in the regression. Both peak VE/VO_2 and peak VO_2 were removed from the multivariate regression.

Because VE increases non-linearly during exercise, the OUES was developed to allow for expression of the relationship between VE and VO_2 in a more linear fashion. To our knowledge, this is the first analysis comparing the VE/ VO_2 ratio at peak exercise and the OUES, which are presumably both reflecting the same physiologic phenomenon. However, our results indicate the correlation between peak VE/ VO_2 and the OUES, while significant, is somewhat modest, suggesting one cannot be used as a surrogate for the other. In fact, analysis of the scatter plot in Fig. 1 between the OUES and peak VE/ VO_2 indicates the relationship follows more of an exponential decay pattern. The survival analysis demonstrates that both peak VE/ VO_2 and the OUES were strong univariate predictors of major adverse events. The multivariate analysis also confirmed the strong prognostic value of the VE/ VCO_2 slope, which has been consistently demonstrated in the past [5]. The only other variable that was retained in the multivariate regression was the OUES, indicating that this expression of ventilatory inefficiency during exercise may be preferred when performing CPX assessments in patients with systolic HF. Moreover, the findings of the present study confirm that ventilatory efficiency during exercise is best described using a multivariate approach [1]. Specifically, determining how the increase in VE matches the increase in both VCO_2 and VO_2 during exercise seems to provide a more comprehensive physiologic perspective and improves the estimate of risk. The combined assessment of both VCO_2 and VO_2 seems appropriate given the response characteristics to these expired gases differ during exercise [6].

Software packages that operate ventilatory expired gas systems automatically calculate and report peak VE/ VO_2 . However, the inclusion of the OUES as an automatically derived variable is not commonplace at this time. The results of the current study in conjunction with previous investigations [4] support automatic calculation of the OUES by these software packages.

In conclusion, the results of the current study support the assessment of ventilatory efficiency through quantification of both the VE– VCO_2 and VE– VO_2 relationships, the latter of which is perhaps optimally described through the OUES in patients with systolic HF [7].

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Fig. 1.

Scatter plot for the OUES and peak VE/VO₂. Legend: OUES, oxygen uptake efficiency slope; VE/VO₂, minute ventilation/oxygen consumption.

Table 1

Survival analysis for key CPX variables.

	Univariate analysis		
	Chi-square	Hazard ratio (95% CI)	p-value
VE/VCO ₂ slope	39.8	1.06 (1.04–1.08)	<0.001
Peak VE/VO ₂	37.2	1.04 (1.03–1.06)	<0.001
OUES	25.7	0.34 (0.22–0.52)	<0.001
Peak VO ₂	17.7	0.89 (0.85–0.94)	<0.001

	Multivariate analysis	
	Chi-square	p-value
VE/VCO ₂ slope	39.8	<0.001
	Residual Chi-square	p-value
OUES	8.2	0.004
Peak VE/VO ₂	1.3	0.25
Peak VO ₂	0.32	0.57

VE/VCO₂, minute ventilation/carbon dioxide production; OUES, oxygen uptake efficiency slope; VE/VO₂, minute ventilation/oxygen consumption; VO, oxygen consumption.