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SIMPLE EXPONENTIAL REGRESSION MODEL TO DESCRIBE THE RELATION BETWEEN MINUTE VENTILATION AND OXYGEN UPTAKE DURING INCREMENTAL EXERCISE

REIZO BABA, EMIKO MORI, NOBUO TAUCHI* and MASAMI NAGASHIMA†

Tokai University Graduate School of Physical Education,
**Department of Pediatric Cardiology, Ogaki Municipal Hospital, and*
†Department of Cardiology, Aichi Children's Health and Medical Center

ABSTRACT

The physiological significance of an exponential regression model between minute ventilation ($\dot{V}E$) and oxygen uptake ($\dot{V}O_2$) during incremental exercise was examined. Thirty-eight subjects, including 12 patients with chronic heart failure, participated in cardiopulmonary exercise testing on a bicycle ergometer. The equation $\dot{V}E = a\, e^{b\dot{V}O_2}$, where a and b are parameters, was used to describe the relation between $\dot{V}E$ and $\dot{V}O_2$ during incremental exercise. Arterialized blood gas analysis was measured before and during exercise. The correlation coefficient of the regression model was high (r = 0.97±0.02). Parameter a negatively correlated with the arterial partial pressure of carbon dioxide during exercise (r=-0.44, p<0.01), and positively correlated with peak $\dot{V}O_2$ (r=0.47, p<0.01). Parameter b negatively correlated with peak $\dot{V}O_2$ (r=-0.86, p<0.01) and positively correlated with the dead space to tidal volume ratio (r=0.68, p<0.01). The regression model, as well as parameters a and b, is physiologically useful in expressing metabolic response to exercise. This model, a specific solution to the differential equation $d\dot{V}E/d\dot{V}O_2=b\dot{V}E$, implies that the more a subject breathes, the greater is the increment in ventilation needed to meet a further increment of metabolic demand.

Key words: oxygen consumption, ventilation, carbon dioxide

INTRODUCTION

The relation between minute ventilation ($\dot{V}E$) and oxygen uptake ($\dot{V}O_2$) during incremental exercise has been considered to be composed of two-[1] or three-line regression models[2]. These models have been theoretically based on the accumulation of lactate above the "ventilatory anaerobic threshold[1,2]."

The validity of these multi-linear models has been questioned, however. Yeh and coworkers[3] showed that abrupt changes in arterial lactate concentration are not found during incremental exercise testing, which results in a curvilinear increase in $\dot{V}E$. According to the alveolar ventilation equation, $\dot{V}E$ is expressed as a function of arterial carbon dioxide partial pressure ($PaCO_2$) and the dead space to tidal volume ratio (VD/VT), as well as carbon dioxide production ($\dot{V}CO_2$).

Address for correspondence: Reizo Baba, M.D., Ph.D. Aichi Medical University School of Medicine, 21Karimata, Yazako, Nagakute-cho, Aichi-gun, Aichi Pref. 480-1195, Japan
Tel: +81-561-62-3311, Fax: +81-561-63-4835 e-mail address: babar@aichi-med-u.ac.jp

A fall in the $PaCO_2$ is known to occur at the maximal stages of exercise testing[4,5]. Also, the V_D/V_T ratio changes during incremental exercise[5,6]. As these changes are gradual and not threshold-like[7], the $\dot{V}_E$-$\dot{V}O_2$ relation could be described as a curvilinear model, rather than as threshold-like linear models.

A non-linear, exponential model has been proposed by Fairshter and coworkers[7]. Also, Baba[8-12] has shown that the relation between $\dot{V}O_2$ and $\dot{V}_E$, i.e., reversing the axes of the relation, during incremental exercise is described by a single logarithmic function. However, the physiological significance of these non-linear models has not been fully studied.

Therefore, the purpose of this study is to examine the physiological significance of an exponential regression model, $\dot{V}_E = a\, e^{b\dot{V}O_2}$, where $\dot{V}_E$ represents minute ventilation and $\dot{V}O_2$ is oxygen uptake during incremental exercise.

METHODS

Subjects

Thirty-eight consecutive subjects (30 males and 8 females), who had been referred to our laboratory during the period between January and June, 2000, for cardiopulmonary testing, were enrolled in the present study. Characteristics of the study subjects are listed in Table I. Written informed consent was obtained from each participant. This study was performed according to the Declaration of Helsinki. Our institutional review board approved the study.

Exercise testing

Exercise testing was usually conducted between 15:00 and 18:00 o'clock, and at least 3 hours after a light meal. An electromagnetically-braked cycle ergometer (P. K. Morgan, UK) was used for the test with a subject pedaling at a rate of 60 rev/min. After 4 minutes of rest, exercise was initiated by 4 minutes of unloaded cycling followed by a uniform increase in work rate by 25 watts every 3 minutes. Subjects were encouraged to reach maximal exercise, which was supported by reaching a gas exchange ratio of no less than 1.0.

Table 1. Correlation matrix of the parameters.

	Parameter *a*	Parameter *b*	Peak $\dot{V}O_2$	$\dot{V}_E$-$\dot{V}CO_2$ slope	$PaCO_2$ rest	$PaCO_2$ ex.	V_D/V_T ex.
Parameter *a*							
Parameter *b*	-0.62*						
Peak $\dot{V}O_2$	0.47*	-0.86*					
$\dot{V}_E$-$\dot{V}CO_2$ slope	-0.031	0.55*	-0.50*				
PaCO2 rest	-0.13	-0.29	0.27	-0.32			
$PaCO_2$ ex.	-0.44*	0.099	-0.15	-0.23	0.70*		
V_D/V_T ex.	-0.15	0.68*	-0.79*	0.51*	-0.14	0.21	

Abbreviations: peak $\dot{V}O_2$ = oxygen uptake at peak exercise; $\dot{V}_E$-$\dot{V}CO_2$ slope = the regression slope between minute ventilation and carbon dioxide production during exercise; $PaCO_2$ rest = arterial partial pressure of carbon dioxide at rest; $PaCO_2$ ex. = arterial partial pressure of carbon dioxide during exercise; V_D/V_T ex. = physiological dead space to tidal volume ratio during exercise. * $p < 0.05$.

Analysis of Expired Gas

Subjects breathed through a Hans Rudolph low-resistance nonrebreathing valve. $\dot{V}CO_2$, (ml/min, STPD), $\dot{V}O_2$ (ml/min, STPD), $\dot{V}E$ (l/min, BTPS), tidal volume (l, BTPS), respiratory rate (breaths per minute), and the mixed expiratory carbon dioxide concentration (%) were continuously measured on a breath-by-breath basis with the Benchmark Metabolic Measurement Cart (P. K. Morgan, UK) equipped with oxygen and carbon dioxide analyzers, which were calibrated with standard gases before each exercise testing. The flow meter was also calibrated before each study with a 3-liter syringe. Obtained data were averaged every 30 seconds and used for analyses.

The peak $\dot{V}O_2$ was calculated for each subject by averaging values obtained during the final 60 seconds of exercise. The $\dot{V}E$-$\dot{V}CO_2$ slope was determined by linear regression analysis between $\dot{V}E$ and $\dot{V}CO_2$ during incremental exercise. The following equation was used to describe the relation between $\dot{V}E$ and $\dot{V}O_2$ during an incremental exercise test:

$$\dot{V}E = a\ e^{b\dot{V}O_2},$$

where *a* and *b* were parameters. The VD/VT ratio was determined by Bohr's equation (14):

$$VD/VT = (PaCO_2 - PeCO_2)/PaCO_2 - VD_{ext}/VT,$$

where $PeCO_2$ is partial pressure of carbon dioxide in mixed expired gas, and VD_{ext} is dead space of the circuit (=120ml).

Arterialized earlobe blood gas sampling

Arterialized blood samples were obtained from the earlobe before exercise and at the end of stage 1 (work rate of 25 watts) of each exercise testing, when the exercise intensity did not exceed anaerobic threshold. The methods of capillary sampling have been previously described by Pitkin et al[15]. Briefly, a stab incision was made in the inferolateral aspect of the pinna after the earlobe was massaged with nicotinic acid for no less than three minutes. The samples were then collected into a glass tube and immediately (usually within 1 minute) used for blood gas analysis by the 278 Blood Gas Analysis System (Chiba-Corning Co. Medfield, Ma). The accuracy of arterialized blood gas analysis has been confirmed as a substitute for arterial gas analysis[15,16].

Statistical analysis

Values were expressed as the mean ± SD. Simple linear regression analysis was used to examine the relationships between parameters *a* and *b* as functions of peak $\dot{V}O_2$, the $\dot{V}E$-$\dot{V}CO_2$ slope, $PaCO_2$ at rest, $PaCO_2$ during exercise, or the VD/VT ratio during exercise. Differences in parameters *a* and *b* among normal subjects, patients with heart disease who did not have CHF, patients with NYHA class I heart failure, and NYHA class II heart failure were analyzed with analysis of variance. If a significant difference was detected by the F tests, mean values were analyzed by Fisher's PLSD test. A p value < 0.05 was considered statistically significant.

RESULTS

All exercise tests were performed without complications. The relation between $\dot{V}E$ and $\dot{V}O_2$ was reliably expressed as an exponential function, $\dot{V}E = a\ e^{b\dot{V}O_2}$ (r = 0.97±0.02, Figure 1). A correlation matrix of parameter *a*, parameter *b*, peak $\dot{V}O_2$, the $\dot{V}E$-$\dot{V}CO_2$ slope, $PaCO_2$ at rest, $PaCO_2$ during exercise, and the VD/VT ratio during exercise are shown in Table II. It is noteworthy that parameter a negatively correlated with $PaCO_2$ during exercise (Figure 2), and positively correlated with peak $\dot{V}O_2$, but not with the $\dot{V}E$-$\dot{V}CO_2$ slope. Also, parameter *b* negatively correlated with peak $\dot{V}O_2$ (Figure 3), positively with the VD/VT ratio during exercise, and also positively with the VE-VCO2 slope. Parameter *a* was not different among groups classified by clinical conditions, whereas parameter *b* was significantly different among groups ($p < 0.01$, Figure 4).

DISCUSSION

The present study shows that the relation between $\dot{V}E$ and $\dot{V}O_2$ during incremental exercise is expressed as a simple mono-exponential function, $\dot{V}E = a\ e^{b\dot{V}O_2}$. Parameter *a* of this equation negatively correlated with $PaCO_2$ during exercise, and positively correlated with peak $\dot{V}O_2$. Parameter *b* correlated positively with the VD/VT ratio during exercise and correlated negatively with peak $\dot{V}O_2$. These findings show that parameters *a* and *b* of the equation are both related to the degree of ventilation during exercise.

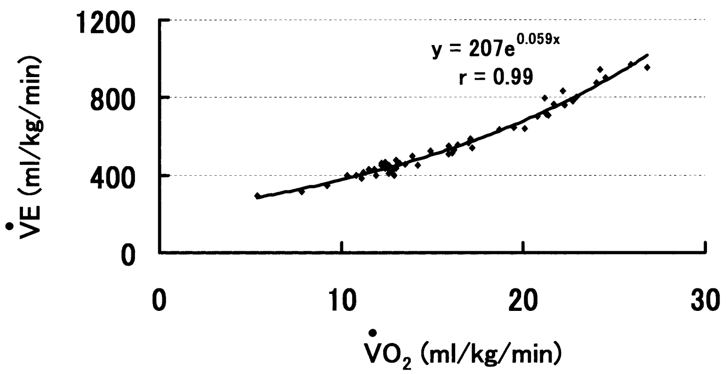

Figure 1: An example of the ventialation ($\dot{V}E$)-oxygen uptake ($\dot{V}O_2$) relation during incremental exercise. The relation is well expressed with the exponential regression model, $\dot{V}E = a\ e^{b\dot{V}O_2}$.

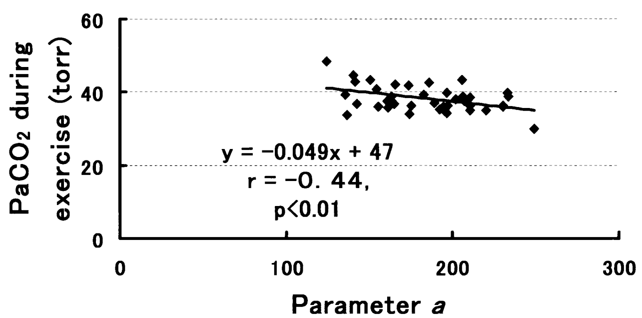

Figure 2: The relationship between arterial partial pressure of carbon dioxide ($PaCO_2$) and parameter *a*.

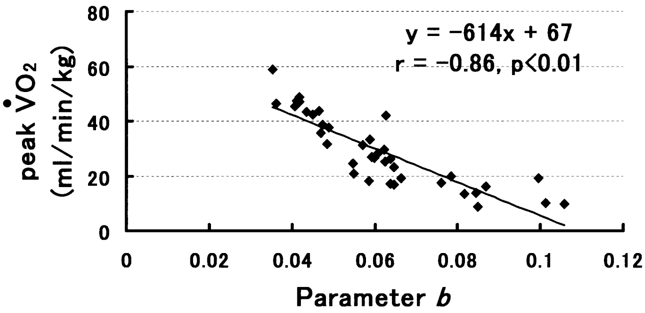

Figure 3: The relationship between peak oxygen uptake (peak $\dot{V}O_2$) and parameter *b*.

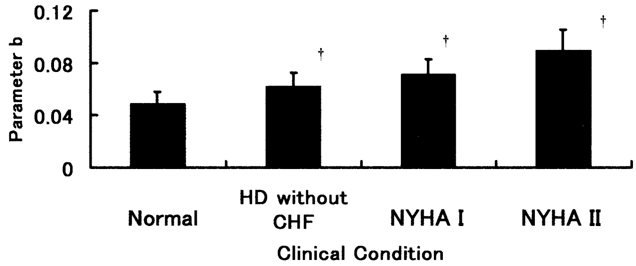

Figure 4: Comparison of parameter *b* among groups (normal subjects, patients with heart disease who do not have chronic heart failure, patients with NYHA class I chronic heart failure, and patients with NYHA class II chronic heart failure)†. $p < 0.05$. between normal subjects.

Physiological and clinical significances of parameter a

Parameter *a*, the *y*-intercept of the regression equation, is a positive number determined for each set of exercise testing data. This demonstrates that some volume of ventilation (= *a*) is needed even when metabolic demand is conceptually zero (Figure 5). A greater value of *a* shows that a larger *y*-intercept, i.e., the volume of ventilation when metabolic demand is conceptually zero, leads to greater ventilation throughout exercise testing (Figure 5). Therefore, *a* is a parameter that represents the degree of ventilation during exercise.

Physiological and clinical significances of parameter b

Parameter *b* is also related to the degree of ventilation during exercise: a greater value of parameter *b* means a greater metabolic response to exercise at a given $\dot{V}O_2$, or a given metabolic demand (Figure 5). This is also supported by our result that parameter *b* correlated with the V_D/V_T ratio during exercise. The finding that parameter *b* strongly correlated with peak $\dot{V}O_2$ and is different among normal subjects, patients with heart disease who do not have chronic heart failure, patients with NYHA class I heart failure, and patients with NYHA class II heart failure, indicates that parameter *b* can be used as an index of exercise tolerance. Major factors

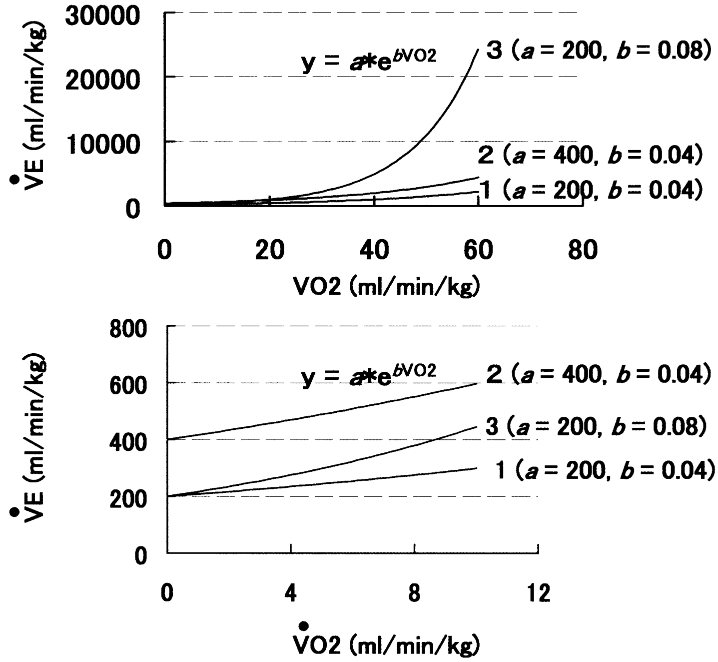

Figure 5: The effects of parameters *a* and *b* on metabolic response to exercise. The upper panel shows the relation of whole exercise data. The lower panel shows a magnified view of the relation around the *y*-intercept. Curve 1 represents the relation between minute ventilation ($\dot{V}_E$) and oxygen uptake ($\dot{V}O_2$) during incremental exercise when parameter *a* is 200 and parameter *b* 0.04. Curve 2 and the curve 3 represent the relation when parameter *a* is doubled (*a* = 400) and when parameter *b* is doubled (*b* = 0.08), respectively. The effect of parameter *a* is pronounced when metabolic demand ($\dot{V}O_2$) is low, as it represents the *y*-intercept of the graph. The effect of parameter *b* is pronounced when exercise intensity is high.

that influence parameter *b* and the metabolic response to exercise and which can be predicted by the modified alveolar gas equation are: 1) CO_2 production (derived from muscle aerobic metabolism as well as from plasma buffer action by bicarbonate), 2) arterial pCO_2 (CO_2 setpoint), and 3) physiological dead space ventilation. Thus, deconditioned subjects or patients with certain diseases, such as congestive heart failure, who have reduced working muscle mass and impaired flow of blood to these muscles, inefficient extraction of and utilization of oxygen by these muscles and early appearance of lactic acidosis, will be expected to have a large parameter *b*.

Regression equation

The regression equation used for the present study is a specific solution to the following differential equation,

$$d\dot{V}_E/d\dot{V}O_2 = b\,\dot{V}_E.$$

This equation means that the rate of increase in $\dot{V}_E$ against the increase in metabolic demand ($\dot{V}O_2$) is linearly proportional to $\dot{V}_E$. In other words, the more a subject ventilates for a given metabolic demand, the greater is the increment of ventilation needed to meet a further increment of metabolic demand. This simple exponential model provides us with further information for our understanding of metabolic response to exercise.

Comparison with $\dot{V}E$-$\dot{V}CO_2$ slope

As discussed above, parameters *a* and *b* are both related to the metabolic response to exercise. The $\dot{V}_E$-$\dot{V}_{CO_2}$ slope is already known as the standard method to evaluate exercise ventilation. What are the differences between the $\dot{V}_E$-$\dot{V}_{CO_2}$ slope and the parameters in the present study? The $\dot{V}_E$-$\dot{V}_{CO_2}$ slope correlated with peak $\dot{V}_{O_2}$, as well as with the V_D/V_T ratio during exercise. However, parameter *b* more closely correlated with peak $\dot{V}_{O_2}$ and the V_D/V_T ratio. Moreover, while parameter *a* correlated with $PaCO_2$ during exercise, the $\dot{V}_E$-$\dot{V}_{CO_2}$ slope did not. These results indicate that the parameters *a* and *b* may be more appropriate indices to describe exercise ventilation.

CONCLUSIONS

The regression model, as well as parameters *a* and *b* in the present study, are physiologically useful in expressing the metabolic response to exercise. Results obtained here provide the physiological background of the oxygen uptake efficiency slope, an objective measure of exercise tolerance.

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