

Research article

## A Systematic Method to Detect the Metabolic Threshold from Gas Exchange during Incremental Exercise

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### Abstract

Incremental exercise consists of three domains of exercise intensity demarcated by two thresholds. The first of these thresholds, derived from gas exchange measurements, is defined as the metabolic threshold ( $\dot{V}O_{2\theta}$ ) above which lactate accumulates. Correctly and reliably identified,  $\dot{V}O_{2\theta}$  is a non-invasive, sub-maximal marker of aerobic function with practical value. This investigation compared variability in selection of  $\dot{V}O_{2\theta}$  among interpreters with different levels of experience as well as from auto-detection algorithms employed by a commercially available metabolic cart (MC). Ten healthy young men performed three replicates of incremental cycle exercise during which gas exchange measurements were collected breath-by-breath. Two experienced interpreters (E) and four novice interpreters (N) determined  $\dot{V}O_{2\theta}$  from plots of specific response variables. Interpreters noted methods used and confidence in their selections.  $\dot{V}O_{2\theta}$  was automatically determined by the MC. Interclass correlations indicated that E agreed with each other (mean difference, 21 mL·min<sup>-1</sup>) and with the MC (23 mL·min<sup>-1</sup>), but not with N (-664 to 364 mL·min<sup>-1</sup>); N did not agree among themselves. Despite good overall agreement between E and MC, differences >500 mL·min<sup>-1</sup> were seen in 50% of individual cases. N expressed unduly higher confidence and used different  $\dot{V}O_{2\theta}$  selection strategies compared with E. Experience and use of a systematic approach is essential for correctly identifying  $\dot{V}O_{2\theta}$ . Current guidelines for exercise testing and interpretation do not include recommendations for such an approach. Data from this study suggests that this may be a serious shortcoming. Until an alternative schema for  $\dot{V}O_{2\theta}$  detection is developed prospectively, strategies based on the present study will give practitioners a systematic and consistent approach to threshold detection.

**Key words:** Incremental exercise testing; oxygen uptake; metabolic threshold; lactate threshold.

### Introduction

During incremental exercise there exist three domains of exercise intensity separated by two thresholds (Tschakert and Hofmann, 2013). The lower intensity domain represents aerobic muscle metabolism where the increase in carbon dioxide output ( $\dot{V}CO_2$ ) matches the increase in oxygen uptake ( $\dot{V}O_2$ ). Within this domain, there are small increases in blood lactate but its level remains stable.

Within the intermediate intensity domain, a sustained increase in blood lactate occurs, and CO<sub>2</sub> produced during cellular respiration (“metabolic CO<sub>2</sub>”) is supplemented by “additional CO<sub>2</sub>” derived from bicarbonate buffering of lactic acid. This results in a disproportionate increase in  $\dot{V}CO_2$  relative to  $\dot{V}O_2$  (Cooper et al., 1992). We refer to this threshold between the lower and intermediate domains as the metabolic threshold ( $\dot{V}O_{2\theta}$ ) due to the metabolic shift that defines this transition. The same physiological transition has been described as the lactate or anaerobic threshold (Wasserman and McIlroy, 1964). Finally, the higher intensity domain is defined by further lactate accumulation and a disproportionate increase in expired ventilation ( $\dot{V}_E$ ) relative to  $\dot{V}CO_2$  (Cooper and Storer, 2001). Notwithstanding mechanistic and semantic arguments about the nature of the transition, identification of a threshold between the lower and intermediate exercise intensity domains has known practical application and value (Myers and Ashley, 1997). Specifically,  $\dot{V}O_{2\theta}$  serves as a key parameter of aerobic function (Cooper and Storer, 2001).

As the point of demarcation between the low and intermediate exercise intensity domains,  $\dot{V}O_{2\theta}$  is a non-invasive, sub-maximal, and effort-independent marker that has proved useful in clinical cardiopulmonary exercise testing. Equations exist for reference values and their lower 95% confidence limits for  $\dot{V}O_{2\theta}$  as detected by gas exchange measures (Davis et al., 1997). Since  $\dot{V}O_{2\theta}$  is reduced in cardiovascular disease (Wasserman and Whipp, 1975), chronic pulmonary disease (Cooper, 1995), end-stage renal disease (Mayer et al., 1988), and various forms of myopathy (Inbar et al., 2001; Tirdel et al., 1998), it may be used to detect an abnormal response to exercise when patient responses are compared to these reference values.  $\dot{V}O_{2\theta}$  also provides an objective means by which to categorize relative exercise intensity. This is of value in prescribing training intensity for endurance exercise training or rehabilitation programs and for evaluating the efficacy of these programs (Coplan et al., 1986; Gibbons, 1987; Hughson and MacFarlane, 1981; Nieuwland et al., 2002). Furthermore,  $\dot{V}O_{2\theta}$  has been utilized when prioritizing patients for heart transplantation as it is an effective predictor of mortality and morbidity associated with surgery (Older et al., 1999; Older et al., 1993) and a better

predictor of 6-month mortality in patients with chronic heart failure (CHF) than  $\dot{V}O_2$  max (Gitt et al., 2002).

Consequently, the utility of  $\dot{V}O_2\theta$  hinges upon its precise identification. There is a scarcity of data, however, with which to estimate the ability of laboratory personnel or computer auto-detection routines to reproducibly identify  $\dot{V}O_2\theta$ . Furthermore, there may be a perception that simply having a rudimentary exposure to the concepts surrounding the detection of  $\dot{V}O_2\theta$  is adequate for its reliable measurement. Differing methodologies used for threshold detection contribute to the confusion as well (Svedahl and MacIntosh, 2003). We are unaware of any data that compare levels of training and expertise of interpreters in the somewhat subjective identification of  $\dot{V}O_2\theta$ . Outstandingly, there does not seem to be a systematic approach to threshold detection wherein specific data displays, procedural steps, and decision trees are available to aid the practitioner in reliably measuring this value.

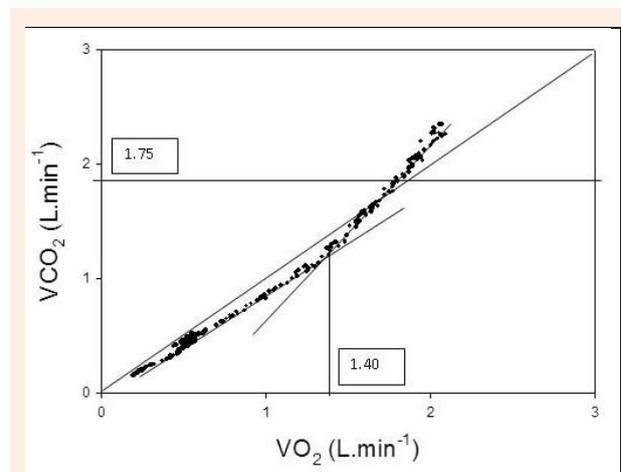
Recommended criteria to be used in selecting  $\dot{V}O_2\theta$  (the first threshold) are available in published reports including use of the “dual criteria” method (systematic rise in the ventilatory equivalent for oxygen,  $\dot{V}_E/\dot{V}O_2$ , while the ventilatory equivalent for carbon dioxide,  $\dot{V}_E/\dot{V}CO_2$ , did not increase) (Caiozzo et al., 1982). The “V-slope” (Beaver et al., 1986) and modified “V-slope” (Sue et al., 1988) methods that identify  $\dot{V}O_2\theta$  from a plot of  $\dot{V}CO_2$  versus  $\dot{V}O_2$  (Figure 1) were not included in the analysis by Caiozzo et al. but have subsequently been shown to be superior to alternative methods of detection (Beaver et al., 1986; Sue et al., 1988). Current recommendations suggest use of a constellation of variables in selecting  $\dot{V}O_2\theta$ . (Boulay et al., 1984) studied different methods of threshold detection and developed a method whereby interpreters assigned a numerical value representing the confidence of each reader’s choice of  $\dot{V}O_2\theta$ . Notably absent, however, is any systematic evaluation of the ability of laboratory personnel to correctly apply these recommendations in the reliable selection of  $\dot{V}O_2\theta$ , specifically with respect to their expertise and experience in performing this function.

## Methods

### Subjects

Ten healthy, non-smoking, recreationally active men volunteered as subjects and performed the ramp cycle ergometer exercise tests described below. Six other people interpreted the exercise data and were designated as interpreters. Two were considered experienced (E1 and E2) in detection of the metabolic threshold ( $\dot{V}O_2\theta$ ) on the basis of their previous training, research, publications, and teaching. The remaining four interpreters (N1-N4) were pulmonary fellows at various stages of training and although familiar with supervision of exercise tests and the concepts surrounding  $\dot{V}O_2\theta$ , were considered novices in its correct detection. The MC used to acquire the gas

exchange data (2900; SensorMedics Corporation, Yorba Linda, CA) has the capability of auto-detecting  $\dot{V}O_2\theta$  using proprietary algorithms. The subjects gave informed consent for their participation in the study which was previously approved by the university’s institutional review board.



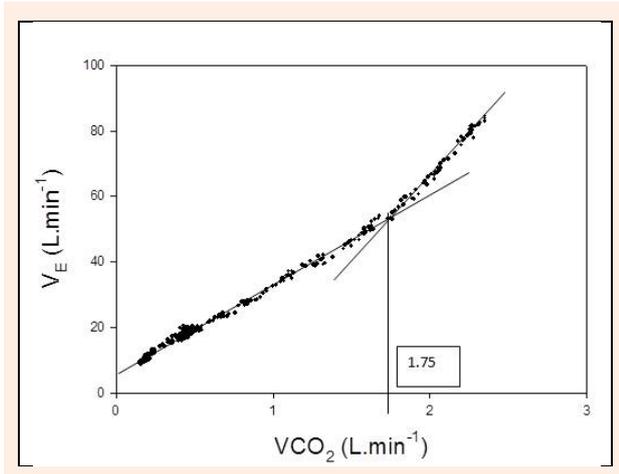
**Figure 1.** The carbon dioxide output ( $\dot{V}CO_2$ ) versus oxygen uptake ( $\dot{V}O_2$ ) relationship. The metabolic threshold ( $\dot{V}O_2\theta$ ) is identified at the point at which  $\dot{V}CO_2$  increases out of proportion to the increase in  $\dot{V}O_2$ .  $\dot{V}O_2\theta$  is identified on the x-axis at a value of 1.40 L/min. The horizontal line at  $\dot{V}CO_2 = 1.75$  L/min represents the ventilatory threshold ( $\dot{V}CO_2\theta$ ) as determined in Figure 2. The line of identify intersects the origin of the x- and y-axes.

Clinical exercise laboratories not only use laboratory personnel to identify  $\dot{V}O_2\theta$ , but often rely upon auto-detection of the value using commercially manufactured metabolic carts (MCs) that use unknown, proprietary algorithms. Such systems are often heavily depended upon to yield a useable value for  $\dot{V}O_2\theta$ , but are rarely systematically validated by comparison with expert human interpreters and could potentially give misleading results and conclusions. The purpose of this investigation, therefore, was to compare the variability in  $\dot{V}O_2\theta$  selected by interpreters of different levels of experience as well as by auto-detection algorithms employed by a commercially available metabolic cart. Implicit in this report is the expertise of the “experienced” interpreters as the standard against which detection of  $\dot{V}O_2\theta$  by novice interpreters and auto detection by a metabolic cart is compared. As a result of this study, we present a systematic approach to  $\dot{V}O_2\theta$  detection as an aid to its reliable identification.

### Exercise tests

The ten exercising subjects completed three maximal leg cycling tests using a 20-watt-per-minute ramp protocol administered on non-consecutive days over a 5-day period. A calibrated electrically braked ergometer (Type 800; Ergoline, Bitz, Germany) was used for all tests. The MC measured breath-by-breath pulmonary ventilation and gas

exchange throughout the warm-up and exercise phases of each test. The subjects breathed through a one-way valve with  $\dot{V}_E$  and concentrations of  $O_2$  and  $CO_2$  measured downstream by a mass flow transducer and paramagnetic and near-infrared gas analyzers, respectively (Markovitz et al., 2004). The expired flow and gas concentration measurements were time aligned and corrected to standard conditions allowing the breath-by-breath calculation of oxygen uptake and carbon dioxide output.



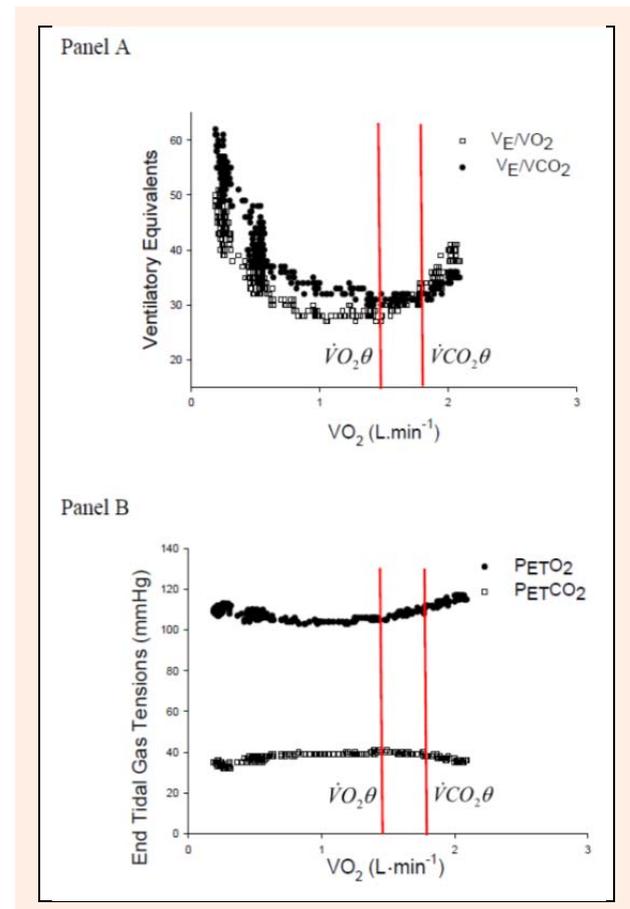
**Figure 2.** The minute ventilation ( $\dot{V}_E$ ) versus  $\dot{V}CO_2$  relationship. The vertical line at  $\dot{V}CO_2 = 1.75 \text{ L}\cdot\text{min}^{-1}$  identifies the ventilatory threshold  $\dot{V}CO_{2\theta}$ .

### Determination of $\dot{V}O_{2\theta}$

All the interpreters were presented with randomized and coded data sets from the 30 (10 subjects  $\times$  3 trials) maximal exercise tests. These data sets included plots of the  $\dot{V}CO_2$  versus  $\dot{V}O_2$  relationship (Figure 1), as well as plots for the ventilatory equivalents for oxygen ( $\dot{V}_E/\dot{V}O_2$ ) and carbon dioxide ( $\dot{V}_E/\dot{V}CO_2$ ) versus  $\dot{V}O_2$  (Figure 3A), and the end-tidal partial pressures for oxygen ( $P_{ET}O_2$ ) and carbon dioxide ( $P_{ET}CO_2$ ) versus  $\dot{V}O_2$  (Figure 3B). Unlike some investigations which allowed interpreters the freedom to choose their own method for detecting  $\dot{V}O_{2\theta}$ , (Gladden et al., 1985) we provided each interpreter with an outline of suggested approaches for its selection. No further information was given. The interpreters were allowed unlimited time for choosing  $\dot{V}O_{2\theta}$  for each of the 30 plots and worked in isolation.

Briefly, it was suggested that interpreters first ascertain  $\dot{V}O_{2\theta}$  using the  $\dot{V}CO_2$  versus  $\dot{V}O_2$  relationship alone (Figure 1), assigning a level of confidence (1 = high, 2 = medium, 3 = low) to the chosen  $\dot{V}O_{2\theta}$ . So as not to confuse  $\dot{V}O_{2\theta}$  with the ventilatory threshold ( $\dot{V}CO_{2\theta}$ ) interpreters were instructed to review Figure 2, the  $\dot{V}_E$  versus  $\dot{V}CO_2$  relationship to identify the  $\dot{V}CO_{2\theta}$ : the point at which  $\dot{V}_E$  increases out of proportion to the increase in  $\dot{V}CO_2$  (Cooper and Storer, 2001). If confidence in the selection of  $\dot{V}O_{2\theta}$  from the  $\dot{V}CO_2$  versus  $\dot{V}O_2$  relationship was 2 or 3, interpreters were asked to refer to Figures 3A

and 3B which displayed  $\dot{V}_E/\dot{V}O_2$ ,  $\dot{V}_E/\dot{V}CO_2$ ,  $P_{ET}O_2$ , and  $P_{ET}CO_2$  respectively. For each method used, interpreters were requested to provide  $\dot{V}O_{2\theta}$  to the nearest 10-50 mL/min, the criteria used to select  $\dot{V}O_{2\theta}$ , and the overall confidence level with which  $\dot{V}O_{2\theta}$  was determined. Interpreters noted whether  $\dot{V}O_{2\theta}$  was determined primarily from the  $\dot{V}CO_2$  versus  $\dot{V}O_2$  relationship, from data contained in Figures 3A and 3B, or from both.



**Figure 3. Panel A.** The ventilatory equivalents for oxygen ( $\dot{V}_E/\dot{V}O_2$ ) and carbon dioxide ( $\dot{V}_E/\dot{V}CO_2$ ).  $\dot{V}O_{2\theta}$ , the first threshold, is identified by the dual criteria of a systematic increase in  $\dot{V}_E/\dot{V}O_2$  without an increase in  $\dot{V}_E/\dot{V}CO_2$ .  $\dot{V}CO_{2\theta}$ , the second threshold, is identified by a systematic increase in  $\dot{V}_E/\dot{V}CO_2$ . **Panel B.** End-tidal gas tensions for oxygen ( $P_{ET}O_2$ ) and carbon dioxide ( $P_{ET}CO_2$ ).  $\dot{V}O_{2\theta}$ , the first threshold, corresponds with the requirement that  $P_{ET}O_2$  systematically increases while  $P_{ET}CO_2$  does not decrease. Note that  $\dot{V}O_{2\theta}$  is identified at  $\dot{V}O_2 = 1.40 \text{ L}/\text{min}$ .  $\dot{V}CO_{2\theta}$ , the second threshold, corresponds with the requirement that  $P_{ET}CO_2$  systematically decreases.

An option on the automated MC system was selected to provide automated detection of  $\dot{V}O_{2\theta}$  for each test through use of proprietary algorithms that utilize the  $\dot{V}CO_2$  versus  $\dot{V}O_2$  relationship alone. None of the interpreters had access to these automated determinations of  $\dot{V}O_{2\theta}$ .

### Statistical analysis

Computed values for  $\dot{V}O_2$  and  $\dot{V}CO_2$  were obtained breath-by-breath and then smoothed using a 9-breath rolling average technique. The data were presented in tabular and graphical format for interpretation. Descriptive statistics provided means and standard deviations for  $\dot{V}O_2\theta$ , frequency distribution for the method used to detect  $\dot{V}O_2\theta$ , and subjective levels of confidence in its detection. Agreement between E, differences between E and N, and differences between E and the MC's auto-detection of  $\dot{V}O_2\theta$ , were determined by interclass correlation coefficients, Bland Altman plots, and the 95% agreement limit. Linear regression was used to illustrate individual comparisons of  $\dot{V}O_2\theta$  determined by the six interpreters and the automated MC. The first comparison was E1 versus E2. Due to their close agreement and since we did not have blood lactate measurements, it was posited *a priori* that  $\dot{V}O_2\theta$  determined by the experienced interpreters would be the gold standard. Whilst we agree that this is not ideal, it does represent a realistic situation faced when interpreting incremental exercise tests. The mean of E1 and E2 was then used in comparison with N1-N4, and  $\dot{V}O_2\theta$  determined by the MC. We fit the data using Huber's robust regression method and calculated confidence (Fox, 1997). Bland-Altman (Bland and Altman, 1986) plots were used to illustrate individual comparisons of  $\dot{V}O_2\theta$  determined by the six interpreters and the automated MC by plotting pair-wise comparisons for differences between interpreters versus their mean. After comparisons were drawn, systematic bias was identified if the slope of the pair-wise comparison was significantly different than zero. Differences in confidence level as well as methods for detecting  $\dot{V}O_2\theta$  were analyzed by Friedman's repeated-measures ANOVA. Post-hoc analysis was performed using Dunn's analysis and a *P*-value less than 0.05 was considered statistically significant.

### Results

All 10 exercising subjects completed the study with a mean ( $\pm$ SD) age of 25 (5) years of age, body weight of 77

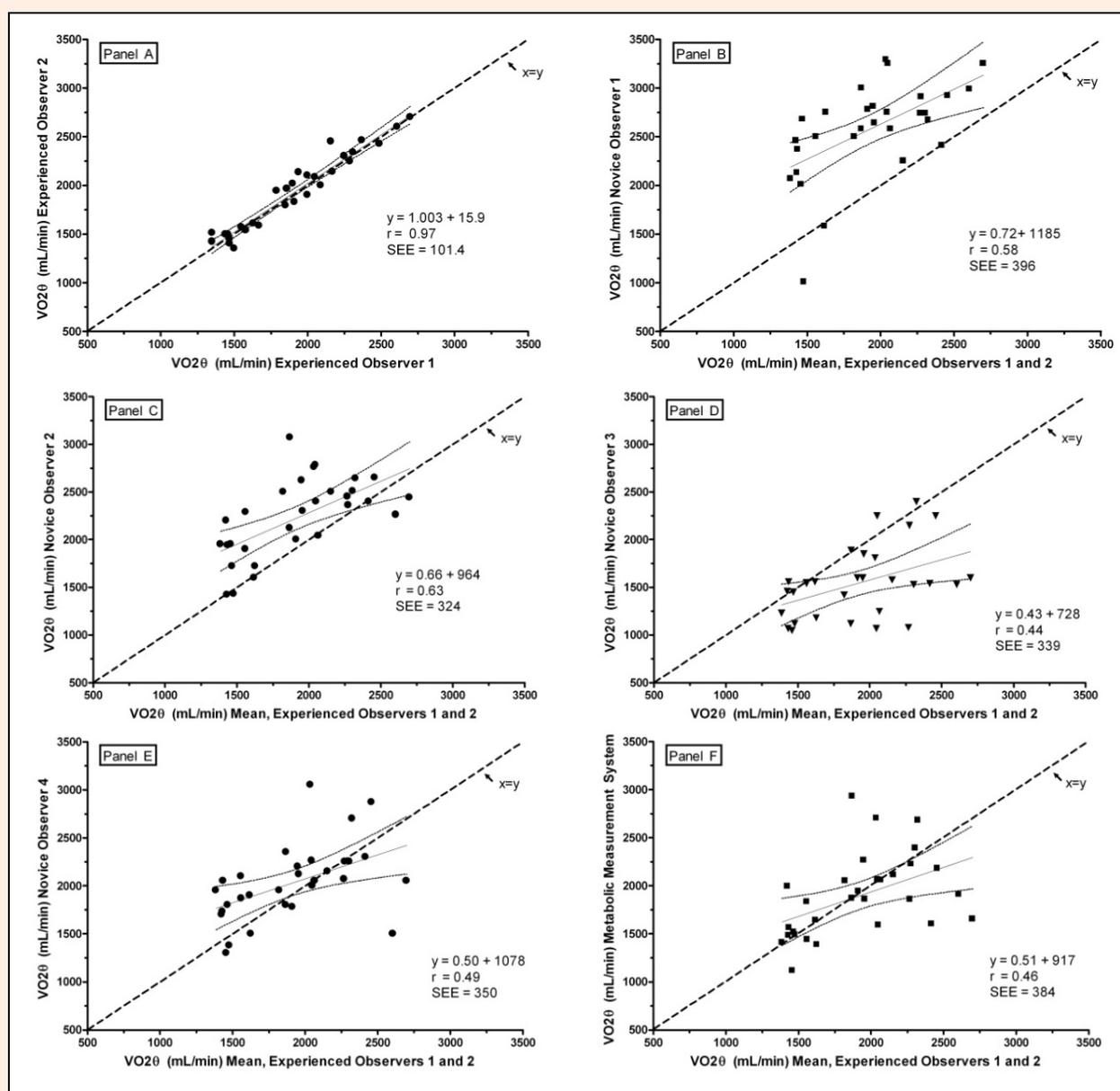
(8) kg, and height of 1.78 (0.09) m. Each reader was able to identify a  $\dot{V}O_2\theta$  on each of the 30 exercise tests. Subject means ( $\pm$ SD) for  $\dot{V}O_2\theta$  determined by each interpreter, as well as the automated MC, are presented in Table 1. Interclass correlation statistics revealed that E1 and E2 had uniform responses in selecting  $\dot{V}O_2\theta$  for the 10 subjects; therefore, this value served as the gold standard to which all other comparisons were made. Linear regression of  $\dot{V}O_2\theta$  selected by E, the mean of E versus N, and the mean of E versus the MC are illustrated in Figure 4, Panels A-F, respectively. The coefficient of determination ( $r^2$ ) for this relationship was 0.97, suggesting a high correlation between  $\dot{V}O_2$  selected by E1 and E2. Regression statistics for the remaining relationships shown in Figure 4B-F have substantially poorer correlations as noted by smaller  $r^2$  values. Additionally, comparing the individual regression lines with the line of identity ( $x = y$ ), clear overestimation of  $\dot{V}O_2\theta$  by N1 and N2, and underestimation by N3 is readily apparent. Both N4 and MC estimates of  $\dot{V}O_2\theta$  are high when  $\dot{V}O_2\theta$  is lower and low when  $\dot{V}O_2\theta$  is higher.

Bland-Altman plots (Figure 5) illustrate the degree of agreement between E1 and E2 (Panel A), the mean of E and N (Panels B, C, D, and E), and the mean of E and the MC (Panel F). Figure 5A indicates that the mean difference between E1 and E2 in selecting  $\dot{V}O_2\theta$  was  $-21 \text{ mL}\cdot\text{min}^{-1}$ . The 95% confidence band spanned a range of  $-217 \text{ mL}\cdot\text{min}^{-1}$  to  $174 \text{ mL}\cdot\text{min}^{-1}$ . Thus, on average, E agreed within  $21 \text{ mL}\cdot\text{min}^{-1}$  across a measurement range of  $1200 \text{ mL}\cdot\text{min}^{-1}$  to  $2800 \text{ mL}\cdot\text{min}^{-1}$  and 95 times out of 100, they agreed within  $\pm 195 \text{ mL}\cdot\text{min}^{-1}$ . There was no evidence of systematic bias across the range of measurements as indicated by a regression slope of 0.04 ( $p = 0.46$ ). Figure 5B-E reveal large mean differences and wide scatters in individual comparisons of E and N. The 95% confidence intervals surrounding the mean differences for the four comparisons illustrated in Panels B-E of Figure 5 were similar ( $\pm 790$ ,  $\pm 676$ ,  $\pm 786$ , and  $\pm 775 \text{ mL}\cdot\text{min}^{-1}$ , respectively) nearly four times greater than the  $\pm 195 \text{ mL}\cdot\text{min}^{-1}$  confidence band for mean  $\dot{V}O_2\theta$  selected by E.

**Table 1.** Values of  $\dot{V}O_2\theta$  for 10 subjects (S1-S10) as determined by two experienced interpreters (E1, E2), four novice interpreters (N1-N4), and an automated metabolic measurement system (MC). Values are means ( $\pm$ SD) in mL.

Subjects	E1 (a)	E2 (b)	N1 (c)	N2 (d)	N3 (e)	N4 (f)	MC (g)
S1	1550 (98)	1547 (57)	2253 (590)	1740 (151)	1520 (61)	1933 (153)	1665 (159)
S2	2217 (250)	2258 (311)	2823 (91)	2593 (74)	1793 (397)	2440 (373)	2279 (105)
S3	2440 (233)	2488 (201)	2857 (423)	2400 (40)	1763 (336)	220 (132)	1828 (345)
S4	1813 (297)	1715 (332)	2570 (157)	2493 (290)	1317 (215)	1970 (281)	2038 (38)
S5	1390 (69)	1460 (46)	2070 (60)	1773 (306)	1117 (99)	1660 (331)	1338 (195)
S6	1873 (410)	1871 (431)	2630 (226)	2130 (279)	1413 (289)	1967 (162)	1789 (199)
S7	2053 (223)	2100 (256)	2987 (310)	2823 (222)	2033 (320)	2700 (350)	2773 (138)
S8	2170 (384)	2239 (316)	2960 (306)	2320 (72)	1877 (361)	1873 (329)	1787 (171)
S9	1877 (261)	1890 (282)	2527 (254)	2113 (390)	1293 (250)	1817 (325)	1791 (369)
S10	1687 (318)	1717 (320)	2030 (884)	1920 (442)	1303 (215)	1767 (347)	1664 (344)
Mean	1907 (254) * d, e; # <sup>c</sup>	1928 (255) † e; # <sup>c</sup>	2571 (330) * e; # <sup>e, f, g</sup>	2230 (227) * e; # <sup>c</sup>	1543 (254) * e; # <sup>f</sup>	2032 (278) # <sup>c, e</sup>	1895 (206) * e; # <sup>c</sup>

Superscripts letters denote significantly (\*  $p < 0.05$ ; †  $p < 0.01$ ; #  $p < 0.001$ ) differences between the columns. Values for each subject represent means (SD) from triplicate trials. Overall means  $\pm$  (SD) are shown in last row and represent averages and variability between subjects.

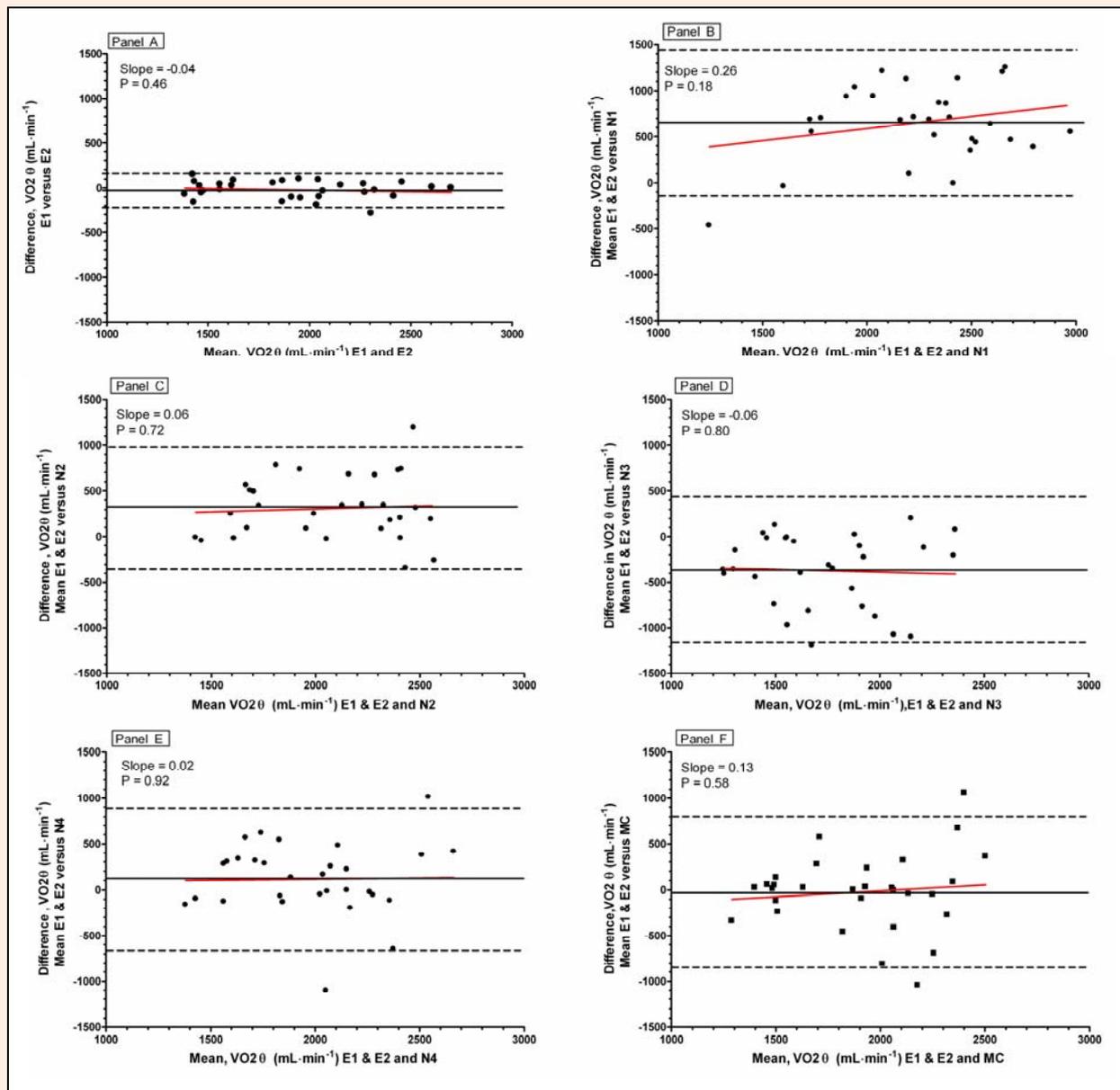


**Figure 4.** Linear regressions of  $\dot{V}O_2\theta$  selected by pairs of interpreters. Data points are means of triplicate trials. The diagonal dashed line represents the line of identity ( $x = y$ ); the solid diagonal line is the regression line; 95% confidence limits are shown by the curved lines. Panel A shows E1 versus E2. Panels B-E show the mean  $\dot{V}O_2\theta$  selected by N1, N2, N3, and N4, respectively versus the mean of E1 and E2. Panel F is the regression of the mean  $\dot{V}O_2\theta$  selected by auto-detection by the metabolic measurement system (MC) versus the mean of E1 and E2.

Slopes of the regression lines in Figure 4B-F were not significantly different from zero, suggesting no systematic bias when comparing E and N. Although the mean difference for the comparison between E and the MC (Figure 5F) was small ( $-23 \text{ mL}\cdot\text{min}^{-1}$ ) and not significantly different, the dispersion of agreement was large with a 95% confidence interval of  $\pm 828 \text{ mL}\cdot\text{min}^{-1}$ .

The confidence level with which interpreters selected  $\dot{V}O_2\theta$  and the method used in its selection are summarized in Table 2. Overall, differences between interpreters for confidence in identifying  $\dot{V}O_2\theta$  was significant ( $p = 0.002$ ). Post hoc analysis revealed, however, that N1 reported high confidence in only 5 out of 30 cases while N2 reported high confidence in 21 out of 30 cases.

This was the only significant difference in reported level of confidence. Notably, the N who disagreed with the E had an unduly high level of confidence in their selection. Additionally, E and N tended to use different strategies to identify  $\dot{V}O_2\theta$  ( $p < 0.0001$ ). The multiple comparisons test indicated that on average, E1 or E2 did not differ in their selection method. E tended to rely on both the  $\dot{V}CO_2$  versus  $\dot{V}O_2$  plot and the dual criteria plots while N tended to select  $\dot{V}O_2\theta$  primarily from the  $\dot{V}CO_2$  vs.  $\dot{V}O_2$  relationship. No significant difference in  $\dot{V}O_2\theta$  selection method was observed among N although N1 tended to rely more on dual criteria plots for selection of  $\dot{V}O_2\theta$ .



**Figure 5.** Bland-Altman plots of the difference between the selections of  $\dot{V}_{O_2}\theta$  by pairs of interpreters versus the mean of their selections. The solid horizontal line represents the mean bias between the pairs of interpreters; the two dashed lines represent the 95% confidence limits of the bias. Each data point is the average of three trials for the ten subjects. Panel A shows E1 vs E2; Panels B-E show the mean of E1 and E2 selections of  $\dot{V}_{O_2}\theta$  versus those of N1-N4; Panel F shows the mean of E1 and E2 selections versus the MC automated selection of  $\dot{V}_{O_2}\theta$ .

**Table 2.** Interpreter confidence and methods used in selecting  $\dot{V}_{O_2}\theta$ . Data represent the average percentage of occurrences for each variable.

Confidence	E1	E2	N1	N2	N3	N4	Mean E	Mean N
High	40%	43%	17%*	70%*	57%	57%	42%	50%
Medium	50%	37%	60%	23%	33%	30%	44%	37%
Low	10%	20%	23%	7%	10%	13%	15%	13%
Method								
$\dot{V}_{CO_2}$ vs. $\dot{V}_{O_2}$ only	30%	13%*	17%	70%*	67%*	60%*	22%	53%
Dual Criteria only	3%	23%	47%	3%	10%	10%	13%	18%
Both	67%	63%	37%	27%	23%	30%	65%	29%

\*  $p < 0.05$ ; E = experienced interpreters; N = novice interpreters; Dual Criteria = use of the  $\dot{V}_E/\dot{V}_{O_2}$  and  $\dot{V}_E/\dot{V}_{CO_2}$  versus  $\dot{V}_{O_2}$  (Figure 3A) and/or the  $P_{ET}O_2$  and  $P_{ET}CO_2$  versus  $\dot{V}_{O_2}$  plot (Figure 3B); Both = use of both the  $\dot{V}_{CO_2}$  versus  $\dot{V}_{O_2}$  plot and the dual criteria plots.

## Discussion

The metabolic threshold ( $\dot{V}O_{2\theta}$ ), or the first threshold identified during incremental exercise testing, is regarded as one of the four important parameters of aerobic performance (Whipp et al., 1981). Previous reports have identified several variables with specific response patterns that identify the physiological transitions between the light, moderate, and heavy domains of exercise intensity (Beaver et al., 1986; Caiozzo et al., 1982; Henson et al., 1989; Sue et al., 1988; Wasserman and McIlroy, 1964).

We have used the classical approach to threshold determination as described by Wasserman and McIlroy (Wasserman and McIlroy, 1964) and acknowledged three-phases of the exercise response. The first phase represents aerobic muscle metabolism where the evolution of exhaled carbon dioxide is proportional to oxygen uptake. This is best seen on the graphical plot of  $\dot{V}CO_2$  versus  $\dot{V}O_2$ . During the second phase, additional  $CO_2$  is derived from bicarbonate buffering of lactic acid and, whilst a change in blood pH is minimized, there is an increase in the ventilatory equivalent for oxygen and the end-tidal oxygen partial pressure. At the same time as this is happening, ventilation remains tightly coupled to  $\dot{V}CO_2$  and the ventilatory equivalent for  $CO_2$  remains constant, as does the end-tidal partial pressure of  $CO_2$ . This traditional threshold detection phenomenon of the “dual criteria” is clearly shown by the first vertical line on Figure 3. Our second vertical red line in Figure 3 indicates the point where accumulation of lactic acid overwhelms the bicarbonate buffering capacity of the blood. When this happens, blood pH falls and unbuffered hydrogen ion stimulates the carotid bodies causing true hyperventilation in response to metabolic acidosis. As a result ventilation becomes uncoupled from  $\dot{V}CO_2$  and this is reflected in an increase in the ventilatory equivalent for  $CO_2$  and a decrease in end-tidal  $CO_2$  as shown in Panels A and B of Figure 3, respectively.

There is general agreement that determination of  $\dot{V}O_{2\theta}$  can be helpful in the interpretation of both clinical and performance exercise tests (Cooper and Storer, 2001), as an important variable in exercise prescription (Coplan et al., 1986; Gibbons, 1987; Hughson and MacFarlane, 1981; Nieuwland et al., 2002), and as a predictor of mortality or morbidity in surgery or CHF (Bechard and Wetstein, 1987; Older et al., 1993). However, if  $\dot{V}O_{2\theta}$  is to be viewed as a reliable parameter of the exercise response and successfully used for the important purposes mentioned above, laboratory personnel responsible for its identification must be adequately trained and experienced in applying systematic methods for its detection. Furthermore, auto-detection of  $\dot{V}O_{2\theta}$  by automated MCs should be viewed cautiously.

The principal findings from this study suggest that 1) individuals experienced and practiced with the detection of  $\dot{V}O_{2\theta}$  who use a systematic approach agree with each other; 2) novices, even when given specific guidelines, do not agree with the experienced users or them-

selves and 3) automated  $\dot{V}O_{2\theta}$  detection algorithms agree, on average, with experienced interpreters, but with notable exceptions that suggest the need for human oversight to avoid erroneous interpretations that could have substantial clinical implications. Previous reports on the ability of interpreters to reach acceptable levels of agreement in their detection of  $\dot{V}O_{2\theta}$  have reached mixed conclusions. Additionally, reader expertise in identifying  $\dot{V}O_{2\theta}$  is rarely reported and in studies that have done so, absolute differences in choosing  $\dot{V}O_{2\theta}$  have ranged between 20 mL·min<sup>-1</sup> (Hansen et al., 2004) and 530 mL·min<sup>-1</sup> (Gladden et al., 1985). If disagreement is the result of inadequate training, experience, or lack of a systematic approach to  $\dot{V}O_{2\theta}$  selection, we stand to lose a valuable parameter of aerobic performance that might influence clinical decisions about cardiopulmonary status, surgical risk, disease prognosis, prescription of exercise training intensity, and evaluating efficacy of rehabilitation and training programs.

In the present study, the E, on average, agreed within 21 mL·min<sup>-1</sup> (1%) in selecting  $\dot{V}O_{2\theta}$  from a total of 30 incremental exercise tests; in absolute measures, agreement was 79 mL·min<sup>-1</sup> (4%). N differed from the experienced interpreters, on average, over a range of -664 mL·min<sup>-1</sup> to 364 mL·min<sup>-1</sup>. In aggregate, the mean absolute difference between E and N was 369 mL·min<sup>-1</sup>. These data are generally consistent with other reports using experienced interpreters. Shimizu et al. (1991) evaluated the effects of ergometer and work rate increment, response variables, and reviewers in selecting  $\dot{V}O_{2\theta}$  in healthy men and men with heart disease. In that study, the intraclass correlation coefficient among the three reviewers was 0.60, and the greatest absolute difference among the reviewers across 138 tests was 70 mL·min<sup>-1</sup> (7%). Data from the present study are similar with respect to agreement among E who, on average, did not differ by more than 21 mL/min (1%). Simonton et al. (1988) reported somewhat larger inter-reader variability in detecting  $\dot{V}O_{2\theta}$  in healthy individuals and patients with CHF. Differences among the three experienced interpreters were 4.6% to 12% and 6% to 8.4% in their patients depending on the exercise protocol selected.

Davis et al. (1976) indicated good agreement among their investigators in identifying  $\dot{V}O_{2\theta}$ . Differences were reported to be 15-30 s in tests that used cycle ergometer work rate increments of approximately 30 watts per minute. Assuming a normal  $\dot{V}O_2$ -work rate ( $\dot{W}$ ) slope of 10 mL·min<sup>-1</sup>·watt<sup>-1</sup> (Hansen et al., 1988), 15-30 s would represent an inter-evaluator difference of about 75-150 mL·min<sup>-1</sup>. Selections were reported to rarely differ by more than 60 s (about 300 mL·min<sup>-1</sup>). These levels of agreement are similar to that reported in the present study between E but not among N. Selection of  $\dot{V}O_{2\theta}$  in the study by Davis et al. was based on the average time at which non-linear increases in  $\dot{V}_E$  and  $\dot{V}CO_2$  were observed relative to  $\dot{V}O_2$  or  $\dot{W}$ .  $\dot{V}O_{2\theta}$  was then discerned from a regression of this average time against  $\dot{V}O_2$ . This meth-

odology is considerably different from that used in the present study and other studies in which selection of  $\dot{V}O_2$  are of primary interest.

In contrast to the above where the interpreters appeared to have substantial experience in  $\dot{V}O_2\theta$  detection, Gladden et al. (1985) studied interpreters from nine separate laboratories who ranged from inexperienced to very experienced. They were given blind plots of gas exchange and ventilation data, but no instructions for choosing  $\dot{V}O_2\theta$ . Like the interpreters in the present study, all were familiar with physiological responses to exercise. In eight of the nine evaluators,  $\dot{V}O_2\theta$  ranged greater than 1.75 min in half of all the tests. Considering the 30-watt-per-minute work rate increment, the 1.75 min range would be equivalent to a  $\dot{V}O_2\theta$  of about 540 mL·min<sup>-1</sup>. Correlations among evaluators for  $\dot{V}O_2\theta$  ranged between 0.30 and 0.93 (median = 0.74). Correlations among the three most experienced evaluators ranged from 0.79 to 0.88. Correlations, however, identify relationships and not agreement. Gladden et al. emphasized this point by reporting that different evaluators did not choose identical  $\dot{V}O_2\theta$ . Mean absolute differences for  $\dot{V}O_2\theta$  between any two evaluators ranged from a low of 100 mL·min<sup>-1</sup> to a high of 530 mL·min<sup>-1</sup>. In the present study, the mean difference among E was 21 mL·min<sup>-1</sup>; the mean absolute differences for the E was 79 mL·min<sup>-1</sup>; 77% of the time absolute differences were less than 100 mL·min<sup>-1</sup> (data not shown). The Bland-Altman plots (Figure 5) further emphasize that E choose different values for  $\dot{V}O_2\theta$  than N. These graphical representations of agreement among E as well as between E and N underscores the value of practice and use of a methodical approach in  $\dot{V}O_2\theta$  selection. Although none of the comparisons exhibited significant bias, the mean differences and individual case differences were large when E were compared to N and the MC.

Observations on the agreement in selecting  $\dot{V}O_2\theta$  within patient groups has also been inconsistent. Belman et al. (1992) reported wide variability in determining  $\dot{V}O_2\theta$  in patients with COPD with only modest intra- and inter-reader agreement between two experienced interpreters. It is possible that the irregular breathing patterns accompanying COPD may have made detection of  $\dot{V}O_2\theta$  by gas exchange difficult in these patients despite the observation of thresholds determined by blood sampling methods. Hansen et al. (2004), however, studied 42 patients with pulmonary arterial hypertension who performed repeated incremental exercise tests, in duplicate, over a period of 15 months. Generally, the two experienced interpreters agreed with each other better than the four lesser experienced interpreters. These data tend to support the findings of the present study; however, the selected group of patients with pulmonary hypertension and the variable time intervals between repeated tests (up to 15 months) may not allow these findings to be generalized to the many other situations in which exercise testing is performed.

Modern, commercially available MCs often in-

clude algorithms for automated detection of  $\dot{V}O_2\theta$ . A systematic evaluation of the accuracy of this determination is limited. The MC used in the present study showed good agreement, on average, with E in detecting  $\dot{V}O_2\theta$ . However, as shown in Panel F in both Figures 4 and 5, the magnitude of disagreement was large and variable. The mean absolute difference of 284 mL·min<sup>-1</sup> was less than that for any N but 20% of the 30 cases differed by 500 mL·min<sup>-1</sup> or more (data not shown). These data make a good case for routine human oversight of  $\dot{V}O_2\theta$  determined by any automated MC.

### Differences in reader confidence and method in selecting $\dot{V}O_2\theta$

In general, confidence levels in selecting  $\dot{V}O_2\theta$  were higher in N although these differences did not reach statistical significance. N exhibited levels of confidence that were essentially equal to those of E which suggests misperception in abilities given the significant lack of agreement in  $\dot{V}O_2\theta$  selection between these two classes of interpreters. This implies a lack of understanding of response patterns and/or haste in identifying  $\dot{V}O_2\theta$ . One value of using a systematic approach is to avoid hasty decisions based on what might appear to be an “obvious” choice for  $\dot{V}O_2\theta$ . In our experience, this obvious choice is often selection of the more abrupt increase in  $\dot{V}CO_2$  near the end of the exercise test.

N used the  $\dot{V}CO_2$  versus  $\dot{V}O_2$  relationship alone to select  $\dot{V}O_2\theta$  more than twice as frequently as E. E appeared to have been somewhat more thorough by also examining the dual criteria plots shown in Figure 3. While use of the  $\dot{V}CO_2$  versus  $\dot{V}O_2$  relationship is thought to be the first approach to identifying  $\dot{V}O_2\theta$  because it relatively insensitive to irregular breathing patterns, use of additional variables such as the dual criteria would be confirming and may therefore improve confidence in  $\dot{V}O_2\theta$  identification. A systematic approach should include a thorough examination of an appropriate constellation of variables to ensure accurate and reproducible selection of  $\dot{V}O_2\theta$ . Furthermore, it should carefully eliminate  $\dot{V}CO_2\theta$  as a candidate for  $\dot{V}O_2\theta$  by using the plot of minute ventilation against carbon dioxide output. Examining this graph, therefore, should be considered one of the first steps in the systematic detection of  $\dot{V}O_2\theta$ .

If  $\dot{V}O_2\theta$  is to be interpreted reliably and used, for example, in exercise prescription, pre-operative risk assessment, and the identification of cardiovascular disease or myopathies, then a standardized approach is required. Current guidelines for exercise testing and interpretation do not emphasize such an approach to threshold detection, and we believe this is a serious shortcoming. This paper exposes the lack of consistency in methods of  $\dot{V}O_2\theta$  determination and the likely lack of reliability of reported values. Additionally, our study has provided useful insights into the common pitfalls of gas exchange threshold

detection and allowed us to refine our standardized instructions now presented in Table 3. Further research is needed to prospectively evaluate such a schema for detecting  $\dot{V}O_2\theta$  in order to establish recognized standards that will improve the physiological and clinical value of this important measurement. Until then, use of the strategy outlined in Table 3 may give practitioners a systematic and consistent approach desperately needed within the field.

## Conclusion

Experience and use of a systematic approach is essential

for correctly identifying the metabolic threshold ( $\dot{V}O_2\theta$ ) during incremental exercise at which point a sustained increase in lactate begins. Current guidelines for exercise testing and interpretation do not include recommendations for such an approach. This paper presents a systematic and practical approach to threshold detection which will aide training of interpreters of incremental cardio-pulmonary exercise tests and lead to greater consistency in their conclusions.

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**Table 3. Guidelines for the systematic method to detect the metabolic (lactate) threshold from incremental exercise data.**

1.	Draw the line of identity on the $\dot{V}CO_2$ versus $\dot{V}O_2$ plot (Figure 1) and identify whether an inflection occurred.
2.	Identify the ventilatory threshold from the inflection on the $\dot{V}_E$ versus $\dot{V}CO_2$ plot (Figure 2) and eliminate this point as a threshold candidate on the $\dot{V}CO_2$ versus $\dot{V}O_2$ plot.
3.	Mark the lower slope (S1) on the $\dot{V}CO_2$ versus $\dot{V}O_2$ plot which should lie below the line of identity. Note that some subjects might hyperventilate during this stage of the study whereupon the data will lie above the line of identity. These data should be discounted for the purposes of identifying the threshold.
4.	Mark the upper slope (S2) on the $\dot{V}CO_2$ versus $\dot{V}O_2$ plot and identify the point of intersection between S1 and S2 (This should lie below the line of identity).
5.	Drop a perpendicular line to the x-axis of the $\dot{V}CO_2$ versus $\dot{V}O_2$ plot and identify $\dot{V}O_2\theta$ (the metabolic threshold) to the nearest 10-50 mL·min <sup>-1</sup> .
6.	Assign a level of confidence to the threshold detection from this plot (1=confident; 2=fairly confident; 3=poorly confident).
7.	If confidence in choosing $\dot{V}O_2\theta$ from the $\dot{V}CO_2$ versus $\dot{V}O_2$ plot was 2 or 3, verify $\dot{V}O_2\theta$ through use of the ventilatory equivalents versus $\dot{V}O_2$ plot (Figure 3A) and the end tidal gas tensions versus $\dot{V}O_2$ plot (Figure 3B).
8.	For the ventilatory equivalents plot, identify the first systematic upward inflection of $\dot{V}_E/\dot{V}O_2$ without a simultaneous increase in $\dot{V}_E/\dot{V}CO_2$ . From this inflection point, drop a perpendicular line to the x-axis of this plot ( $\dot{V}O_2$ ) and identify $\dot{V}O_2\theta$ to the nearest 10-50 mL·min <sup>-1</sup> .
	For the plot of end tidal gas tensions, identify the first systematic increase in $P_{ET}CO_2$ without a simultaneous decrease in $P_{ET}CO_2$ . From this inflection point, drop a perpendicular line to the x-axis of this plot ( $\dot{V}O_2$ ) and identify $\dot{V}O_2\theta$ to the nearest 10-50 mL·min <sup>-1</sup> .
9.	Where the plots of ventilatory equivalents and end-tidal gas tensions can be plotted one above the other with identical x-axes, use a vertical cursor to select the threshold that best represents upward inflections on both plots (as described above).
10.	Assign confidence levels (1=confident; 2=fairly confident. 3=poorly confident) to section of $\dot{V}O_2\theta$ from these plots.

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### Key points

- Experience and use of a systematic approach is essential for correctly identifying the metabolic threshold ( $\dot{V}O_{2\theta}$ ).
- Current guidelines for exercise testing and interpretation do not include recommendations for such an approach.
- Until an alternative schema for  $\dot{V}O_{2\theta}$  detection is developed prospectively, strategies based on the present study will give practitioners a systematic and consistent approach to threshold detection.

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