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Estimation of the $\dot{V}O_{2\ peak}$, ventilatory threshold and the respiratory compensation point based on the gas exchange kinetics during the transition to constant-load exercise

Estimação do $\dot{V}O_{2\ peak}$, do limiar ventilatório e do ponto de compensação respiratória baseada na cinética das trocas gasosas durante a transição para exercício com carga constante

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Abstract
The main goal of this work was to estimate the peak O_2 uptake ($\dot{V}O_{2\ peak}$), the ventilatory threshold (VT) and the respiratory compensation point (RC) based on the kinetics of the $\dot{V}O_2$, the CO_2 output ($\dot{V}CO_2$) and the pulmonary ventilation ($\dot{V}E$) for a given steady state workload. Thirty-two physically active healthy male subjects were submitted to an exercise equivalent to 50% of the maximal estimated workload, followed by a progressive workload (12.5 W/min) until exhaustion. During exercise, respiratory gas exchanges were measured breath-by-breath. $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}E$ time responses to constant workload were modeled through a triple exponential function using non-linear regression. VT and RC were detected automatically during progressive exercise, resulting in 73.7 ± 9.1% and 86.4 ± 7.2% of the $\dot{V}O_{2\ peak}$, respectively. Models of $\dot{V}O_{2\ peak}$, VT and RC were obtained through multiple linear regressions, and validated by the leave-one-out method. All models presented high significance ($\dot{V}O_{2\ peak}$: $r^2 = 0.84$, SE = 230.2 ml/min; VT: $r^2 = 0.79$, SE = 208.1 ml/min; and RC: $r^2 = 0.78$, SE = 232.5 ml/min; $p < 0.001$) and were adequately validated, resulting in mean error of 238 ml/min. In conclusion, VT, RC as well as the $\dot{V}O_{2\ peak}$ were satisfactorily estimated through gas exchange kinetics. Therefore, this approach could be used as a potential tool for estimating maximal and sub-maximal responses to progressive exercise.
Keywords: Anaerobic threshold, Constant workload, Oxygen kinetics.

Resumo
O objetivo central deste trabalho foi estimar o pico de captação de oxigênio ($\dot{V}O_{2\ peak}$), o limiar ventilatório (VT) e o ponto de compensação respiratória (RC) com base na cinética do $\dot{V}O_2$, da eliminação de CO_2 ($\dot{V}CO_2$) e da ventilação pulmonar ($\dot{V}E$) para uma determinada carga em regime permanente. Trinta e dois homens saudáveis e fisicamente ativos foram submetidos a um exercício equivalente a 50% da carga máxima estimada, seguido de cargas progressivas (12,5 W/min) até a exaustão. As trocas gasosas foram medidas ciclo-a-ciclo respiratório. As respostas temporais de $\dot{V}O_2$, $\dot{V}CO_2$ e $\dot{V}E$ à carga constante foram modeladas por uma função exponencial tripla empregando regressão não linear. Os valores de VT e RC foram detectados automaticamente durante o exercício progressivo, resultando em 73,7 ± 9,1% e 86,4 ± 7,2% de $\dot{V}O_{2\ peak}$, respectivamente. Modelos de $\dot{V}O_{2\ peak}$, VT e RC foram obtidos através de regressão linear múltipla e validados pelo método leave-one-out. Todos os modelos apresentaram alta significância ($\dot{V}O_{2\ peak}$: $r^2 = 0,84$, SE = 230,2 ml/min; VT: $r^2 = 0,79$, SE = 208,1 ml/min; e RC: $r^2 = 0,78$, SE = 232,5 ml/min; $p < 0,001$) e foram validados adequadamente, resultando num erro médio de 238 ml/min. Em conclusão, VT, RC e $\dot{V}O_{2\ peak}$ foram satisfatoriamente estimados através da cinética das trocas gasosas, sendo este método uma ferramenta potencial para a estimativa das respostas máximas e sub-máximas a exercício progressivo.
Palavras chave: *Carga constante, Cinética do oxigênio; Limiar anaeróbio.*

Introduction

Oxygen uptake ($\dot{V}O_2$) response to different workloads has been the subject of many studies, such as its dependence on the muscular mass (Carter *et al*., 2000a; 2000b), physical training (Koga *et al*., 1997) and type of exercise (Hughson *et al*., 2000). Early studies (Crow and Kushmerick, 1982; Wasserman and Whipp, 1983) investigated $\dot{V}O_2$ time response and its interaction with $\dot{V}CO_2$ and $\dot{V}E$ for different stimuli, showing that $\dot{V}CO_2$ response was slower than $\dot{V}O_2$ as well as $\dot{V}E$ was slower than $\dot{V}CO_2$.

Based on the concepts theorized by Whipp *et al*. (1982), several authors (Barstow *et al*., 1996; Bauer *et al*., 1999; Carter *et al*., 2000a, 2000b; Demarle *et al*., 2001; Perrey *et al*., 2001) have studied $\dot{V}O_2$ kinetics, describing three phases of $\dot{V}O_2$ response to a step workload (Figure 1). *Phase 1*: known as the cardio-dynamic component (Demarle *et al*., 2001), corresponds to the fast increase in the alveolar $\dot{V}O_2$, which sustains a transient plateau 15-20 s after on-transition (Hughson, 1990; Molé and Hoffman, 1999); *Phase 2*: called the primary component, mainly corresponds to the increase in muscular O_2 consumption (Demarle *et al*., 2001; Molé and Hoffman, 1999), characterized by an exponential $\dot{V}O_2$ increase up to an apparent steady state, within 2-3 minutes for healthy subjects; *Phase 3*: is the slow component, when the $\dot{V}O_2$ rises above the predicted work requisition (Barstow *et al*., 1993; Demarle *et al*., 2001; Koga *et al*., 1997). Similarly, different models have been applied to describe $\dot{V}CO_2$ and $\dot{V}E$ kinetics, such as a single exponential function (Wasserman and Whipp, 1983), a linear function superimposing the exponential component (Casaburi *et al*., 1992) or a triple exponential function (Scheuermann *et al*., 1999).

As well established in the literature, physical training improves physical fitness (Hagberg, 1987), determining an increase in the peak $\dot{V}O_2$ ($\dot{V}O_{2\,peak}$) and aerobic capacity, associated with the higher mitochondrial enzymatic potential (Green *et al*., 1999), which, in turn, increases the fatty acids oxidation (Bergman and Brooks, 1999; Phillips *et al*., 1996) and may cause a delay in the onset of blood lactate accumulation (Bergman *et al*., 1999). These metabolic adaptations may determine a lower ventilatory exertion and a delay in the ventilatory

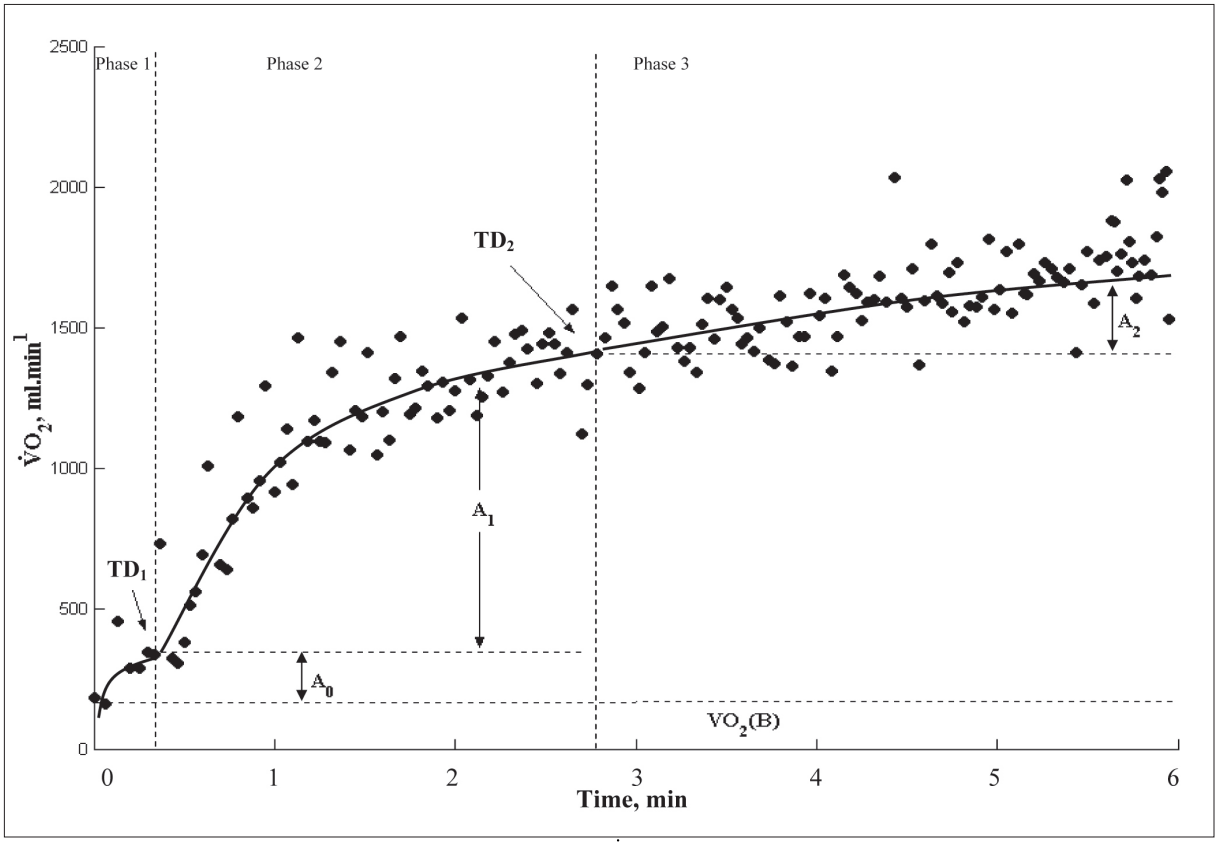

Figure 1. Temporal profile of individual breath-by-breath $\dot{V}O_2$ response from one representative subject performing exercise at 125 W. Features of triple exponential model used to describe the $\dot{V}O_2$ response. Parameters correspond to those in Equation 2. TD_1 and TD_2, primary and slow time delays; A_0, A_1 and A_2, asymptotic values for cardio-dynamic, primary and slow components; and $VO_2(B)$, baseline $\dot{V}O_2$ at rest. The vertical dashed lines mark the $\dot{V}O_2$ kinetics phases.

threshold (VT) as well as the respiratory compensation point (RC). Furthermore, previous studies (Casaburi *et al*., 1987; Demarle *et al*., 2001; Gaesser, 1994; Yoshida *et al*., 1992) reported that $\dot{V}O_2$ kinetics could also be modified after endurance training.

Herein, two theoretical complementary assumptions could be drawn: 1) training delays the time response of the lactate blood concentration, and also increases $\dot{V}O_{2\,peak}$, VT and RC; 2) the dynamic responses of $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}E$ are dependent on the physical fitness. Assuming the hypotheses stated above were true, through the mathematical decomposition of the gas exchange time responses, it would be theoretically possible to predict the maximal ($\dot{V}O_{2\,peak}$) and sub-maximal (VT and RC) functional capacity. Moreover, maximal exercise test results can be modified by several intervenient factors such as the evaluator subjectivity and experience, and concerning the emotional and physical stress as well as the risks associated to a maximal stress, as assuring its reliability, the use of a constant load sub-maximal test, may represent an alternative way for estimating the functional capacity as well as the transition of the oxidative and glycolytic pathway and the beginning of the metabolic acidosis. Accordingly, this study proposes to establish a relation among the ventilatory thresholds and the gas exchange kinetics, and to comprehensively develop a model to estimate the maximal and sub-maximal ventilatory responses based on the gas exchange kinetics.

Methods

Subjects

Thirty-two low risk healthy male subjects (Table 1) volunteered for this study. All volunteers were physically active (Fleg *et al*., 2000) and non-smokers. The exclusion criteria followed the recommendations of The American Heart Association (Fletcher *et al*., 2001). The experimental protocol and all possible risks associated with the participation in the study were outlined, and informed consent was obtained from each subject. The study was approved by the Ethical Human Research Committee of the Hospital Universitário Clementino Fraga Filho, Federal University of Rio de Janeiro.

General protocol

Each subject was preliminarily instructed to arrive at the laboratory rested and well-hydrated, at least 3 hours postprandial, and to avoid strenuous exercise in the 48 hours preceding the test. The exercise protocol consisted of a modified incremental test up to volitional fatigue. Exercise was performed on a mechanically braked cycle ergometer (Monark, Sweden), with seat height adjusted according to lower limb length and handlebar matched to the subject's riding position.

The protocol consisted of four phases: 1) Resting phase – 4 min in passive rest, 2) Constant load phase – 6 min with a constant workload equivalent to 50% of the predicted maximal workload (Equation 1), as described by Wasserman *et al*. (1999), 3) Incremental workload phase – the work rate increased by a ramp function of 12.5 W/min (60 rpm) until volitional exhaustion, and 4) Recovery phase – 15 min in passive rest.

$$WL_{MÁX} = \frac{(56.5 - 0.55 \cdot A) \cdot BM - 260}{11.4} \quad (1)$$

where $WL_{MÁX}$ is the maximal workload for the cycle ergometer, A is the age (years), and BM is the body mass (kg).

Measurement of the pulmonary gas exchange

Throughout the tests, pulmonary gas exchange variables were determined breath by breath. Subjects

Table 1. Physical characteristics of the subjects

n=32	Mean (SD)	Range
Age, yrs	28.4 (9.3)	17.0 - 45.0
BM, kg	71.9 (11.3)	50.4 - 106.6
Ht, cm	174.6 (8.9)	152 - 191
PF, %	15.02 (7.5)	5.7 - 27.3
FFM, kg	61.1 (9.8)	38.7 - 71.7
$\dot{V}O_{2\,peak}$, l/min	2.32 (0.49)	1.45 - 3.34
$\dot{V}O_{2\,peak}$, ml/min·kg	31.49 (7.33)	15.52 - 48.91
HR_{max}, bpm	191 (11)	176 - 203

BM, body mass; Ht, height; PF, percentage of fat; FFM, fat free mass; $\dot{V}O_{2\,peak}$, peak oxygen uptake; HR_{max}, peak heart rate. Values are mean (standard deviation).

breathed through a low-resistance facemask attached to a pneumotachometer Fleisch nº 3 (HP, USA) connected to a differential pressure transducer Micro-Switch 163PC0D36 (Honeywell, USA). Gases were continuously drawn from the facemask connection through a sampling capillary tube (60 ml/min) and analyzed for O_2, CO_2 and N_2 concentrations by a mass spectrometer (MGA2000, Airspec, UK). Expiratory and inspiratory flow rates and volumes were calibrated according to standard procedures from our laboratory (Abreu *et al*., 2000; Santos and Giannella-Neto, 2004). Expiratory and inspiratory flow rates and volumes were calibrated according to standard procedures from our laboratory. After analog-to-digital conversion (60 Hz) the flow rate and gas concentration underwent time alignment, and $\dot{V}O_2$ were calculated and displayed for every breath. Heart rate was continuously monitored using an electrocardiograph (Dixtal, Brazil).

Gas exchange kinetics

A critical point is to select the ideal model that expresses the characteristics of the metabolic dynamic response. Given that the constant load might be below or above VT, $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}E$ kinetics were determined by a triple exponential function (Equation 2).

$$\hat{Y} = Y(B) + A_0 \cdot \left(1 - e^{-t/\tau 0}\right) + A_1 \cdot \cdot \left(1 - e^{-(t-TD_1)/\tau 1}\right) + A_2 \cdot \left(1 - e^{-(t-TD_2)/\tau 2}\right) \quad (2)$$

where $\hat{Y}$ represents each dependent variable (i.e., $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}E$); Y(B), is the baseline value, calculated as the average $\dot{V}O_2$ ($\dot{V}CO_2$ or $\dot{V}E$) for the last 30 s before the exercise; A_0, A_1 and A_2 (ml/min) are the asymptotic values for the exponential terms, expressing, respectively, the amplitude of the cardio-dynamic, primary and slow components; τ_0 τ_1 and τ_2(s) are the exponential time constants; and TD_1 and TD_2 are time delays from the primary and slow phases, respectively. A non-linear regression was applied to fit the time responses of $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}E$, in which the coefficients were obtained by least squares.

The O_2 deficit (DO_2), corresponding to the period in which the consumed O_2 is lower than O_2 requirement, was calculated as the difference between the O_2 volume that would be consumed if the steady state was reached immediately at the onset of exercise and $\dot{V}O_2$ measured during the exercise period (Equation 3).

$$DO_2 = T \cdot \left[\dot{V}O_2(B) + A_0 + A_1 + A_2\right] - \int_0^T \dot{V}O_{2SS}(t)dt \quad (3)$$

where T is the duration of the constant-load phase (i.e. 6 min), and $\dot{V}O_{2\,ss}(t)$ is $\dot{V}O_2$ during the constant load phase, calculated by Equation 2.

Ventilatory threshold and Respiratory Compensation Point

The $\dot{V}O_2$, $\dot{V}CO_2$ and the $\dot{V}E$ increase similarly up to VT. However, above VT, the buffering of the lactic acid leads to a nonlinear increase in $\dot{V}CO_2$ relative to $\dot{V}O_2$ with a subsequent increase in $\dot{V}E$. Furthermore, the ventilatory equivalent for $\dot{V}CO_2$($\dot{V}E/\dot{V}CO_2$) remains constant or decreases slightly, while the ventilatory equivalent for $\dot{V}O_2$ ($\dot{V}E/\dot{V}O_2$) increases (Wasserman and Whipp, 1983). Above RC, $\dot{V}E$ rises at a rate higher than that of $\dot{V}CO_2$, with a concomitant increase in $\dot{V}E/\dot{V}CO_2$.

VT and RC were detected automatically, as described in a recent study (Santos and Giannella-Neto, 2004), and consisted of searching for a breakpoint in $\dot{V}E/\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$. Briefly, the breath-by-breath values for $\dot{V}E/\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$ were fitted by a fifth-degree polynomial smoothing spline (least square method). The maxima obtained from the 1st order derivatives of the fitted polynomials of $\dot{V}E/\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$ were used to calculate the VT and the RC values respectively. Finally, $\dot{V}O_{2\,peak}$ was computed as the mean $\dot{V}O_2$ during the last 30 s before the off-transition.

Data modelling

As outlined on the hypotheses speculated in this study, a forward multiple linear regression (least square error method) was applied to relate VT and RC with $\dot{V}O_{2\,peak}$ to the dynamic responses of $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}E$ characterized by their respective parameters (Equation 2). Independent variables were chosen (piecewise forward) from the parameters of Equation 2, i.e., A_0, A_1, and A_2, τ_0, τ_1 and τ_2, TD_1 and TD_2 as well as DO_2 (Equation 3), according the partial coefficient correlation (PCC) and the significance (*P*-value). The i^{th} independent variable was rejected when the increase in the determination coefficient (r^2) from *i* - 1 to *i* was less than 0.005.

Statistics

Data were expressed as means ± standard deviation (SD). The regression coefficients were obtained by the least square method and the explained variance was given by r^2. One-way analysis of variance and the post-hoc Tukey test were applied to discriminate where significant differences occurred for the gas exchange response parameters. The F ratios were interpreted as demonstrating a significant main effect when $p < 0.05$.

The models obtained were cross-validated by the leave-one-out method (Ancona *et al*., 2005), and the results were expressed as the estimated standard error (SE). Measured and estimated values for $\dot{V}O_{2\,peak}$, VT and RC were compared throughout the Bland and Altman method (Bland and Altman, 1986). The reliability of the models was expressed by the limit of agreement (LOA), calculated as ± 2 SD. Additionally, 95% of the confidence interval was estimated by the Student t-paired test. All data were processed in Matlab version 6.13.1 (Mathworks, USA) and the statistical analysis was performed in Statistica v.5.1 (Statsoft, USA).

Results

$\dot{V}O_{2\,peak}$ presented by the subjects during incremental exercise was 2.3 ± 0.5 l/min. VT and RC were automatically detected for all subjects, averaging, respectively, 73.7 ± 9.1% and 86.4 ± 7.2% of the $\dot{V}O_{2\,peak}$.

Gas exchange kinetics

Figure 2 shows an example of $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}E$ temporal profile, and the triple exponential function on the left panel. Regression residuals are presented on the right panel (*observed - expected*), where the dispersion as a function of time is noticeably stable, corroborating the model adequacy. $\dot{V}CO_2$ and $\dot{V}E$ kinetics appears slower than that of $\dot{V}O_2$, confirming one of the theoretical bases of the present study. In consequence, VT reflects the disproportionality between CO_2 output and O_2 uptake, and, similarly, RC depends on the ventilatory response. Thus, it could be expected that decomposing the time response of these variables could estimate the physiological response to any other workload.

$\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}E$ kinetics were modelled according to Equation 2, resulting in highly significant determination coefficients (> 80% of the explained variance). The correlation coefficients between the

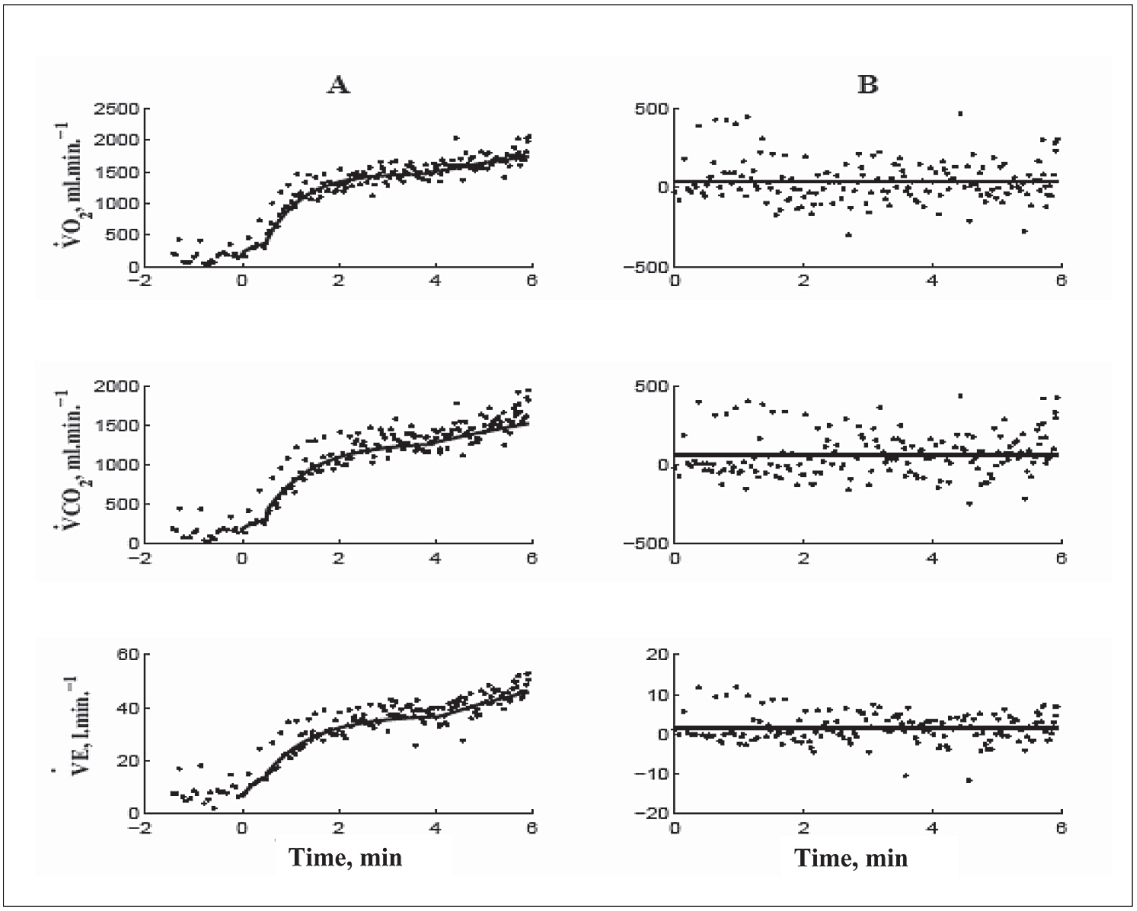

Figure 2. A: Best fit of oxygen uptake ($\dot{V}O_2$), CO_2 output ($\dot{V}CO_2$) and pulmonary ventilation ($\dot{V}E$) from one representative subject during on-transition from rest to exercise cycling at 50% of $\dot{V}O_{2\,peak.}$ Continuous lines were obtained through non-linear regression using the triple exponential model (Equation 2). **B**: Residuals corresponding to the fits of $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}E$ illustrated in A.

triple exponential functions and the breath-by-breath $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}E$ averaged, respectively, 0.94 ± 0.02, 0.92 ± 0.02 and 0.92 ± 0.03. Figure 3 illustrates the comparison of the time constants of $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}E$. Except for the cardio-dynamic component (τ_0), which did not present differences between $\dot{V}O_2$ and $\dot{V}E$, both the primary (τ_1) and slow (τ_2) components extracted from $\dot{V}E$ were significantly slower than $\dot{V}CO_2$, and, furthermore, $\dot{V}CO_2$ was slower than $\dot{V}O_2$ ($p < 0.05$).

Table 2 summarizes all coefficients obtained for the triple exponential model applied for $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}E$. The time delays of the primary component (TD_1) for $\dot{V}O_2$ and $\dot{V}E$ were significantly different ($p < 0.01$), but no differences were observed in time delays for $\dot{V}CO_2$ compared to $\dot{V}O_2$, and $\dot{V}CO_2$ compared to $\dot{V}E$. Furthermore, the time delays of the slow component were different among all variables ($\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}E$, $p < 0.01$).

Ventilatory threshold modelling

Multiple linear regression results for $\dot{V}O_{2\,peak}$, VT and RC are summarized in Table 3. Concerning each coefficient extracted from the exponential models, low PCC values were obtained for modelling $\dot{V}O_{2\,peak}$, VT or RC. Otherwise, significant cumulative r^2 were obtained for all $\dot{V}O_{2\,peak}$ (0.86) VT (0.81) and RC (0.87).

$\dot{V}O_{2\,peak,}$ RC and VT estimation, and the Bland and Altman (1986) analysis are displayed in Figure 4. The $\dot{V}O_{2\,peak}$ model resulted in r = 0.92 between observed and expected values, which was equivalent to 83.5% ($p < 0.001$) of the explained variance, and a standard error (SE) equal to 230.2 ml/min. For VT, significant correlation was obtained (r = 0.89; $r^2 = 0.79$; SE = 208.1 ml/min; $p < 0.001$), and similarly, the RC was also satisfactorily estimated (r = 0.88; $r^2 = 0.78$; SE = 232.5 ml/min; $p < 0.001$).

The models were cross validated using the leave-

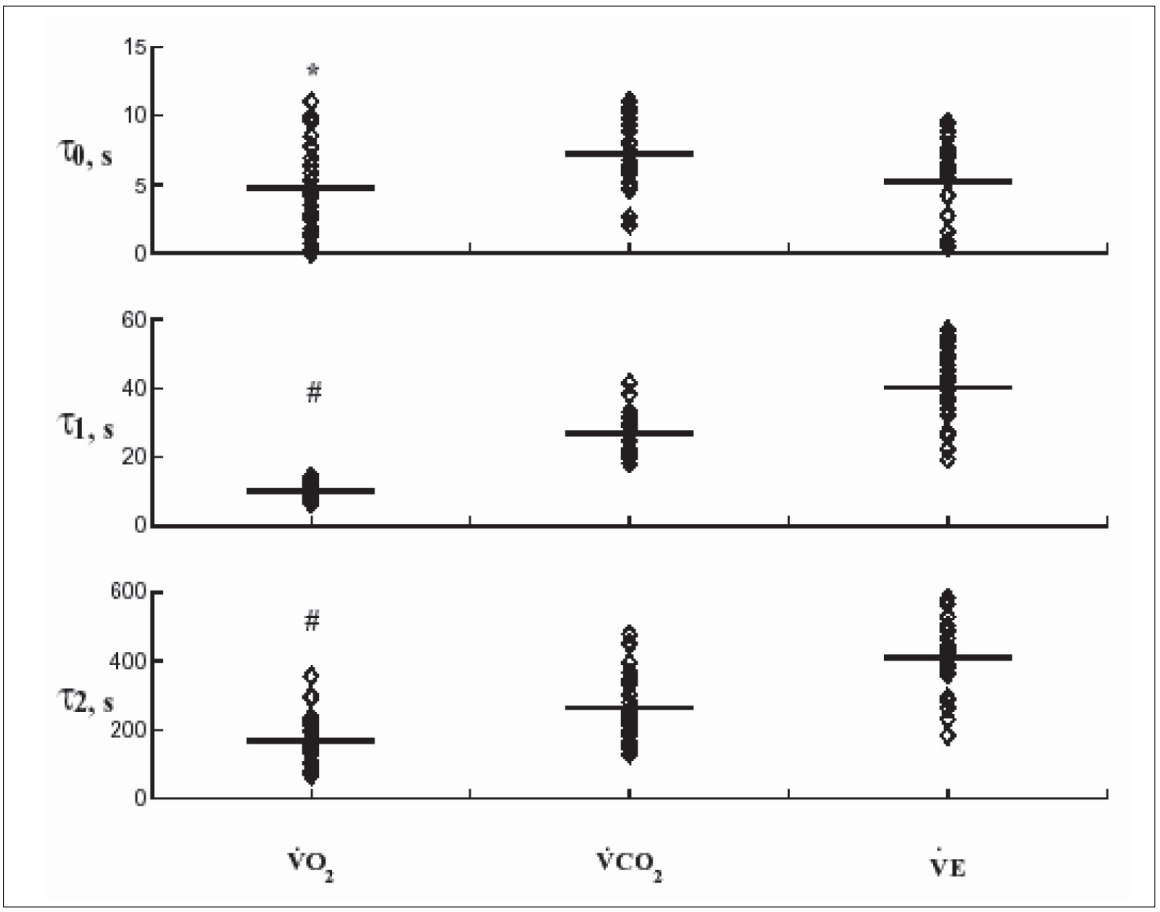

Figure 3. Relation among time constants of $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}E$ extracted from the triple exponential model. τ_0, τ_1 and τ_2 are the time constants of the cardio-dynamic, primary and slow components respectively. Horizontal lines are mean values and open diamonds are individual data. #, significant differences among $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}E$; *, significant differences between $\dot{V}O_2$ and $\dot{V}CO_2$, and between $\dot{V}CO_2$ and $\dot{V}E$. ($p < 0.05$).

Table 2. Summary of parameter estimates for $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}E$ kinetics during steady state exercise

Parameter	$\dot{V}O_2$	$\dot{V}CO_2$	$\dot{V}E$
B, l/min	0.24 ± 0.09	0.25 ± 0.08	8.2 ± 3.2
A_0, l/min	0.59 ± 0.18	0.77 ± 0.41	49.61 ± 12.12
τ_0, s	4.8 ± 3.0	7.2 ± 2.5	5.2 ± 2.6
A_1, l/min	0.83 ± 0.25	0.82 ± 0.20	20.78 ± 5.54
TD_1, s	16.5 ± 14.6	23.41 ± 11.45	33.8 ± 28.5
τ_1, s	10.3 ± 2.4	26.9 ± 5.6	40.2 ± 10.6
A_2, l/min	0.26 ± 0.22	0.48 ± 0.12	12.45 ± 3.31
TD_2, s	105.4 ± 37.16	129.4 ± 25.3	135.7 ± 20.2
τ_2, s	169.3 ± 69.3	263.5 ± 91.1	411.2 ± 114.6
DO_2, l	2.42 ± 0.98	–	–

Values are mean ± SD; $\dot{V}O_2$, O_2 uptake; $\dot{V}CO_2$, CO_2 output; $\dot{V}E$, pulmonary ventilation; B, baseline values for $\dot{V}O_2$, $\dot{V}CO_2$ or $\dot{V}E$; A_i, amplitude of each component; τ_i, time constants of each component; TD_i, time delay; and DO_2, O_2 deficit.

Table 3. Summary of the multiple linear regression for modeling the $\dot{V}O_{2\,peak}$, the ventilatory threshold (VT) and the respiratory compensation point (RC)

	$\dot{V}O_{2\,peak}$			**VT**			**RC**	
	β_i	cR^2		β_i	cR^2		β_i	cR^2
Intercept	4.4025	–	Intercept	3.9558	–	Intercept	2.8574	–
DO_2	-0.2844	0.6703	DO_2	-0.0004	0.3588	DO_2	-0.0014	0.4836
$VO_2(B)$	-0.0012	0.7618	A_{1VCO2}	0.0003	0.4847	$VO_2(B)$	0.0009	0.5881
TD_{2VO2}	-0.0022	0.7949	A_{1VO2}	-0.0502	0.5778	A_{0VO2}	-0.0076	0.6500
VE(B)	0.0000	0.8160	τ_{0VO2}	-0.0625	0.6579	τ_{0VCO2}	0.0587	0.6952
τ_{1VE}	-0.0107	0.8341	TD_{2VE}	-0.0083	0.7231	τ_{1VE}	-0.0013	0.7589
τ_{2VCO2}	-0.0011	0.8479	τ_{1VO2}	0.0005	0.7586	TD_{1VO2}	-0.0135	0.8098
TD_{1VCO2}	0.0065	0.8613	TD_{1VO2}	-0.0068	0.7913	τ_{2VCO2}	-0.1814	0.8656
			A_{2VO2}	-0.2076	0.8130			

$\dot{V}O_{2\,peak}$, peak O_2 uptake; VT, $\dot{V}O_2$ equivalent to the ventilatory threshold (VT); RC, $\dot{V}O_2$ equivalent to the respiratory compensation point (RC); β_i, regression coefficient for the i^{th} term; cR^2 cumulative determination coefficient.

one-out method, the results of which confirmed their capacity for estimating $\dot{V}O_{2\,peak}$ (SE = 177.96 ml/min, $r^2 = 0.92$), VT (SE = 159.35 ml/min, $r^2 = 0.90$) and RC (SE = 147.68 ml/min, $r^2 = 0.93$). Only one subject presented results that exceeded two SD (95% LOA) for all models. In general, substantially low standard errors were attained, evidencing the high reliability of the respective models.

Discussion

The present study aimed to estimate the ventilatory response during maximal exercise based on time response of the respiratory gas exchange during steady state workload. The estimation of the physiological response to exercise, as well as the relationship between ventilatory thresholds and the cardiovascular system and metabolism has been the concern of several previous studies (Barstow *et al*., 1996; Bearden and Moffatt, 2000; Bergman and Brooks, 1999; Wasserman and Whipp, 1983). However, to our knowledge, this study is the first to describe and relate the gas exchange kinetics to the ventilatory thresholds using a comprehensive mathematical modelling procedure. Moreover, this study demonstrated a close relationship between the time response of the gas exchange and the $\dot{V}O_{2\,peak}$, the VT and RC.

The subjects were physically active. The regularity of the activity, ranging from as low as one training session per week to five, might explain the high dispersion found in $\dot{V}O_{2\,peak}$ (Fleg *et al*., 2000; Fletcher *et al*., 2001). Among others, $\dot{V}O_{2\,peak}$ depends on the age, decreasing 8-10% per decade after age 30 years (Green *et al*., 1999; Fletcher *et al*., 2001). Herein, age explained 11.6% of the $\dot{V}O_{2\,peak}$ variance ($r = 0.34$, $p < 0.05$). The lower

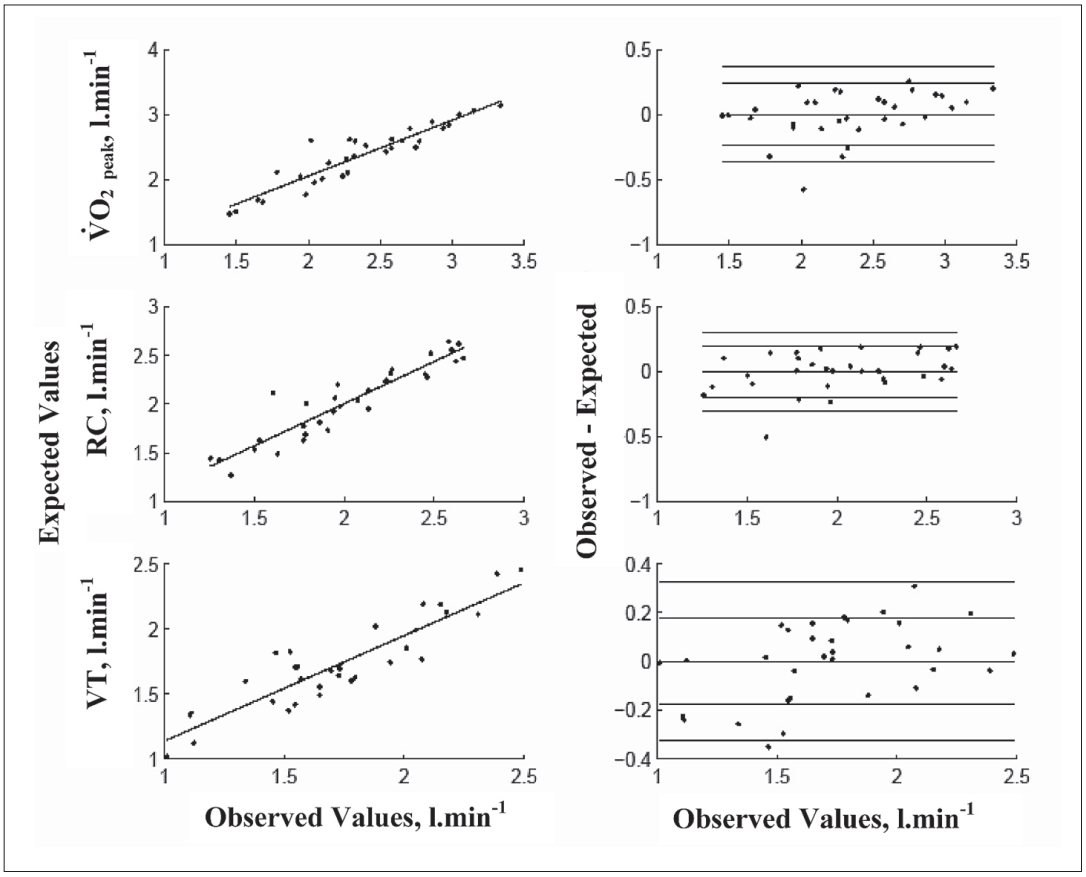

Figure 4. Peak oxygen uptake ($\dot{V}O_{2\,peak}$), the respiratory compensation point (RC) and the ventilatory threshold (VT) estimated through multiple linear regression with the coefficients presented in Table 3. The graphs on the left show the expected values as a function of the observed values (data points). The continuous lines are the linear regression for $\dot{V}O_{2\,peak}$, RC and VT. The graphs on the right are Bland and Altman plots. These graphs plot the difference between observed and expected values for $\dot{V}O_{2\,peak}$, RC and VT (y-axis) against observed values (x-axis). Central lines are mean difference; the two external lines are 95% of the limit of agreement (LOA), and the two internal lines are 95% of the confidence interval ($p < 0.001$).

$\dot{V}O_{2\,peak}$ values were obtained for the older (38-45 years) and slightly physically active subjects. Nevertheless, given that the scope of the present study was to predict $\dot{V}O_{2\,peak}$, we expect that a large variability of the sample would increase the models' general applicability. Additionally, all tests were accomplished in a cycle ergometer, representing an overload mainly for the lower limbs, which may cause early fatigue (Bergman *et al*., 1999; Casaburi *et al*., 1992; Fleg *et al*., 2000), and further involve an absolute O_2 consumption 10-20% below their treadmill $\dot{V}O_{2\,peak}$ (Fleg *et al*., 2000).

As described in a recent study (Santos and Giannella-Neto, 2004), the ventilatory thresholds (VT and RC) were determined automatically in all subjects, attaining 23.21 ± 2.86 ml/min·kg (VT) and 27.20 ± 2.26 ml/min·kg (RC). Previous studies (Billat, 1996; Coyle *et al*., 1988) showed the VT to be equivalent to 80-90% of $\dot{V}O_{2\,peak}$ in trained athletes, but ranging from 60 to 70% of $\dot{V}O_{2\,peak}$ in non-athletes (Fleg *et al*., 2000; Grassi *et al*., 1999). Herein, the values obtained for VT and RC were 73.7% and 86.4% of $\dot{V}O_{2\,peak}$, which exceeded the expectance for non-conditioned subjects. On the other hand, the exercise protocol (Whipp *et al*., 1981), based on a low rate of increase in work rate (12.5 W/min), might imply slower $\dot{V}O_2$ kinetics, overestimating the VT and RC (Beaver *et al*., 1986). Moreover, the early fatigue could explain the low $\dot{V}O_{2\,peak}$, and consequently, high relative values for VT and RC (Bergman *et al*., 1999; Fleg *et al*., 2000).

Gas exchange kinetics theorized by Whipp *et al*. (1981; 1982) was described by a single exponential function as postulated in the early 70's (Di Prampero *et*

al., 1970; Whipp, 1971). However, such a model did not consider the interaction among respiratory, metabolic and cardiovascular systems. Subsequently, other models were developed using the sum of two (Barstow *et al*., 1993; Bearden and Moffatt, 2000) or three (Barstow *et al*., 1996; Bearden and Moffatt, 2000; Koga *et al*., 1999; Langsetmo *et al*., 1997) exponential functions. Even though there are divergences in the literature concerning the most suitable model (Bearden and Moffatt, 2000; Carter *et al*., 2000a; 2000b), at exercise intensities above VT, the $\dot{V}O_2$ kinetics has been frequently described by a triple exponential function (Barstow and Molé, 1991; Carter *et al*., 2000b; Langsetmo *et al*., 1997). In agreement with Burnley *et al*. (2000), as illustrated in the Figure 2, the triple exponential function resulted in a regular error distribution and further, high correlation with the breath-by-breath values, corresponding to 88.4, 85.3 and 84.9% of the explained variance for $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}E$ respectively.

The $\dot{V}CO_2$ kinetics was previously described (Casaburi *et al*., 1992) as a single exponential function, and $\dot{V}E$ as an exponential superimposed by a line. These authors reported significant correlation between blood lactate concentration and the time constants of $\dot{V}O_2$ and $\dot{V}E$ (0.70 and 0.52 respectively). These findings corroborate for the hypothesis that there is an association between ventilatory thresholds (VT and RC) and gas exchange kinetics, and similarly to the present results, a faster temporal response of $\dot{V}O_2$ has been attributed to the higher $\dot{V}O_{2\,peak}$. Studies involving healthy (Koga *et al*., 1999; Wasserman and Whipp, 1983), as well as cardiac transplanted subjects (Cerretelli *et al*., 1992), have shown $\dot{V}O_2$ faster than that $\dot{V}CO_2$ temporal response followed by $\dot{V}E$. Accordingly, in the present study, except the cardio-dynamic component, which did not show differences, both the time constants (τ_1 and τ_2) of $\dot{V}CO_2$ were significantly higher than that of $\dot{V}O_2$ and further, $\dot{V}E$ time constants were higher than $\dot{V}CO_2$.

Previous works (Gaesser, 1994; Phillips *et al*., 1995; Williams *et al*., 2001) have reported a speeding in $\dot{V}O_2$ time response after endurance training as a result of the increase in the capillary and mitochondrial density. Koga *et al*. (1999), comparing $\dot{V}O_2$ kinetics in supine and upright position, showed slower kinetics in the supine position, which was attributed to the insufficient blood perfusion and O_2 delivery to the active muscles (Koga *et al*., 1999). Concerning these findings, it would be reasonable to assert that both the intramuscular characteristics and the blood perfusion are key factors in determining the $\dot{V}O_2$ time response to exercise. Moreover, the balance between the O_2 delivery and requirement has been accepted as one of the main limiting factors for $\dot{V}O_2$ kinetics (Hughson, 1990; Grassi *et al*., 2000).

Contrary to the cardio-dynamic and primary components, the physiological mechanism of the $\dot{V}O_2$ slow component remains not well explained. Several causes have been attributed to the slow component, such as the rise in the plasma catecholamines, the increase in $\dot{V}E$ and the muscular temperature (Casaburi *et al*., 1987; Carter *et al*., 2000a; 2000b; Langsetmo and Poole, 1999; Poole *et al*., 1991); to the lactate catabolism (Barstow *et al*., 1996; Carter *et al*., 2000a; Poole *et al*., 1991); or to the lower efficiency of the muscular fibres type II to synthesize ATP (Crow and Kushmerick, 1982). In the present study, no significant association between the aerobic capacity and the time constant of $\dot{V}O_2$ slow component ($\tau_2(\dot{V}O_2)$) was obtained. The reduction in $\tau_2(\dot{V}O_2)$ may have significant implications, particularly for fatigue tolerance in athletes, the sedentary as well as in patients with heart or lung diseases (Bauer *et al*., 1999; Carter *et al*., 2000b). In a recent study, Carter *et al*. (2000b) attributed the reduction in $\tau_2(\dot{V}O_2)$ to $\dot{V}E$ decreasing (9-14%). In the present work, the faster the $\dot{V}E$ the higher the $\dot{V}O_{2\,peak}$, VT and RC, mainly concerning the primary (PCC = -0.59, on average; $p < 0.05$) and slow (PCC = -0.13, on average; not significant) time constants.

Regarding $\dot{V}O_2$ kinetics, the higher partial correlation coefficients were obtained between the cardio-dynamic and primary time constants and VT (PCC = -0.54 and PCC = -0.57; respectively; $p < 0.05$). $\dot{V}CO_2$ presented significant correlations between τ_2 and RC (PCC = -0.54; $p < 0.05$). Each gas exchange kinetics parameter proved to be weak as estimators of the ventilatory thresholds explaining up to 35% of the variance. But, although a single variable could not explain the ventilatory threshold, this finding supported the hypothesis that by combining distinct kinetic parameters, the ventilatory thresholds could be satisfactorily estimated.

Recent works focused on the effect of 6-8 weeks of endurance training in healthy subjects and reported a delay in the onset of blood lactate accumulation (Bergman *et al*., 1999; Carter *et al*., 2000a; Casaburi *et al*., 1987), and similarly, a reduction in the slow component (around 35%) (Carter *et al*., 2000a; Casaburi *et al*., 1987). These findings showed that even though modest alterations in $\dot{V}O_{2\,peak}$ (3%) or VT (4%) could be induced by training, $\dot{V}O_2$ kinetics may be significantly modified. Additionally, other studies (Phillips *et al*., 1995; Yoshida *et al*., 1992) reported that $\dot{V}O_2$ could reach

steady state 18-25% faster after endurance training, and further, reduce the primary component time constant by 27-57%. Finally, Demarle *et al*. (2001) showed a rise in the aerobic endurance, without changes in $\dot{V}O_{2\,peak}$, associated to an increase in VT, and reported a drop of 46% in $\tau_1(\dot{V}O_2)$ and of 34% in the oxygen deficit. Herein, the $\dot{V}O_2$ primary component was more correlated with VT (-0.57), while the O_2 deficit exhibited significant correlation with $\dot{V}O_{2\,peak}$, VT and RC ($r = -0.58$, on average; $p < 0.05$).

Several papers reported that $\dot{V}O_2$ kinetics can be modified after endurance training (Casaburi *et al*., 1987; Demarle *et al*., 2001; Gaesser, 1994; Yoshida *et al*., 1992), showing a progressive drop in $\dot{V}O_2$ time constants (Casaburi *et al*., 1987; Gaesser, 1994; Yoshida *et al*., 1992), and further resulting in a decreased DO_2 (Whipp and Ozyener, 1998). Moreover, training may increase the $\dot{V}O_{2\,peak}$ (Green *et al*., 1999; Hagberg, 1987), as well as delay the onset of blood lactate concentration and acidosis (Bergman *et al*., 1999). The statements above support the hypothesis of the present study, that of a relation between the magnitude of $\dot{V}O_{2\,peak}$, VT and RC and the gas exchange kinetics, and thus it is reasonable to assert that by means of mathematical decomposition of the gas exchange time responses, it is theoretically possible to predict the maximal ($\dot{V}O_{2\,peak}$) and sub-maximal (VT and RC) functional capacity.

According to the present results, a close relation was noted between $\dot{V}O_{2\,peak}$, VT and RC, and the gas exchange kinetics. Although no cause-effect can be attributed, the strong correlations yielded here evidenced a solid association between the gas exchange kinetics and the ventilatory thresholds, resulting in 83.5%, 79.3% and 77.4% of the explained variance (for $\dot{V}O_{2\,peak}$, VT and RC respectively), corresponding to low standard errors of around 210 ml/min. The models were validated through the leave-one-out method, confirming the predictive capacity to estimate $\dot{V}O_{2\,peak}$ (SE = 177.96 ml/min, $r^2 = 0.92$), VT (SE = 159.35 ml/min, $r^2 = 0.90$) and RC (SE = 147.68 ml/min, $r^2 = 0.93$).

Early studies proposed different protocols for measuring or estimating $\dot{V}O_{2\,peak}$, used as a fundamental index for exercise prescription (Billat *et al*., 1996). Afterwards, other protocols were designed to estimate the anaerobic threshold, applied to exercise prescription for the healthy and athletes (Billat *et al*., 1996), for lung (Casaburi *et al*., 1992), and heart disease patients (Maiorana *et al*., 2000; Zhang *et al*., 1994), among others. The applicability of $\dot{V}O_{2\,peak}$, VT and RC for exercise prescription, for training management or for quantifying the severity of physical limitations is indisputable. On the other hand, all referred studies employed progressive and maximal exercise protocols. Zhang *et al*. (1994) were the firsts to demonstrate the possibility to estimate $\dot{V}O_{2\,peak}$ and VT during a steady state exercise, based on DO_2 and the difference between the measured $\dot{V}CO_2$ and CO_2 produced by the oxidative pathway. The present work was the first to apply the kinetic components extracted from a steady state exercise to forecast $\dot{V}O_{2\,peak}$ and the ventilatory thresholds with high accuracy.

In conclusion, the present model extracted from steady state cycle exercise was adequate to express $\dot{V}O_{2\,peak}$, VT and RC for healthy and physically active male subjects. Finally, it is reasonable to assert that there is co-dependence between the ventilatory thresholds and the gas exchange kinetics, and, furthermore, the maximal and sub-maximal ventilatory and metabolic responses to exercise can be estimated based only on a sub-maximal test.

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