

Comparison of modeling techniques used to characterize moderate and heavy phase two recovery $\dot{V}O_2$ kinetics in old men

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RESUMEN

Se evaluó la cinética de absorción pulmonar de oxígeno ($\dot{V}O_2$) off-transitoria (recuperación del ejercicio) de las respuestas de intensidades moderada (M) e intensa (H) al ejercicio submáximo (Sub = M + H) al comparar entre varias estrategias de modelado comunes para evaluar el mejor modelo de ajuste exponencial. El parámetro estimado de la fase 2 de $\dot{V}O_2$ fue la constante de tiempo (off- $\tau\Phi_2\dot{V}O_2$) en hombres adultos mayores [n = 9; 72 (± 4) años; media (\pm sd)]. Una prueba tipo rampa ($12 \text{ W} \cdot \text{min}^{-1}$) hasta el límite de tolerancia para determinar el $\dot{V}O_{2\text{peak}}$ y el umbral estimado de lactato ($\dot{V}_E T$). Ejercicio de ciclo de carga constante a 50 W (M) y a tasas de trabajo correspondientes a 80% $\dot{V}_E T$ (M) y a 120% $\dot{V}_E T$ (H). Cada una duró 6 min precedidos una línea de base (LB) de 6 min de ciclismo de 20 W, se repitió cuatro a seis veces. $\dot{V}O_2$ se midió de respiración a respiración. Pedaleando a 60 rpm, la prueba inició con una LB del último minuto del final del ejercicio, seguido de una disminución de potencia (sin advertir al sujeto) de vuelta al pedaleo sin resistencia por 6 min de recuperación (RE). Datos de cada transición se filtraron, interpolaron a intervalos de 1 s y su ensamblado promedio produjo una respuesta única para cada sujeto e intensidad. Las respuestas se modelaron con regresión no lineal y modelos exponenciales de uno (1C), dos (2C) y tres (3C) componentes (tiempo de retraso) de ventanas de ajuste diferente. Off- $\Phi_2\dot{V}O_2$ Sub fue fisiológicamente y estadísticamente bien descrita, y cinéticamente distinguida (off- $\tau_2\dot{V}O_2$) por las funciones de doble exponencial dos componentes (2C) para M ($\tau_2 = 56 \pm 14$ s) y triple exponencial tres componentes (3C) ($\tau_2 = 39 \pm 7$, $^{ab}P < 0.05$) para H en hombres adultos mayores.

Palabras clave. Adultos mayores, recuperación del ejercicio, cinética de la captación off- O_2 , fase dos de O_2 , modelado exponencial, constante de tiempo.

ABSTRACT

We kinetically assessed pulmonary oxygen uptake ($\dot{V}O_2$) off-transient ($P_{\text{ost}} - E_{\text{exercise}} R_{\text{recovery}}$) response during moderate (M)- and heavy (H)-intensity (Sub = M + H) exercise comparing among several common modelling strategies to assess the best fitting exponential model. The parameter estimated for phase 2 $\dot{V}O_2$ was the time constant (off- $\tau\Phi_2\dot{V}O_2$) in older male adults [n = 9; 72 (± 4) yrs; mean (\pm sd)]. Subjects performed an incremental ramp test ($12 \text{ W} \cdot \text{min}^{-1}$) to the limit of tolerance to determine $\dot{V}O_{2\text{peak}}$ and the estimated lactate threshold ($\dot{V}_E T$). Constant-load cycle exercise was performed at 50 W (M) and work rates corresponding to 80% (M) and 120% $\dot{V}_E T$ (H). Each transition in work rate lasted 6 min and was preceded by 6 min cycling at a baseline of 20 W; transitions at each intensity were repeated 4-6 times. $\dot{V}O_2$ was measured breath-by-breath. Each subject pedalled at 60 rpm and protocol began with a base line off 1 min end exercise load-cycling, followed by a step decrease in power output (without warning the subject) back to loadless cycling lasting 6 min in duration (PER). Data from each transition were filtered, interpolated to 1 s intervals and ensemble-averaged to yield a single response profile for each subject and intensity. Responses were modelled by means of nonlinear regression techniques with one-(1C), two-(2C) and three-component (time delay) (3C) exponential models using different fitting windows. The off- $\Phi_2\dot{V}O_2$ for Sub was both physiologically and statistically well described and kinetically characterized (off- $\tau_2\dot{V}O_2$) by a two component doble exponential function (2C) for M ($\tau_2 = 56 \pm 14$ s), and by a threecomponent triple exponential function (3C) ($\tau_2 = 39 \pm 7$, $^{ab}P < 0.05$) for H in old men.

Key words. Old men, post-exercise recovery, off- O_2 uptake kinetics, phase two O_2 exponential modelling, time constant.

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INTRODUCTION

Current considerations of the pulmonary post-exercise recovery (PER) oxygen uptake ($\dot{V}O_2$) needs greater understanding of $\dot{V}O_2$ kinetics control and, it is considered important for improving the human condition, crucially for patients suffering from pathologically slowed $\dot{V}O_2$ kinetics as well as the growing elderly population.¹ The time course of PER $\dot{V}O_2$ response (off-transient $\dot{V}O_2$) related to the intensity of previous exercise in old adults^{2,3} it has been modelled by using nonlinear regression to fit a model to data well and give us parameters that help us understand the system,⁴ reach valid scientific conclusions, and design new experiments. A mathematical model is a description of process that can help we think about physiological processes or mechanisms, so we can design better experiments and comprehend the results.⁵ Nevertheless, we should obtain best-fit values to be interpreted in the context of the mathematical-process model, because there is a need for an assessment for the best exponential mathematical model from a number of publications in the literature on modelling the off-transient $\dot{V}O_2$ response during submaximal exercise in old men with different exponential mathematical models.^{2,6}

The $\dot{V}O_2$ kinetic models has been developed, trying to describe mechanism related with kinetics of muscle oxygen consumption in the search of the characteristics of effective physiological systems integration.^{2,7-9} At the end of the work, the recovery of the $\dot{V}O_2$ returns to resting values following a complex function in which it is possible to identify also various components based on the intensity of the exercise preceding the recovery period (off-transient $\dot{V}O_2$ response). The moderate-to-heavy aerobic exercise off-transient $\dot{V}O_2$ response, shows an initial rapid decline, similar to recovery from light exercise, named the off-transient phase one $\dot{V}O_2$ response (off- Φ_1 $\dot{V}O_2$) followed by a more gradual decline to baseline resting levels, the off-transient phase two $\dot{V}O_2$ response (off- Φ_2 $\dot{V}O_2$). With mild aerobic exercise of relatively short duration, about one-half of the total recovery oxygen consumption takes place within 30 sec, with complete recovery within several minutes, minutes, the decline in oxygen consumption follows a single component exponential model termed the fast component of recovery oxygen consumption.⁹ During the exercise of low and moderate intensity, two phases in the $\dot{V}O_2$ off-kinetics are recognized and characterised the off- Φ_1 $\dot{V}O_2$; and the primary component, also called off- Φ_2 $\dot{V}O_2$. Recovery from strenuous exercise presents a different picture; in addition to the fast component of the recovery (off- Φ_2 $\dot{V}O_2$), a slow com-

ponent phase of recovery exists (Φ_3).^{10,11} This slow phase of the off-transient kinetics becomes more prominent at higher work rate.^{7,8,12,13} This additional Φ_3 , called the slow component of $\dot{V}O_2$ off-kinetics, is present (off- Φ_3 $\dot{V}O_2$) during the exercise of heavy intensity and strenuous exercise.¹⁴ The recovery of the $\dot{V}O_2$ dynamics at moderate¹⁵, and heavy intensity exercise^{16,17} have been modelled $\dot{V}O_2$ kinetics during work-to-work transitions compared to rest-to-work transitions; as well as, the off-transient $\dot{V}O_2$ response to sumaximal exercise has been modelled in old adults.^{2,6,18} However those different mathematical exponential models for modelling the $\dot{V}O_2$ PER, have not been assessed to search for the best model to fit submaximal exercise data.

The aim of the current study was to assess, from different exponential mathematical models previously published,¹⁹⁻²¹ both a simple and best valid kinetic exponential mathematical models for the off- Φ_2 $\dot{V}O_2$ response during submaximal exercise in old men. An analysis is made of approaches to developing models for best predicting the kinetics of the $\dot{V}O_2$ adsorption recovery after submaximal exercise.

Hypothesis

If the exponential Φ_2 $\dot{V}O_2$ off-transient response to forcing functions of submaximal exercise is similarly modelled by single mono-exponential function, one component, two component and three component models in terms of time constant duration, thus off- Φ_2 $\dot{V}O_2$ time constant estimated values should not be significantly different to each other, in old men.

MATERIAL AND METHODS

The cardiopulmonary methodology used in this study has been already described somewhere else;^{20,21} however in brief, the ventilation and pulmonary gas exchange ($\dot{V}O_2$, $\dot{V}CO_2$), ventilation, $\dot{V}O_2$ and $\dot{V}CO_2$ were calculated breath-by breath by a computer based programme.²² Inspired and expired air was sampled continuously (1 $mL \cdot s^{-1}$) at the mouth, and analysed for fractional concentrations of O_2 , CO_2 , and N_2 using a respiratory mass spectrometer (Perkin Elmer MGA-1100 or Airspec MGA2000) daily calibrated.²⁰ The electrocardiograph (Harcos, Sauborn Model 500-1100) measures the bioelectric potentials of the heart, inputs the ECG signals into a computerized oscilloscope (Perkin Elmer EM 530 B), and records these voltages in a microcomputer.²⁰ All the input signals were stored on a hard disc system for later analyses.

Subjects

Nine old healthy male adults participated in this study. The University's Review Board for Research Using Human subjects approved this research.

Ramp test

On the initial visit to the laboratory each subject performed and incremental exercise test in the upright position on an electrically-braked cycle ergometer (Lode, Model H-300-R), in which after initiated at 60 rpm by 4 min "loadless" (actual constant power output approximately 20 W) pedaling, the power output increased as a ramp function at 15 W·min⁻¹ to volitional fatigue^{20,23} for the determination of the $\dot{V}_E T$, peak $\dot{V}O_2$ uptake ($\dot{V}O_{2\text{peak}}$), heart rate peak and maximal work rate.²¹

$\dot{V}O_{2\text{peak}}$

The $\dot{V}O_2$ averaged over the final 15 s of the incremental test prior to fatigue was taken as $\dot{V}O_{2\text{peak}}$.

Ventilatory threshold ($\dot{V}_E T$)

The $\dot{V}_E T$ as a non-invasive method²⁴ was expressed as a percentage of the $\dot{V}O_2\text{max}$. The $\dot{V}O_2$ corresponding to the time of the $\dot{V}_E T$ ¹⁹ and the work rate corresponding to the $\dot{V}O_2$ at 80% $\dot{V}_E T$ and also at 120% $\dot{V}_E T$ were calculated.^{20,21}

Submaximal constant-loadless leg cycling exercise tests

The $\dot{V}O_2$ off-transient tests and their kinetics were performed during subsequent visits to the laboratory. Subjects performed constant-load leg cycling exercise where the power output increased as a step function from "loadless" cycling to a power output corresponding to moderate or heavy-intensity exercise.²¹ The intensities of exercise consisted in square waves of 50 W (MA, absolute power output of moderate-intensity), power outputs corresponding to 80% $\dot{V}_E T$ (MR, relative power output of moderate-intensity) and 120% $\dot{V}_E T$ (H, relative power output of heavy-intensity). Each subject performed all three submaximal exercise intensities (MA, MR, H) during the course of the study. Each subject pedalled at 60 rpm and protocol began with a baseline off 1 min end exercise (BSL1) load-cycling, followed by a step decrease in power output (without warning the subject) back to loadless cycling lasting 6 min in duration (entire off-transition, recovery of exercise). Each subject performed 4-6 transitions for the 50 W (MA) and 80% $\dot{V}_E T$

protocols, and 2 to 4 repetitions for the 120% $\dot{V}_E T$ protocol; they were assigned per visit as followed: 50 W (< $\dot{V}_E T$), 80% $\dot{V}_E T$ (< $\dot{V}_E T$), and 120% $\dot{V}_E T$ (> $\dot{V}_E T$).²¹ Subjects pedalled while breathing to measure the ventilation and gas exchange calculated by a computer based programme.^{20,23}

Modelling

The $\dot{V}O_2$ off-transient responses < $\dot{V}_E T$ and > $\dot{V}_E T$ exercise intensities were modelled by using the one component (1C), two component (2C) and three component (3C) exponential mathematical expressions with seven fitting models (Table 1) previously published.²¹ These seven fitting models, from A to G (Table 1) using the fitted period of time (fitting window) from either 20 s (0.3333 min) or one min baseline (BL1) after the offset of the exercise (end of the ergometric exercise) to (→) either 3 min off-transient $\dot{V}O_2$ response or 6 min EER were the 1C,4P_{0.3333 → 6 min} (model A) and 2C,7P_{0.3333 → 6 min} (model E); 2C,7P_{BL1 → 3 min} (model D); 1C,3P_{BL1 → 6 min} (model B), 1C,4P_{BL1 → 6 min} (model C), 2C,7P_{BL1 → 6 min} (model F) and 3C,10P_{BL1 → 6 min} (model G), to estimate off $\tau\Phi_2 \dot{V}O_2$. The fitting models A-C were used to assess the best fit compared to multiple component models (D-G) (Table 1). The multi-component models E (omitting phase one), F and G (except for moderate-intensity PER) that fitted data from the offset towards the recovery of exercise steady-state of the submaximal exercise that included BSL1 (Table 1) were used to assess the best physiological ($\Phi_2\text{Phys}$) and statistical ($\Phi_2\text{Stat}$) or both ($\Phi_2\text{PhysStat}$) fit of $\Phi_2 \dot{V}O_2$ off-transient response from submaximal exercise. We assessed modelling primarily on whether the information provided by these exponential mathematical models resulted consistent with current understanding of the $\dot{V}O_2$ off-transient response (Phys); as well as, statistical (Stat) merits.²¹ The kinetic analysis was assessed in terms of the time constant two (off- $\tau\Phi_2$). Estimates of the parameters of the off response ($\Phi_2 \dot{V}O_2 \tau$) was compared together with a statistical analysis of how well each model fitted $\dot{V}O_2$.^{21,24-26} Amplitudes both from phase two (the fundamental A_2) and from phase three (A_3) were also expressed in terms of functional gain ($G = \Delta\dot{V}O_2/\Delta\text{WorkRate}$) from models F and G (Table 1) respectively.¹⁷

Data analysis

The breath by breath MA, MR and H data were interpolated to 1 s interval, and each repetition was time aligned and assembled averaged to provide a single response for each subject for determining the kinetics of the $\dot{V}O_2$ off-transient response to submaximal exercise.²¹



Table 1. Seven different exponential mathematical fitting models (A to G) used to assess the $\dot{V}O_2$ off-transient response during submaximal exercise in old men.

Model number	Fitting model	Temporal parameter									
		1 A_{amplitud} ($\text{mLO}_2 \cdot \text{min}^{-1}$)	2 A_1	3 A_2	4 A_3	5 T_{ime}	6 D_{elay}	7 TD_2	8 TD_3	9 τ_1	10 τ_2
A	1C,4Parameters 0.3333 min to 6 min*	[Virtual BSL]-	✓	-	-	-	-	-	-	✓	-
B	1C,3P BSL1 min to 6 min	✓	✓	-	-	-	-	-	✓	-	-
C	1C,4P BSL1 min to 6 min	✓	✓	-	-	-	✓	-	-	✓	-
D	2C,7P BSL1 min to 3 min	✓	✓	✓	-	-	✓	✓	-	✓	✓
E	2C,7P 0.3333 min to 6 min	[Virtual BSL]-	✓	✓	-	-	✓	✓	-	✓	✓
F	2C,7P BSL1 min to 6 min	✓	✓	✓	-	-	✓	✓	-	✓	✓
G	3C,10P BSL1 min to 6 min	✓	✓	✓	✓	-	✓	✓	✓	✓	✓

-: no estimated temporal parameter. *Fitting (period of time) window. BL1: one min end exercise baseline. 0.3333: 20 s after BL1. 6 min: six min end recovery exercise. 1, 2, and 3 in A, TD, and τ (time constant) refer to the phases one, two, and three, respectively, in $\dot{V}O_2$ off-transient response during submaximal exercise. 1C, 2C, and 3C: one component (one TD), two components (two TDs), and three components (three TDs) models. 1C,3P (single monoexponential function): $\dot{V}O_2(t) = A_0 + A_1 \cdot (1 - e^{-(t/\tau_1)})$; 1C,4P: $\dot{V}O_2(t) = A_0 + A_1 \cdot (1 - e^{-(t-TD_1)/\tau_1})$; 2C,7P: $\dot{V}O_2(t) = A_0 + A_1 \cdot (1 - e^{-(t-TD_1)/\tau_1}) + A_2 \cdot (1 - e^{-(t-TD_2)/\tau_2})$; 3C,10P: $\dot{V}O_2(t) = A_0 + A_1 \cdot (1 - e^{-(t-TD_1)/\tau_1}) + A_2 \cdot (1 - e^{-(t-TD_2)/\tau_2}) + A_3 \cdot (1 - e^{-(t-TD_3)/\tau_3})$. $\dot{V}O_2(t)$: mass rate of change per unit of time ($d \dot{V}O_2 / dt$) assuming TD = 0; a_0 : baseline; a is the $\dot{V}O_2$ distance value from a_0 to the $\dot{V}O_2$ recovery required, or recovery steady-state (i.e., the difference between the end exercise baseline and the unloaded pedalling recovery-exercise $\dot{V}O_2$ response). $1 - e^{-(t/\tau)}$: the negative exponential distribution (Evans, Hasting and Peacock, 1993). $e^{-(t/\tau)}$: the die-away factor with the time constant τ , for an exponential decrease (off-transient $\dot{V}O_2$ response). t : time in which the transient $\dot{V}O_2$ response is gradually (exponentially) dying away; when $t = \tau$ means the time required for the transient $\dot{V}O_2$ response to die away to e^{-1} part ($e^{-1} = 1/2.71828 = 0.3678$) of its original value, thus, $\tau = 1 - 0.3678 = 0.63$, and $e = 2.718281 = [(1 + n^{-1})]^n$, $n \geq 10$ and e is incommensurable with one.

Statistical analyses

The goodness of fit by each fitting model was assessed using the lowest residual sum of squares (RSS values) from a computerized nonlinear regression technique.²⁷ The best statistical fit exponential mathematical model was assessed using the RSS values for models that fit the same number of experimental data points or the mean square error (MSE values) for models which fit a different number of experimental data points by performing a Fisher's test (F_{vaue} , at 0.05 level of significance and one tailed) described previously.^{21,25,26}

Data treatment consisted of group analyses performed using either a One Way Analysis of Variance (ANOVA); All Pairwise Multiple Comparison Procedures (Holm-Sidak post-hoc analysis) or Kruskal-Wallis ANOVA on Ranks procedure Dunn's Method (when variances of the dependent variable were unequal or the distribution of the dependent variable was not normal), to compare kinetic temporal parameters from the exercise square waves.²⁶ Student *t*-test was used to assess for significant differences between the estimated parameter means from two groups with the same number of parameters.²⁶ The probability level denoted significance at $p \leq 0.05$.

RESULTS

Physical characteristics and ramp exercise test

As expected the physical characteristics, maximal cardiorespiratory and $\dot{V}_E T$ values were above average fitness (Table 2). The moderate submaximal power output (W), $\dot{V}O_2$ both in terms of % $\dot{V}_E T$ and % $\dot{V}O_2$ peak, and $\dot{V}_E T$ in terms of W resulted low compared those from H intensity exercise (Table 2). The slope (coefficient) of the M_{MODERATE} $\dot{V}O_2$ - power output relationship and the $\dot{V}O_2$ during loadless cycling (constant) were: $\dot{V}O_2/W = 12.01 \pm 1.3 \text{ mL} \cdot \text{min}^{-1} \cdot \text{W}$ ($n = 18$, $R = 0.98$, $P < 0.001$); and $\dot{V}O_{2,\text{off loadless}} = 750 \pm 126 \text{ mL} \cdot \text{min}^{-1}$. The $\dot{V}O_2$ off-transient time course for absolute (50 W), relative moderate (80% $\dot{V}_E T$), and relative heavy (120% $\dot{V}_E T$) square-wave exercise tests from our nine old subjects sample are presented in figure 1.

Modelling

The statistical assessment of the Φ_2 $\dot{V}O_2$ off-transient response to submaximal exercise in old men, with seven exponential mathematical fitting models, showed that model A fitter Stat best ($P < 0.05$) compared model B, and also model F did compared models B and C (Table 3). Models F and G fitted similarly ($P < 0.05$) the Φ_2 $\dot{V}O_2$ off-transient response to heavy intensity exercise (Table 3); however, taking in consideration the current understanding of the $\dot{V}O_2$ off-transient response (Phys, physiological me-

aning) the model F fitted Phys best moderate intensity exercise (M: MA and MR) and model G also did for heavy intensity exercise. The $\dot{V}O_2$ off-transient response to relative heavy intensity exercise in old men, was fitted Stat best ($P < 0.05$) by complex models F and G compared model E (Table 3). Nevertheless, on fitting the $\dot{V}O_2$ entire off-transient response to relative heavy intensity exercise, model E ($2C, 7P_{0.3333 \rightarrow 6 \text{ min}}$) perhaps is more practical when phase one is extremely difficult to be fitted, because it omits phase one and is less complex compared model G.

Estimated temporal parameters

- **Baseline (BSL).** Analyses showed that the BSLs ($\text{mL} \cdot \text{min}^{-1}$) were $1,335 \pm 389$ (mean \pm SD) for model B, $1,324 \pm 383$ for model C, $1,328 \pm 387$ for model D, and $1,334 \pm 394$ for model F from the $\dot{V}O_2$ off-transient response ($BSL_{\text{TOTAL}} = 1,330.2 \pm 382.6$) to submaximal exercise. The BSL $1,773 \pm 328$ from model G was similar to that from model F (1772 ± 327) for heavy intensity exercise.
- **Functional gain (G , $\text{mL} \cdot \text{min}^{-1} \cdot \text{W}^{-1}$).** Analysis showed that the effect of submaximal exercise on the fundamental gain (G_2) resulted for MA intensity exercise from model F (8.4 ± 1.0) low compared heavy intensity exercise from model F (10.7 ± 1.8), and MR exercise from model F (7.3 ± 1.1) low compared either heavy heavy intensity exercise from model G (10 ± 2.6) ($F_{\text{value}} = 6.8$, $P < 0.002$); and also the total gain (G_{TOT}) resulted for both the MA exercise from model F (8.4 ± 1.1) and the MR exercise

Table 2. Subject characteristics and data for maximal and submaximal exercise in nine old men.

Age (years)	Height (cm)	Mass (kg)	Work rate max (watts)	$\dot{V}O_2$ peak		$\dot{V}_E T$	
				($\text{L} \cdot \text{min}^{-1}$)	($\text{mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)	($\text{mL} \cdot \text{min}^{-1}$)	(% $\dot{V}O_2$ peak)
72 \pm 4	173 \pm 4	78 \pm 11	126 \pm 18	2.4 \pm 0.3	29.3 \pm 7.4	1,323 \pm 129	60 \pm 6
50 W ^a							
				Moderate intensity exercise		Heavy intensity exercise	
$\dot{V}O_2$ ($\text{mL} \cdot \text{min}^{-1}$)	% $\dot{V}_E T$	% $\dot{V}O_2$ peak	PO (W)	$\dot{V}O_2$ ($\text{mL} \cdot \text{min}^{-1}$)	% $\dot{V}_E T$	% $\dot{V}O_2$ peak	PO (W)
1,780 ^a \pm 135	87 ⁱ \pm 11	54 ^k \pm 12	35 ^{e,g} \pm 10	1,020 ^{a,c} \pm 168	76 ⁱ \pm 10	46 ^k \pm 10	93 ^f \pm 13
				$\dot{V}O_2$ ($\text{mL} \cdot \text{min}^{-1}$)	% $\dot{V}_E T$	% $\dot{V}O_2$ peak	$\dot{V}_E T$ (w)
				1,790 ^{b,d} \pm 363	122 ^j \pm 13	83 ^l \pm 16	65 ^h \pm 14

All data are mean \pm SD. ^aAbsolute PO. $\dot{V}_E T$: ventilatory threshold. PO: power output. % $\dot{V}_E T$ calculated as ($\dot{V}O_2$ exercise intensity)/($\dot{V}O_2$ $\dot{V}_E T$) $\times 100$. % $\dot{V}O_2$ peak calculated as ($\dot{V}O_2$ exercise intensity)/($\dot{V}O_2$ peak) $\times 100$. Significant differences between means with different letter, allocated by ANOVA procedure: Tukey test: ^{a,b;c,d}F_{ratio} = 18, $P < 0.001$; Kruskal-Wallis ANOVA based on Ranks: ^{e,f;g,h}H_{ratio} = 25.8, $P < 0.001$. Student-Newman-Keuls test: ^{i,j;f}F_{ratio} = 33.5, $P < 0.001$; Student-Newman-Keuls test: ^{k,l}F_{ratio} = 15, $P < 0.001$.

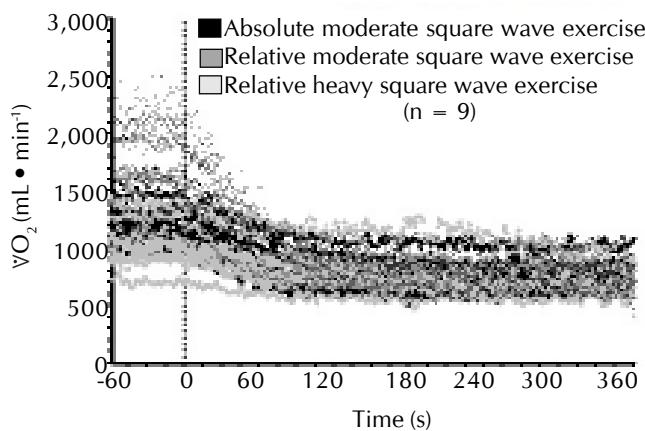


Figure 1. Group off-transient pulmonary oxygen uptake ($\dot{V}O_2$) response profiles to absolute moderate (50 W), relative moderate (80% $\dot{V}_E T$), and relative heavy (120% $\dot{V}_E T$) square wave exercise. Exercise offset (start) is at zero min. Data points (symbols) are the breath-by-breath interpolated to second-by-second pulmonary $\dot{V}O_2$ (experimental data) from one min (-60) baseline. The nine old subjects submaximal exercise at each intensity ($n = 9$) are displayed.

from model F (7.3 ± 1.1) low compared either the heavy intensity exercise from model F (10.7 ± 2.0) or the heavy intensity exercise from model G (10.8 ± 1.9) ($F_{value} = 11.5$, $P < 0.001$) for $\dot{V}O_2$ off-transient response.

- **Time delay (TD, s).** Analyses showed that the phase one $TD\dot{V}O_2$ off-transient response from models B, C, and D resulted similar (2.7 ± 7.8) compared those from either M exercise (3.2 ± 2.9) or heavy intensity exercise (2.0 ± 2.926); the phase two $TD\dot{V}O_2$ off-transient response from model A (2.04 ± 7.15) resulted low compared those from models D (23.7 ± 8.9) and F (25.5 ± 5.5) for submaximal exercise; as well as, model E (8.2 ± 5.7) resulted low compared model G (27.0 ± 5.5) for heavy intensity exercise ($H = 62.0$, $P \leq 0.001$).
- **Time constant (τ , s).** Analyses showed that the phase one $\tau \dot{V}O_2$ off-transient response from models B (60.0 ± 36.0), and C (48.1 ± 12.8) were higher compared those from either models D (22.2 ± 9.9) and model F (19.8 ± 10.2) for submaximal exercise or that from model G for heavy intensity exercise (13.3 ± 7.3) ($F_{value} = 23.382$, $P < 0.001$). The phase two $\tau \dot{V}O_2$ off-transient response from model F (42.43 ± 7.35) for heavy intensity exercise resulted low compared M exercise (56.0 ± 14.0) ($t = 2.8$, $P < 0.013$). The phase two $\tau \dot{V}O_2$ off-transient response from model F for MA exercise (51.01 ± 12.7) and for MR exercise (61.0 ± 14.1) resulted higher compared those from models E ($35.0 \pm$

5.6) and G (38.8 ± 6.7) for heavy intensity exercise ($H = 25$, $P \leq 0.001$). The MRT_{exp} (s) from model F for M exercise (54.0 ± 10) resulted similar to that from model G for heavy intensity exercise (55.4 ± 8.52).

Thus, generally speaking models E (for H exercise only), F (for M exercise) and G (heavy intensity exercise) fitted best compared either the simple models (A, B, C) or the complex model D (Table 3) for the $\Phi_2 \dot{V}O_2$ off-transient response to submaximal exercise (Figure 2). The summary of these best physiological and statistical fitting exponential mathematical models for submaximal exercise in old men are shown in table 4.

DISCUSSION

Since the $\dot{V}O_2$ asymptote is significantly delayed for work rate (W) above the ventilator threshold¹⁹ then it was not a surprise that the moderate submaximal power output (W), $\dot{V}O_2$ both relative to $\dot{V}_E T$ and relative to $\dot{V}O_2$ peak, and $\dot{V}_E T$ in terms of W resulted low compared those from heavy intensity exercise.

Modelling

We formally statistically characterize the off-transient (recovery) $\dot{V}O_2$ kinetics in old men within the moderate exercise both absolute and relative at 80% $\dot{V}_E T$, and heavy relative at 120% $\dot{V}_E T$ exercise domains. A precise physiological-biochemical explanation for the recovery oxygen consumption, remains elusive, because no comprehensive explanation exists about specific contributory factors.^{5,28}

Statistical assessment of the $\Phi_2 \dot{V}O_2$ off-transient response to submaximal exercise in old men, with seven exponential mathematical fitting models (A to G), showed that model A ($1C4P_{omitting \ phase \ one}$) fitter Stat best compared model B ($1C,3P_{entire \ VO2 \ off-response}$, single monoexponential function), and also model F ($2C,7P_{entire \ VO2 \ off-response}$) did compared models B and C ($1C,4P_{entire \ VO2 \ off-response}$). Models F and G ($3C,10P_{entire \ VO2 \ off-response}$) fitted similarly the $\Phi_2 \dot{V}O_2$ off-transient response to heavy intensity exercise; however, taking in consideration the current understanding of the $\dot{V}O_2$ off-transient response (Phys, physiological meaning) the model F fitted Phys best moderate intensity exercise (MA and MR)⁹ and model G also did for heavy intensity exercise.^{10,11} In consequence, the $\dot{V}O_2$ off-transient response to relative heavy intensity exercise in old men, was fitted Stat best by complex models F and G compared model E. However, on fitting the $\dot{V}O_2$ entire off-transient response to relative heavy intensity exercise, model E (omitting phase one) is both more practical when

Table 3. Residual sum of squares and mean square error estimates for kinetic analysis of VO_2 during the off-transient of recovery steady-state submaximal exercise as estimated by seven different exponential mathematical models and their 21 two out mathematical model permutations in nine old men.

Seven fitting models	Exercise intensity					
	Moderate (50 Watts)		Moderate (80% V_ET)		Heavy (120% V_ET)	
	RSS ($\times 10^5$)	MSE	RSS ($\times 10^5$)	MSE	RSS ($\times 10^5$)	MSE
A 1C,4P _{0.3333 min → 6 min}	4.50 ± 2.45	1,336 ± 727	6.02 ± 4.15	1,804 ± 1,262	7.97 ± 8.23	2,378 ± 2,466
B 1C,3P _{BSL1 min → 6 min}	6.25 ± 3.10	1,376 ± 875	7.90 ± 5.37	1,906 ± 1,311	13.40 ± 12.82	3,229 ± 3,107
C 1C,4P _{BSL1 min → 6 min}	5.96 ± 3.15	1,432 ± 757	21.11 ± 42.69	1,855 ± 1,284	12.16 ± 12.42	2,865 ± 3,045
D 2C,7P _{BSL1 min → 3 min}	2.99 ± 1.59	1,240 ± 592	3.61 ± 1.99	1,548 ± 854	6.40 ± 8.25	2,746 ± 3,541
E 2C,7P _{0.3333 min → 6 min}	-	-	-	-	7.39 ± 7.13	2,231 ± 2,164
F 2C,7P _{BSL1 min → 6 min}	7.22 ± 4.24	1,347 ± 709	11.59 ± 9.53	2180 ± 1800	10.00 ± 11.27	2,428 ± 2,750
G 3C,10P _{BSL1 min → 6 min}	-	-	-	-	9.96 ± 11.06	2,444 ± 2,703
21 Fitting Model Permutations "Simple" vs. "Complex"						
N ^a	Moderate (50 Watts)		Moderate (80% V_ET)		Heavy (120% V_ET)	
	F_{RSS}	F_{MSE}	F_{RSS} F_{value} ^b	F_{MSE} Calculated ^b	F_{RSS}	F_{MSE}
1 1C,4P _{0.3333 → 6 min} ^A	1C,3P _{BL1 → 6 min} ^B	-	6.26*, ^A	-	4.98*, ^A	-
2 1C,4P _{0.3333 → 6 min}	1C,4P _{BL1 → 6 min} ^C	-	1.20*, ^C C_{om}	-	0.50	-
3 1C,4P _{0.3333 → 6 min}	2C,7P _{BL1 → 3 min} ^D	-	0.08	-	0.18	-
4 1C,4P _{0.3333 → 6 min}	2C,7P _{0.3333 → 6 min} ^E	-	-	-	-	8.58*, ^C C_{om}
5 1C,4P _{0.3333 → 6 min}	2C,7P _{BL1 → 6 min}	-	0.18	-	3.59*, ^C C_{om}	-
6 1C,4P _{0.3333 → 6 min}	3C,10P _{BL1 → 6 min} ^G	-	0.0	-	0.0	-
7 1C,3P _{BL1 → 6 min} ^B	1C,4P _{BL1 → 6 min}	-	0.0	-	0.0	-
8 1C,3P _{BL1 → 6 min}	2C,7P _{BL1 → 3 min}	-	0.10	-	0.22	-
9 1C,3P _{BL1 → 6 min}	2C,7P _{0.3333 → 6 min}	-	-	-	-	0.17
10 1C,3P _{BL1 → 6 min}	2C,7P _{BL1 → 6 min}	11.87*, ^C C_{om}	-	28.14*, ^C C_{om}	-	29.98*, ^C C_{om}
11 1C,3P _{BL1 → 6 min}	3C,10P _{BL1 → 6 min}	-	0.0	-	0.0	17.23*, ^C C_{om}
12 1C,4P _{BL1 → 6 min} ^C	2C,7P _{BL1 → 3 min}	-	0.15	-	0.19	-
13 1C,4P _{BL1 → 6 min}	2C,7P _{0.3333 → 6 min}	-	-	-	-	0.04
14 1C,4P _{BL1 → 6 min}	2C,7P _{BL1 → 6 min}	20.65*, ^C C_{om}	-	96.59*, ^C	-	25.39*, ^C C_{om}
15 1C,4P _{BL1 → 6 min} ^b	3C,10P _{BL1 → 6 min}	-	0.0	-	0.0	12.85*, ^C C_{om}
16 2C,7P _{BL1 → 3 min} ^b	2C,7P _{0.3333 → 6 min}	-	-	-	-	-
17 2C,7P _{BL1 → 3 min}	2C,7P _{BL1 → 6 min}	-	0.16	-	0.57	-
18 2C,7P _{BL1 → 3 min}	3C,10P _{BL1 → 6 min}	-	0.0	-	0.0	-
19 2C,7P _{0.3333 → 6 min} ^E	2C,7P _{BL1 → 6 min}	-	-	-	-	0.24
20 2C,7P _{0.3333 → 6 min} ^F	3C,10P _{BL1 → 6 min}	-	-	-	-	1.44*, ^C C_{om}
21 2C,7P _{BSL1 min → 6 min} ^F	3C,10P _{BSL1 min → 6 min}	-	-	-	-	1.79*, ^C C_{om}

All RSS and MSE data are mean ± SD. V_ET : estimated lactate threshold. -: it did not apply. RSS: residual sum of squares (expressed as RSS $\times 10^5$). MSE: mean square error. 1C, 2C, and 3C refer the one component, two components, and three components exponential mathematical models. 3P, 4P, 7P, and 10P refer the three, four, seven, and ten parameters respectively. A to G: seven fitting models as in table 1. ^aThe number of circular permutations (nP'x) for model comparisons (N) was calculated according to Zar (1996); i.e., $7P'2 = (7!)/[(7-2)! * 2] = 21$, permutations. ^bThe best statistical fit model was assessed using either the RSS values for models which fit the same number of experimental data points or the MSE values for models which fit a different number of experimental data points by performing a Fisher's test [F_{value}] at 0.05 level of significance and one tailed*: $F_{\text{tabulated}}[0.05 (1\alpha) = 1.15]$ (Motulsky and Ransnas, 1987; Zar, 1996). If $F_{\text{calculated}} > F_{\text{tabulated}}$ then "complex" model fits best; contrary wise, if $F_{\text{calculated}} < F_{\text{tabulated}}$, then "simple" model fits best. BL1: one min baseline. 0.3333 min: the VO_2 corresponding to 20 s after the end exercise with the recovery exercise transient. 3 min: three min recovery exercise transient. 6 min: six min recovery exercise transient. →: fitting (period of time) window.

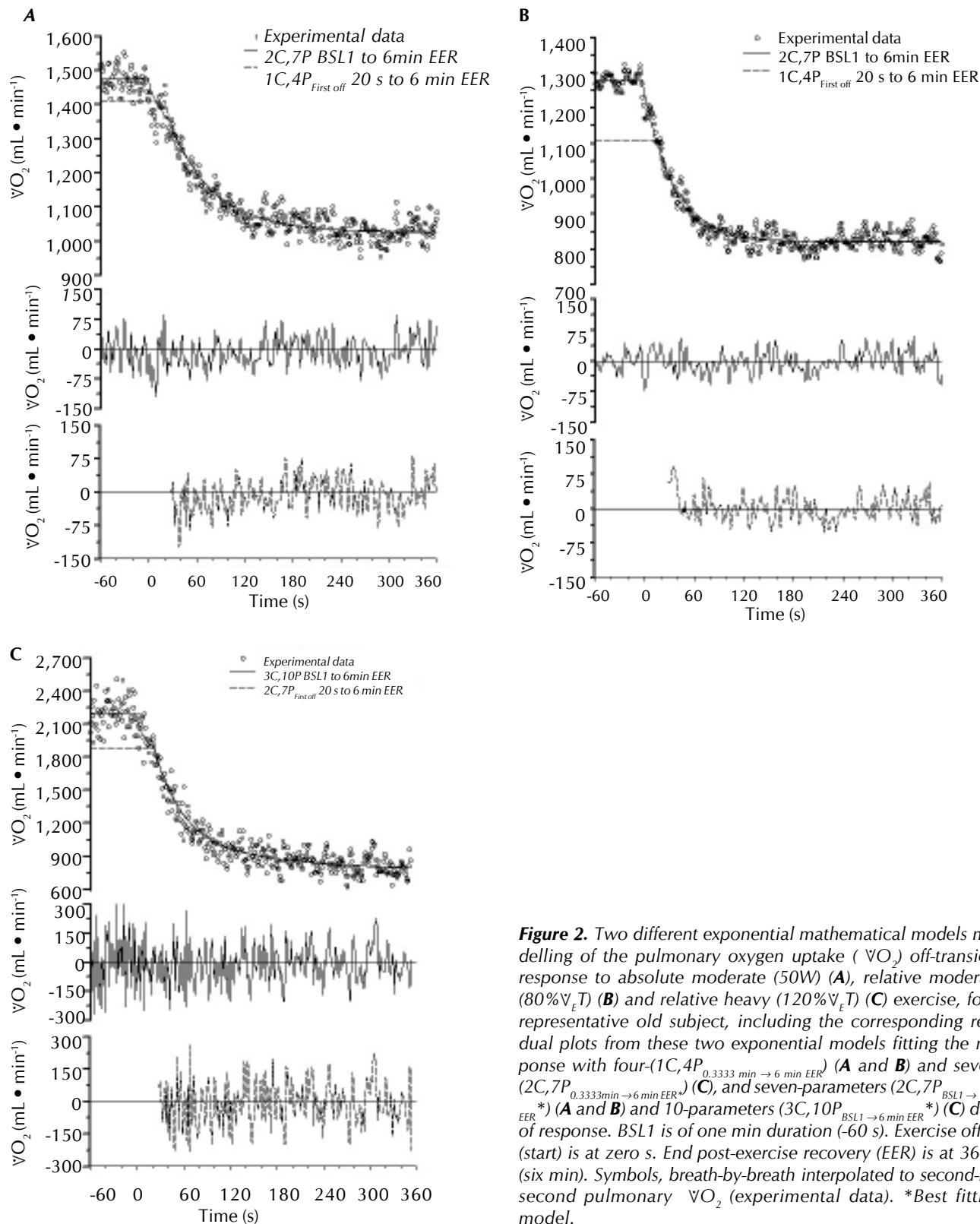


Figure 2. Two different exponential mathematical models modelling of the pulmonary oxygen uptake ($\dot{V}O_2$) off-transient response to absolute moderate (50W) (A), relative moderate (80% V_T) (B) and relative heavy (120% V_T) (C) exercise, for a representative old subject, including the corresponding residual plots from these two exponential models fitting the response with four-(1C,4P_{0.3333 min → 6 min EER}) (A and B) and seven-(2C,7P_{0.3333 min → 6 min EER}) (C), and seven-parameters (2C,7P_{BSL1 → 6 min EER}*) (A and B) and 10-parameters (3C,10P_{BSL1 → 6 min EER}*) (C) data of response. BSL1 is of one min duration (-60 s). Exercise offset (start) is at zero s. End post-exercise recovery (EER) is at 360 s (six min). Symbols, breath-by-breath interpolated to second-by-second pulmonary $\dot{V}O_2$ (experimental data). *Best fitting model.

Table 4. The best physiological and statistical fitting models and their exponential mathematical models, that characterized the (τ_2) phase two off-transient $\dot{V}O_2$ during submaximal (moderate and heavy) exercise in nine old men.

Exponential mathematical model	Fitting Model	$\tau\Phi_2 \dot{V}O_2$
Moderate intensity (50 Watts, 80 % $\dot{V}_E T$) exercise		
$\dot{V}O_2(t) = A_0 + A_1 \cdot [1 - e^{-(t-TD1)/\tau_2}] + A_2 \cdot [1 - e^{-(t-TD2)/\tau_2}]$	$\therefore \Phi_{2\text{Isolated_Stat \& Phys}} \dot{V}O_2(t) = A_0 + A_2 \cdot [1 - e^{-(t-TD2)/\tau_2}]$	$\tau''\Phi_1'', \tau\Phi_{2\text{Isolated_Stat \& Phys}}$
Relative (120 % $\dot{V}_E T$) Heavy intensity exercise		
$\dot{V}O_2(t) = A_0 + A_1 \cdot [1 - e^{-(t-TD1)/\tau_2}] + A_2 \cdot [1 - e^{-(t-TD2)/\tau_2}]$	$\therefore \Phi_{2\text{Semi-Isolated}} \dot{V}O_2(t) = A_0 + A_2 \cdot [1 - e^{-(t-TD2)/\tau_2}]$	$\tau''\Phi_1'', \tau\Phi_{2\text{Semi-Isolated}}$
$\dot{V}O_2(t) = A_0 + A_1 \cdot [1 - e^{-(t-TD1)/\tau_1}] + A_2 \cdot [1 - e^{-(t-TD2)/\tau_2}] + A_3 \cdot [1 - e^{-(t-TD3)/\tau_3}]$	$\therefore \Phi_{2\text{Isolated_Phys \& Stat}} \dot{V}O_2(t) = A_0 + A_2 \cdot [1 - e^{-(t-TD2)/\tau_2}]$	$\tau''\Phi_1'', \tau\Phi_2_{\text{Isolated_Stat \& Phys}}, \Phi_3''$

Exercise transient $\dot{V}O_2$: pulmonary $\dot{V}O_2$ uptake (O_2) corporal response from the end (off) of the exercise of an application of an ergometric forced function to the 6 min end exercise recovery. $\dot{V}_E T$: ventilatory threshold. Stat: statistically significant based on Fisher's test. Phys: physiological sense based on the differentiation of the phases and the numeric values of the estimated temporal parameters, of the transient $\dot{V}O_2$ response, according to the intensity of the exercise modelled. $\dot{V}O_2(t)$: mass rate of change per unit of time ($d \dot{V}O_2 / dt$), $\text{mL} \cdot \text{min}^{-1}$. TD: time delay. s : A_0 , baseline (the $\dot{V}O_2$ at the start of the model, A_0 is a "virtual" baseline). A : the $\dot{V}O_2$ distance value from A_0 to the $\dot{V}O_2$ required for phase one (A_1), phase two (A_2) and phase three (A_3) amplitudes, mL ; $1 - e^{-(t/\tau)}$, the negative exponential distribution (Evans, Hasting and Peacock, 1993); $e^{-(t/\tau)}$, the die-away factor with the time constant t (s), for an exponential increase (off-transient $\dot{V}O_2$ response); t : the time in which the transient $\dot{V}O_2$ response to die away to e^{-1} part ($e^{-1} = 1/2.71828 = 0.3678$) of its original value, thus, $\tau = 1 - 0.3678 = 0.63$, and $e = 2.718281 = [(1 + n^1)]^n$, $n \geq 10$ and 'e' is incommensurable with one. One component (1C), TD1. Two components (2C), TD1 and TD2. Three components (3C), 2C and TD3. 4P: four parameters ($a_1, a_2, a_3, TD2, \tau_2$). 7P: seven parameters ($a_0, a_1, a_2, TD1, TD2, \tau_1, \tau_2$); 10P, ten parameters (7P, $a_3, TD3, \tau_3$). The "Φ" means that even the mathematical exponential model fit the entire experimental data, phase one ("Φ₁") did not behave in an exponential way and probably phase three will not ("Φ₃").

phase one is extremely difficult to fit it and is less complex compared model G.²⁹

Estimated temporal parameters

- **• $\dot{V}O_2$ baseline (BSL).** As expected, models B, C, D, and F that fitted entire $\dot{V}O_2$ off-transient response to submaximal exercise showed similar baselines; and also the baseline from model G was similar to that from model F for heavy intensity exercise.
- **Functional gain (G, $\text{mL} \cdot \text{min}^{-1} \cdot \text{W}^{-1}$).** Analysis showed that the effect of submaximal exercise on the fundamental gain (G_2) resulted for MA exercise from model F low compared heavy intensity exercise, and MR exercise from model F low compared either heavy intensity exercise from model F or heavy intensity exercise from model G; and also the total gain (G_{TOT}) resulted for both the MA exercise from model F and the MR exercise from model F low compared either the heavy intensity exercise from model F or the heavy intensity exercise from

model G for the $\dot{V}O_2$ off-transient response. These differences in functional gains agreed with the fact that $\dot{V}O_2$ ($\text{mL} \cdot \text{min}^{-1} \cdot \text{W}^{-1}$) above ventilatory threshold exceeds that for moderate exercise.^{8 30-32}

- **Time delay (TD).** Analyses showed that the $TD\Phi_1 \dot{V}O_2$ entire (except model D) off-transient response from models B (single mono-exponential function), C (one component mono-exponential function), and D (two component bi-exponential function omitting the last three recovery min) resulted similar compared those from either M exercise or heavy intensity exercise, consistent with a system manifesting linear control dynamics for $\Phi_1 \dot{V}O_2$ off-transient response to submaximal exercise.^{8,15,17} In contrast, the $TD\Phi_2 \dot{V}O_2$ off-transient response from model A (one component mono-exponential function omitting $\Phi_1 \dot{V}O_2$) resulted low compared those from models D and F (two component doble-exponential function) for submaximal exercise; as well as, model E (two component bi-exponential function omitting $\Phi_1 \dot{V}O_2$) resulted low compared model G (three com-



ponent triple exponential function) for heavy intensity exercise, that we explain, on one side because those fitting models omitting one of the $\dot{V}O_2$ faces did no accomplish with the Phys merit and on the other hand, because at exercise intensity above $\dot{V}_E T$, the off-transient $\Phi_2 \dot{V}O_2$ response is more complex.^{3,5,15}

- **Time constant (τ).** Analyses showed that the $\tau \Phi_1 \dot{V}O_2$ off-transient response from models B, and C were higher compared those from either models D and model F for submaximal exercise or that from model G for heavy intensity exercise and this is due to the fact that those models did not fitted well neither Phys nor Stat the entire $\dot{V}O_2$ off-transient response.⁵ The $\tau \Phi_2 \dot{V}O_2$ off-transient response from the model F for heavy intensity exercise resulted low compared M intensity exercise, in agreement with the fact that the two component doble exponential function (model F) fitted well identifying two off-phases of response and kinetically characterized (off- $\tau \Phi_2 \dot{V}O_2$) both Phys and Stat merits (best off-Phys- $\tau \Phi_2 \dot{V}O_2$ -Stat) for M intensity exercise but not the more complex heavy intensity exercise off-transient response.^{8,17} Evermore, since during moderate intensity exercise the $\tau \dot{V}O_2$ is greater if exercise is initiated from a raised work rate and metabolic rate at the level of pulmonary gas exchange,³¹ then may be it also explain the slow off- $\tau \Phi_2 \dot{V}O_2$ for M exercise observed in our study, but the mechanisms responsible for these are under study.^{31,33} In contrast and, due to the current knowledge that off-transient phase two $\dot{V}O_2$ response is more complex with the off-transient supra- $\dot{V}_E T$, where it has been observed that this response consists of a 'fundamental' phase (off- $\Phi_2 \dot{V}O_2$) well described by an exponential, and subsequent delayed phase yielding a slowly developing supplemental rise in $\dot{V}O_2$ (off- $\Phi_3 \dot{V}O_2$) that could be much less prominent at the off-transient of less intensity exercise;^{8,15,32} the phase two $\tau \dot{V}O_2$ off-transient response from model F for MA intensity exercise and for MR intensity exercise resulted higher (longer kinetics) compared those from models E (two component bi-exponential function omitting $\Phi_1 \dot{V}O_2$) and G for heavy intensity exercise, in agreement on one hand with the observation that the $\dot{V}O_2$ kinetics across the recovery transient is independent of the metabolic profile during exercise and hence independent of the slow off- $\tau \Phi_3 \dot{V}O_2$ contribution to the particular exercise metabolic rate.^{2,34} On the other hand, small but consistent deviations from dynamic linearity in the $\dot{V}O_2$ response to moderate-intensity cycling have been reported by during square-wave transitions in different regions of the moderate-intensity domain.¹⁸ The two component bi-exponential function omitting $\Phi_1 \dot{V}O_2$ (model

E) for heavy intensity exercise only, should be useful when the off- $\Phi_1 \dot{V}O_2$ is very difficult to be well fitted with model G.^{21,29} In consequence, in this study the three component triple exponential function, fitted well and kinetically characterized (off- $\tau_2 \dot{V}O_2$) both Phys and Stat merits (best off-Phys- $\tau \Phi_2 \dot{V}O_2$ -Stat) for entire recovery- $\Phi_2 \dot{V}O_2$ transient response to heavy intensity exercise, allowing us to isolate off-Phys- τ_2 -Stat from both off- $\tau_1 \dot{V}O_2$ and off- $\tau_3 \dot{V}O_2$ entire response from 120% $\dot{V}_E T$ exercise domain. Since recovery oxygen consumption, reflects the metabolic demands of work transitions of the daily life, in addition to physiologic perturbations caused by exercise that last into recovery, then on studying the PER oxygen kinetics, these best fitting models (2C,7P_{PER} for M; 3C,10P_{PER} for H), they can be potentially useful for comparison among different experimental interventions in human physiology.

CONCLUSIONS

The statistical assessment of the $\Phi_2 \dot{V}O_2$ off-transient response to submaximal exercise in old men, with two component (2C) and three component (3C) exponential mathematical fitting models, showed that the two component doble-exponential function (2C,7Parameters) fitted entire $\dot{V}O_2$ off-transient response well and kinetically characterized off- $\tau \Phi_2 \dot{V}O_2$ both Phys and Stat merits (best off-Phys- $\tau \Phi_2 \dot{V}O_2$ -Stat) allowing us to isolate off-Phys- τ_2 -Stat from off- $\tau_1 \dot{V}O_2$ entire response for moderate (50W and 80% $\dot{V}_E T$) intensity PER. Also, the three component triple exponential function (3C,10Parameters), fitted entire $\dot{V}O_2$ off-transient response well and kinetically characterized off- $\tau_2 \dot{V}O_2$ both Phys and Stat merits (best off-Phys- $\tau \Phi_2 \dot{V}O_2$ -Stat) allowing us to isolate off-Phys- τ_2 -Stat from both off- $\tau_1 \dot{V}O_2$ and off- $\tau_3 \dot{V}O_2$ entire response for heavy (120% $\dot{V}_E T$) exercise domain. The 'fundamental' phase two $\dot{V}O_2$ sumaximal PER (off- $\Phi_2 \dot{V}O_2$) was both physiologically and statistically well described and kinetically characterized (off- $\tau_2 \dot{V}O_2$) by a two component doble exponential function for moderate-, and by a three component triple exponential function for heavy-intensity exercise in old men.

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