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Effects of Acute Hypoxia on the Estimation of Lactate Threshold from Ventilatory Gas Exchange Indices During an Incremental Exercise Test

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Summary

The purpose of this study was to investigate the validity of non-invasive lactate threshold estimation using ventilatory and pulmonary gas exchange indices under condition of acute hypoxia. Seven untrained males (21.4±1.2 years) performed two incremental exercise tests using an electromagnetically braked cycle ergometer: one breathing room air and other breathing 12 % O_2. The lactate threshold was estimated using the following parameters: increase of ventilatory equivalent for O_2 (V_E/VO_2) without increase of ventilatory equivalent for CO_2 (V_E/VCO_2). It was also determined from the increase in blood lactate and decrease in standard bicarbonate. The V_E/VO_2 and lactate increase methods yielded the respective values for lactate threshold: 1.91±0.10 l/min (for the V_E/VO_2) vs. 1.89±0.1 l/min (for the lactate). However, in hypoxic condition, V_E/VO_2 started to increase prior to the actual threshold as determined from blood lactate response: 1.67±0.1 l/min (for the lactate) vs. 1.37±0.09 l/min (for the V_E/VO_2) (P=0.0001), i.e. resulted in pseudo-threshold behavior. In conclusion, the ventilatory and gas exchange indices provide an accurate lactate threshold. Although the potential for pseudo-threshold behavior of the standard ventilatory and gas exchange indices of the lactate threshold must be concerned if an incremental test is performed under hypoxic conditions in which carotid body chemosensitivity is increased.

Key words
Exercise • Hypoxia • Lactate threshold

Introduction

During a muscular exercise performance, metabolic stress is closely associated with the intensity of the work being performed. Low to moderate exercise can be performed utilizing aerobically produced ATP, i.e. oxidative phosphorylation. When heavy exercise is performed, increased energy requirements are compensated by anaerobic glycolysis which results in an increase of blood lactate concentration. The point at which the blood lactate concentration increases significantly above its resting levels have subsequently been termed as the anaerobic or lactate threshold (Wasserman *et al.* 1994). It is generally agreed that lactic acidosis is predominantly buffered by the bicarbonate system (i.e. the increase in arterial lactate concentration and the decrease in the arterial bicarbonate concentration are approximately equal for suprathreshold work rates),

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resulting carbonic acid yields extra CO_2 to be excreted by the lungs in addition to that produced from cellular respiration (Beaver *et al.* 1986, Stringer *et al.* 1992).

Various invasive and non-invasive methods have been introduced to determine the lactate threshold during an exercise test in which the work rate is increased progressively to the limit of tolerance. The lactate threshold can be determined invasively by measuring blood lactate and standard bicarbonate concentrations and can also be estimated non-invasively by a ventilatory response to the exercise-induced metabolic acidosis (Wasserman *et al.* 1990). A systematic rise in the ventilatory equivalent for O_2 (V_E/VO_2) and end-tidal PO_2 ($P_{ET}O_2$) is seen at the lactate threshold without a decrease in the end-tidal PCO_2 ($P_{ET}CO_2$) and without an increase in ventilatory equivalent for O_2 (V_E/VCO_2) (Whipp *et al.* 1986, Wasserman *et al.* 1994).

The lactate threshold and its non-invasive estimation from the ventilatory and pulmonary gas exchange indices are widely used in clinical and sports medicine for different purposes. The lactate threshold can be used to evaluate a subject's aerobic capacity and fitness (Wasserman *et al.* 1994, Spurway 1992), establishing an optimum training work rate intensity for normal subjects and rehabilitation programs for patients with respiratory and cardiac diseases (Casaburi *et al.* 1995, Whipp 1996, Patessio *et al.* 1997), and even preoperative evaluation of patients undergoing major surgery (Older *et al.* 1993).

However, a number of factors might affect the sensitivity of non-invasive estimation of the lactate threshold from ventilatory and pulmonary gas exchange indices during an incremental exercise test. Under the conditions of acute hypoxia which is known to have a strong stimulatory effect on carotid body receptors, the ventilatory response may have been increased out of proportion with the metabolic demands (Rausch *et al.* 1991, Ward 1994). Therefore, we wished to ascertain in the present study, whether the lactate threshold can be validly estimated non-invasively as compared to conventional methods, which were based on ventilatory and pulmonary gas exchange indices, under the conditions of acute hypoxia.

Methods

Seven sedentary healthy male subjects participated in the study. The mean age (± S.E.M.), height and weight were 21.4±1.2 years, 179.2±2.7 cm and 76.2±4.2 kg, respectively. Each subject gave his written informed consent which was approved by the Institutional Ethics Committee before participating in the investigation. The subjects were requested to refrain from taking alcohol, drug, caffeine and from participating in strenuous exercise for a period of twelve hours prior to testing.

During the exercise test, the subjects breathed through a low dead-space (90 ml), a low-resistance (< 1.5 cm H_2O/l/s at 3 l/s) turbine volume transducer (Alpha Technologies, VMM) for continuous measurement of inspired and expired volumes and flows. The system was calibrated immediately before each experiment by infusing known volumes of room air within a range of mean flows and flow profiles spanning the expected exercise range. Respired air was drawn from the mouthpiece continuously (1 ml/s) and sampled by a quadrupole mass spectrometer (CaSE, QP9000) for continuous monitoring of O_2, CO_2 and N_2 concentrations in the respired air. The heart rate was monitored beat by beat from the R-R interval of a standard six-lead ECG (Quinton 5000). Arterial O_2 saturation was measured continuously throughout the test from the subject´s finger using pulse oximetry (Ohmeda, 3700). The arterial O_2 saturation was not allowed to drop below 70 %, especially in the hypoxia study.

Following the analogue-to-digital conversion, electrical signals from these devices were sampled every 20 ms and processed on-line by a digital computer for computation and display, breath-by-breath, of ventilatory and gas exchange variables, i.e. minute ventilation (V_E BTPS), O_2 uptake (VO_2 STPD), CO_2 output (VCO_2 STPD), end-tidal partial pressures of O_2 and CO_2 ($P_{ET}O_2$ and $P_{ET}CO_2$), and the ventilatory equivalents for O_2 and CO_2 (V_E/VO_2, V_E/VCO_2), as previously described by Beaver *et al.* (1981) and Jenkins *et al.* (1989). The calibration and validation procedures have been described previously (Beaver *et al.* 1981).

The arterialized blood (McLoughlin *et al.* 1992) was sampled at rest and after 3 min of cycling at 20 W. During the ramp phase, samples were taken at approximately 1-min intervals. At each sampling point, after clearance of the catheter, two 3 ml samples were drawn into heparinized syringes: one for blood gases and acid-base analysis (Instrumentation Laboratories, model 1306), and the other for lactate analysis (Analox, GM7 Microstat).

Each subject performed two incremental exercise tests to exhaustion (Whipp *et al.* 1981) on a computer controlled, electromagnetically braked cycle ergometer (Lode, Excalibur) while breathing either room air

(normoxia) or air with 12 % O_2 (hypoxia) on different days. The exercise test consisted of an initial period of 4 min of cycling at the 20 W as a warm-up, followed by and increasing rate at 15 W/min to the limit of the subject's tolerance. The subjects were required to maintain a constant pedaling frequency within a range of 60-80 rpm.

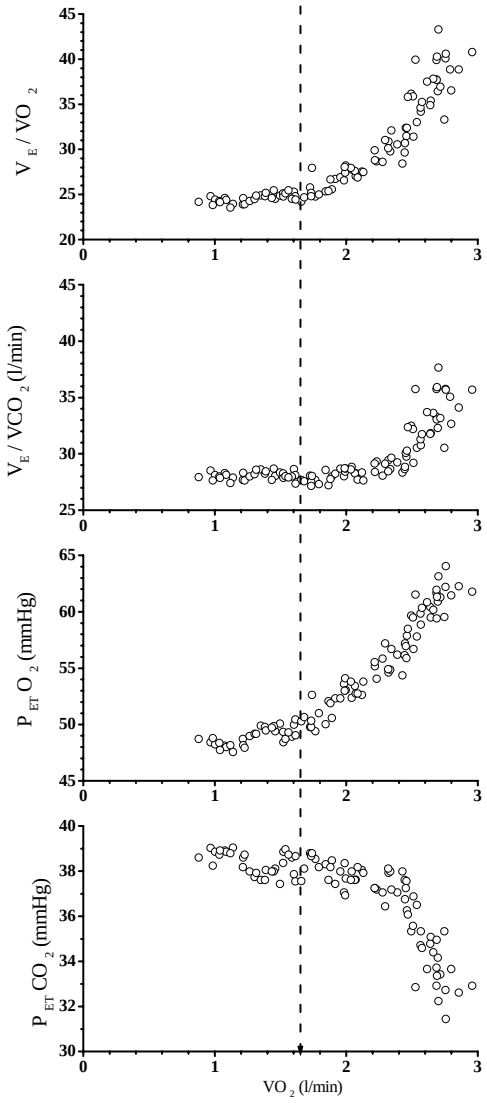

Fig. 1. Ventilatory equivalents for O_2 and CO_2 (V_E/VO_2, V_E/VCO_2), end-tidal PO_2 ($P_{ET}O_2$) and end-tidal PCO_2 ($P_{ET}CO_2$) as a function of O_2 uptake (VO_2) during an incremental exercise with breathing 12 % O_2. Vertical dashed line reflects the onset of estimated lactate threshold.

The maximal VO_2 (VO_2max) was taken as the highest O_2 attained at the end of the ramp test. For each subject two computer plots were prepared: 1) VO_2 was plotted on the X-axis with V_E/VO_2, V_E/CO_2, $P_{ET}CO_2$ and $P_{ET}O_2$ on the Y-axis; and 2) VO_2 was plotted on the X-axis with blood lactate and standard bicarbonate on the Y-axis. All plots were randomly number-coded for the determination of lactate threshold. Criteria for the lactate threshold estimation were based on the increase in V_E/VO_2 and $P_{ET}O_2$ without a corresponding increase in V_E/CO_2 and decrease in $P_{ET}CO_2$ (Fig. 1) (Whipp *et al.* 1986). In addition, systematic increases in blood lactate and decreases in standard bicarbonate values were used for determination of the lactate threshold (Fig. 2).

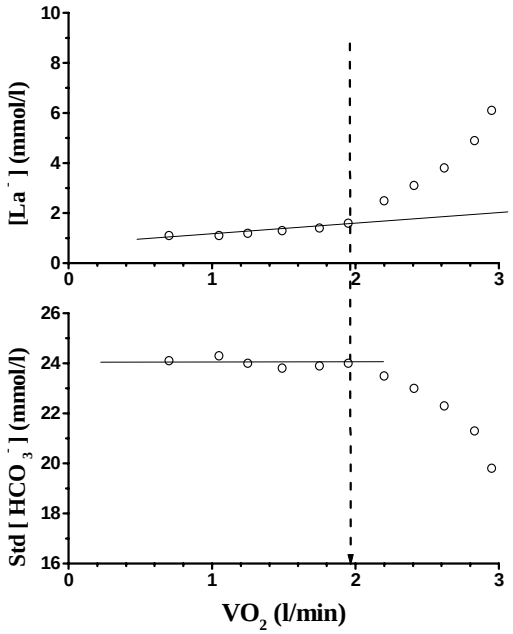

Fig. 2. The determination of the lactate threshold from the blood lactate concentration ($[La^-]$) and standard bicarbonate concentration ($[HCO_3^-]$) as a function of O_2 uptake (VO_2) during an incremental exercise test with breathing 12 % O_2. The vertical dashed line represents the actual lactate threshold.

Table 1. O_2 uptake at maximal exercise performance (VO_2max) and O_2 uptake for each kilogram body weight (VO_2max/kg), O_2 uptake at the determined lactate threshold (LT/kg), determined lactate threshold (LTblood) and estimated lactate threshold (LT V_E/VO_2) and maximal exercise capacity for the normoxia and hypoxia studies.

	Normoxia	**Hypoxia**
VO_2max (l/min)	3.42±0.10	2.64±0.20*
VO_2max/kg (ml/min/kg)	45.02±1.50	34.63±2.20*
LT/kg	25.08±0.60	21.94±1.10
LT blood (l/min)	1.91±0.10	1.67±0.10*†
LT (V_E/VO_2) (l/min)	1.89±10	1.37±0.09†
Wmax (W)	262±13	209±11*

* Indicates a significant difference from the normoxia study. † significantly different from the blood lactate response in the hypoxia study

A paired t-test was used to for evaluating the statistical significance of differences between normoxia and hypoxia responses. Significance was accepted at $p<0.05$.

Results

The VO_2max and the lactate threshold for each kilogram of body weight were reduced markedly in all subjects during the hypoxia study (34.6±2.2 ml/min/kg and 21.9±1.1 ml/min/kg) compared to the normoxia study (45.02±1.5 ml/min/kg and 25.1±0.6 ml/min/kg, respectively; P=0.0001) (Fig. 3). In addition, the maximal work rate was also reduced significantly during the hypoxia study (209±11 W) and compared to the normoxia study (262±13 W) (P=0.0001) (Table 1).

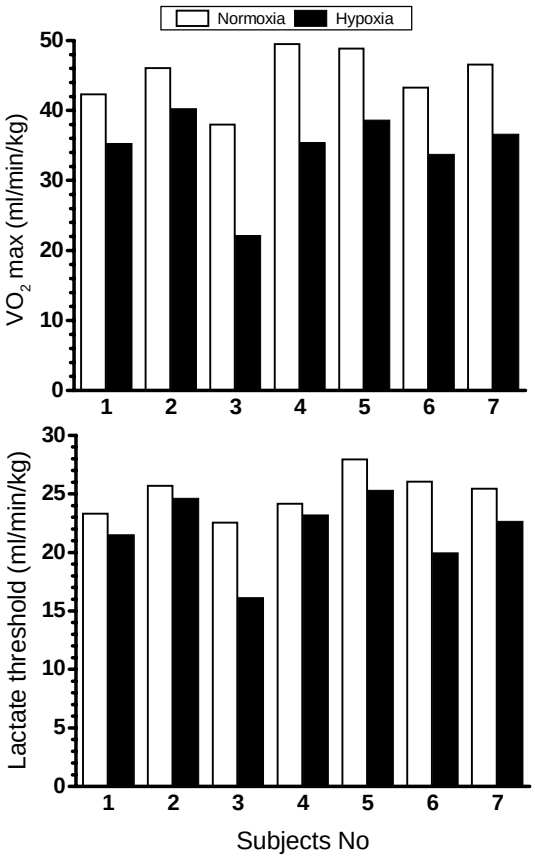

Fig. 3. The individual values for the O_2 uptake at the end of the maximal exercise performance (VO_2 max) to body weight ratio for the normoxia (white column) and for the hypoxia (black column) and O_2 uptake at the lactate threshold to body weight ratio for the normoxia (white column) and for the hypoxia (black column).

The estimated lactate threshold by the use of conventional methods was associated with a determined lactate threshold from the onset of the systematic increase in blood lactate and decrease in standard bicarbonate concentrations in a control study (Fig. 4): 1.9±0.1 ml/min (normoxia) vs. 1.9±0.1 l/min (hypoxia). In contrast, in the hypoxia study, V_E/VO_2 and $P_{ET}O_2$ started to increase (Fig. 1) prior to the onset of systematic increase in blood lactate concentration and the decrease in blood bicarbonate concentration (Fig. 2). The individual values for the comparison of estimated and determined lactate thresholds are given in Figure 4. The estimated lactate threshold from conventional methods was systematically lower than the actual lactate threshold determined from blood lactate and bicarbonate levels in all subjects: 1.67±0.10 l/min (normoxia) vs 1.37±0.09 l/min (hypoxia) (P=0.0001) (Table 1).

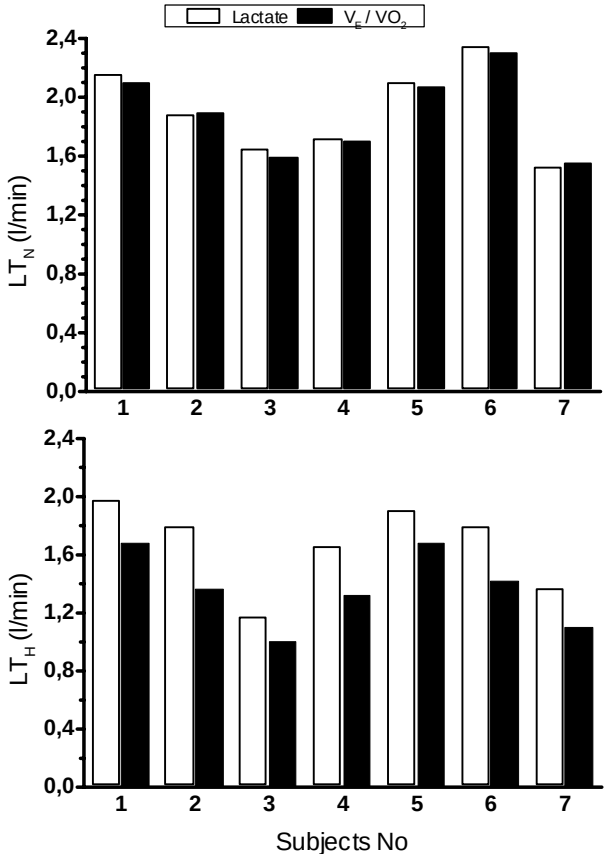

Fig. 4. The individual values for comparison of the determined (white column) and estimated (black column) lactate thresholds for the normoxia (LT_N) and for the hypoxia (LT_H) studies.

Discussion

The demonstration in the present investigation that the standard indices for non-invasive estimation of the lactate threshold may provide unequivocal but erroneous estimates under the condition of acute hypoxia therefore warrants careful consideration.

Despite many investigations, there is no

adequate explanation for a single mechanism or a combination of mechanisms for the lactate threshold. Several factors, including O_2 availability, substrate utilization muscle fiber types and enzymatic factors have been proposed to be involved in the lactate increase during exercise (Ivy *et al.* 1980, Walsh and Banister 1988, Wasserman *et al.* 1994). In the present study, we did not focus on the dispute involving lactate kinetics and reduced O_2 levels in inspired air. However, when hypoxic conditions are induced by manipulation of the fractional concentration of inhaled O_2 during an incremental ramp exercise test, the VO_2max, VO_2 at the lactate threshold and maximal work rate are significantly reduced compared to normoxic conditions (Hughson and Kowalchuk 1995). These findings support that the O_2 availability has marked effects on lactate kinetics (Linnarsson *et al.* 1974, Wasserman *et al.* 1994).

A valid and reliable estimation of the lactate threshold is important for numerous physiological and pathophysiological purposes, e.g. establishing an appropriate exercise training program (Whipp 1996, Casaburi *et al.* 1995, Hoogeveen *et al.* 1999), assessing the normalcy or changes of the O_2 transport system response to exercise and identifying the sources of systemic limitation (e.g. muscle, circulation, heart, lungs) (Wasserman *et al.* 1994). Recently, even in the preoperative evaluation of patients undergoing heart, lung or major abdominal surgery, a high level of mortality has been reported if lactate threshold is inappropriately low, i.e. below 11 ml/kg/min (Older *et al.* 1993, Stevenson 1996).

Despite many studies on lactate threshold and its estimation from ventilatory and pulmonary gas exchange indices (Ahmaidi *et al.* 1993, Wasserman *et al.* 1994, Thin *et al.* 2002), some studies discussed the existence of the lactate threshold concepts and its detection from respiratory gas exchange indices (Yeh *et al.* 1983, von Duvillard and Hagan 1994). However, according to the results of the present study, there are clear lactate threshold points, but the source of the problem is rather focused on the non-invasive estimation of the lactate threshold from ventilatory and pulmonary gas exchange indices (Meyer *et al.* 1996, Gaskill *et al.* 2001).

There was a close correlation between the lactate threshold estimation and its determination under normoxia condition. However, we have observed systematically lower lactate threshold values (i.e. a false negative response) obtained by conventional methods for the hypoxia study which was 300 ml/min lower than the actual threshold determined from lactate and standard bicarbonate estimations (Fig. 4). This apparent threshold behavior was first described by Whipp *et al.* (1987), who termed this phenomenon as a "pseudo-threshold", and which was subsequently demonstrated in other studies (Ward and Whipp 1992, Ozcelik *et al.* 1999) by a direct lactate determination.

In subjects with functioning peripheral chemoreceptors, acute hypoxia provides an additional challenge to the inferences which can be drawn from the responses to incremental muscular exercise. There is general agreement that carotid bodies represent the primary site of hypoxic ventilatory responsiveness in humans (Rausch *et al.* 1991, Ward 1994)because hypoxia is known to potentate the ventilatory response to muscular exercise (Lugliani *et al.* 1971) through carotid body chemosensitivity. It may be expected that the ventilatory response is increased even in the sub-threshold region of an incremental exercise test. The reduction or an enhancement of carotid body activity by hyperoxia or hypoxia could result in the differentiation between lactate concentration and ventilation (Mateika and Duffin 1994). In addition, catecholamines may also have an effect which is known to increase during exercise with hypoxic breathing (Warner and Mitchell 1991).

The present study shows a correlation between the invasive determination and the non-invasive estimation of the lactate threshold. Although the potential for pseudo-threshold behavior of standard ventilatory and gas exchange indices of the lactate threshold could be involved if an incremental test is performed under conditions where carotid body chemosensitivity is increased.

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