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Comparison of model estimates of phase two on-transient $\dot{V}O_2$ uptake kinetics during submaximal exercise in old men

Javier Padilla,*,** John M. Kowalchuk,**,*** Albert W. Taylor,**,**** Donald H. Paterson**,****

RESUMEN

Introducción. El análisis cinético de las respuestas transitorias de captación pulmonar de oxígeno ($\dot{V}O_2$) durante ejercicio moderado (M_{OD}) e intenso (I_{NT}) (M_{OD} + I_{NT} = S_{UB}) fueron comparados con estrategias comunes de modelado para evaluar el mejor. **Material y métodos.** Comparamos el parámetro estimado constante de tiempo para la fase 2 de $\dot{V}O_2$ ($\tau\Phi_2\dot{V}O_2$) en adultos mayores (n = 9; 71(± 5) años; media (± DE)). Estos hicieron una prueba de rampa (12 W•min^{-1}) hasta el límite de su tolerancia para determinar el $\dot{V}O_{2pico}$ y estimar el umbral láctico ($\hat{\theta}_L$). También hicieron ejercicio de carga constante a 50 Watts (M_{OD}) y a 80% (M_{OD}) y 120% $\hat{\theta}_L$ (I_{NT}). Cada transición de cada carga duró 6 min, fue precedida por 6 min de pedaleo a una línea de base de 20 W y se repitió de 4 a 6 veces por intensidad. El $\dot{V}O_2$ se medió de respiración por respiración. Los datos de cada transición fueron filtrados, interpolados a intervalos de 1 s y promediados en ensamblado para obtener un perfil de respuesta única por persona e intensidad y ajustados con regresión no lineal a base de modelos exponenciales de uno (1C; ventana apropiada desde 0.3333 min M_{OD} hasta su final o hasta la fase de transición 2 3 I_{NT}), dos (2C) y tres componentes (3C) desde el inicio hasta el final del ejercicio. Además, los datos fueron colocados en "bins" discretos de tiempo de 10 s (10 s bins) para modelarlos con 1C. **Resultados.** El 1C,4$P_{0.3333 \rightarrow 3\ min}$ fue el más apropiado para modelar la $\Phi_2\dot{V}O_2$ S_{UB} y distinguir $\tau\Phi_2\dot{V}O_2$. Los datos de la $\Phi_2\dot{V}O_2$ fueron fisiológicamente mejor modelados con 2C,7$P_{LíneaBasal_Inicio\ hasta\ FinalEjercicio}$ M_{OD} y 3C,10$P_{LíneaBasal_Inicio\ hasta\ FinalEjercicio}$ I_{NT} y, permitieron describir dentro del modelado la $\tau\Phi_2\dot{V}O_2$. Estas $\tau\Phi_2\dot{V}O_2$ fueron similares entre ellas en nuestros voluntarios (media general ± DE: $\tau_{datos\ de\ \dot{V}O2\ segundo\text{-}por\text{-}segundo}$ = 46 ± 15 s, $\tau_{datos\ de\ \dot{V}O2\ 10\text{-}s\ bins}$ = 43 ± 7 s).

Palabras clave: *Adultos mayores, cinética de la captación de O_2, fase dos del O_2; modelado exponencial, constante de tiempo.*

ABSTRACT

Introduction. The kinetic analysis of the $\dot{V}O_2$ on transient response during moderate (M_{OD}) and heavy (H_{VY}) intensity (M_{OD} + H_{VY} = S_{UB}) exercise was compared by using several common modelling strategies to assess the best one. **Material and methods.** We compared the parameter estimate for the phase 2 $\dot{V}O_2$ time constant ($\tau\Phi_2\dot{V}O_2$) in older male adults (n = 9; 71 (± 5) yrs; mean (± sd)). Subjects performed an incremental ramp test (12 W•min^{-1}) to the limit of tolerance to determine $\dot{V}O_{2peak}$ and the estimated lactate threshold ($\hat{\theta}_L$). Constant load cycle exercise was performed at 50 W (M_{OD}) and work rates corresponding to 80% (M_{OD}) and 120% $\hat{\theta}_L$(H_{VY}). 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. 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; fitting window 0.3333 min from exercise onset to either end M_{OD} or phase 2 3 transition H_{VY}), two (2C) and three component (3C) (fitting window from start exercise to end exercise) exponential models. In addition to this, data were placed into discrete time bins of 10 s (10 s bins $\dot{V}O_2$ data) to be modelled using 1C exponential model. **Results.** The 1C,4$P_{0.3333 \rightarrow 3\ min}$ best fitted $\Phi_2\dot{V}O_2$ data for S_{UB} and allowed us to characterize $\tau\Phi_2\dot{V}O_2$. The $\Phi_2\dot{V}O_2$ data were physiologically best fitted with models 2C,7$P_{BaseLine_Start\ to\ End\ exercise}$ for M_{OD} and 3C,10$P_{BaseLine_Start\ to\ End}$ for H_{VY} and they allowed us an intra modelling characterization of the $\tau\Phi_2\dot{V}O_2$. These $\tau\Phi_2\dot{V}O_2$ were similar to each other in our old male volunteers (Overall mean ± SD: $\tau_{second\text{-}by\text{-}second\ \dot{V}O2\ data}$ = 46 ± 15 s, $\tau_{10\text{-}s\ bins\ \dot{V}O2\ data}$ = 43 ± 7 s).

Key words: *Old men, O_2 uptake kinetics, phase two O_2, exponential modelling, time constant.*

* Escuela Superior de Medicina del Instituto Politécnico Nacional.
** Canadian Centre for Activity and Ageing, School of Kinesiology.
*** Department of Physiology and Faculties of Health Sciences &
**** Medicine and Dentistry, The University of Western Ontario, London, Ontario, Canada N6A 3K7.

INTRODUCTION

During whole-body exercise in normal people, the increased vascular conductance to improve muscle blood flow and oxygenation is the key to this on-transient elevation in pulmonary oxygen uptake ($\dot{V}O_2$). At the start (onset) of exercise, muscle blood flow and therefore O_2 delivery, increase to meet the metabolic demand of contracting muscle mass. Because O_2 delivery can have a profound effect on muscle metabolism and function,[1] it has been of considerable interest to understand the nature of cardiovascular control mechanisms responsible for adjusting muscle blood flow and O_2 delivery to muscle metabolic demand in terms of O_2 consumption ($\dot{V}O_{2\,consumption}$), specially in the ageing process of the human beings.[2-5] A simple and common approach has to investigate the dynamic response of $\dot{V}O_2$ to step transitions in exercise intensity, by mathematical modelling[1,6] of this $\dot{V}O_2$.on-transient response. In consequence, different exponential mathematical models has been used, in studies oriented to the quantification of the dynamic response characteristics of this physiological regulatory $\dot{V}O_2$ and $\dot{V}O_{2\,consumption}$ system, in the search of unique insight into underlying mechanisms not obtainable through examination of the steady state.[1] Quantifying the three parameters of a dynamic response, that is:

1. The time delay ($T_{ime}D_{elay}$) from onset of stimulus to onset of response.
2. Rate of adaptation of the response (τ, the time constant).
3. The magnitude of the response (amplitude or gain); and also determining the number of distinct phases of a O_2 on-transient response.[2-5]

Three main theoretical phases has been observed (Φ_1, Φ_2, Φ_3,) of the on-transient $\dot{V}O_2$ responses ($\Phi_1\dot{V}O_2$, $\Phi_2\dot{V}O_2$, $\Phi_3\dot{V}O_2$,) to an ergometric exercise.[1,6] The first $\Phi_1\dot{V}O_2$ named by Whipp[1] cardiodynamic phase, consists in an increased pulmonary perfusion with no significant change in the mixed venous O_2 and carbon dioxide (CO_2) tensions[1] and Whipp[2] postulated (p) that during $\Phi_1\dot{V}O_2$, the $\dot{V}O_2$ increases its response following the onset of exercise lasting approximately 20 s; so that, $\Phi_2\dot{V}O_2$ starts approximately 20 s after the beginning of exercise and finishes at 3 min exercise ($\Phi_{2postulated}\dot{V}O_2$).[1] The $\Phi_2\dot{V}O_2$ is an exponential instantaneously rate of change[2] that is proportional to the magnitude of response from a baseline or required level and it is of the most importance because it reflects the rate of increasing of $\dot{V}O_{2\,M}$. The $\Phi_2\dot{V}O_2$ begins at the end of $\Phi_1\dot{V}O_2$ and slows progressively towards its steady-state (asymptotic) value for moderate-intensity exercise ($M_{ODERATE}$) or unsteady-state (slow component) for heavy- intensity exercise (H_{EAVY}); ($M_{ODERATE}$ + H_{EAVY} $S_{UBMAXIMAL}$) . The end of $\Phi_2\dot{V}O_2$ is associated with a transient decrease of pulmonary respiratory exchange ratio as a result of increased muscle tissue storage of metabolic CO_2.[3] The $\Phi_3\dot{V}O_2$ is a slow increase in $\dot{V}O_2$ that ends in a plateau for $M_{ODERATE}$.[2] The $\Phi_3\dot{V}O_2$ consists in slow increase in $\dot{V}O_2$ named slow component for H_{EAVY}[4] and whether or not the slow component is an exponential response is motive of debate.[4,5]

These $\Phi_1\dot{V}O_2$, $\Phi_2\dot{V}O_2$, and $\Phi_3\dot{V}O_2$ on-transient responses to ergometric exercise have been described by monoexponential functions[7] that include $T_{ime}D_{elay}$ such as a one-component model (1C), an exponential function with one $T_{ime}D_{elay}$; twocomponent model (2C), two exponential terms with one $T_{ime}D_{elay}$ each one; and threecomponent model (3C), three exponential terms with a $T_{ime}D_{elay}$ for each one.[7] These exponential empirical 1C, 2C, and 3C models, allow us to screen for $\dot{V}O_2$ on-transient mass rate of change per unit of time ($\dot{V}O_2$ kinetics) during $S_{UBMAXIMAL}$. The $\dot{V}O_2$ kinetics assessment is based on the time required for the transient $\dot{V}O_2$ response to reach 63% of final amplitude named the kinetic parameter, time constant (τ).[5,7-9]

The purpose of this work consisted in assessing the best mathematical exponential models, previously published, to characterize the $\Phi_2\dot{V}O_2$ on-transient response ($\Phi_{2postulated}\dot{V}O_2$ and $\Phi_{2Isolated}\dot{V}O_2$) to $S_{UBMAXIMAL}$, in search for determinant mechanisms of the $\dot{V}O_2$ kinetics in old men. The comparison of modelling assessment techniques have been used to characterise $\dot{V}O_2$ kinetics during the on-transient of $S_{UBMAXIMAL}$ in young[5,8] but in old men it has not.

On one hand, $\dot{V}O_2$ Φ_2 on-transient kinetics is slow-age related;[10] on the other hand, body constitution is age-related;[11,12] and also the $\dot{V}O_2$ Φ_2 on-transient[3] is characterized by reduced venous oxygen content consequent to the increased muscle oxygen extraction due to the metabolic rate, which leads to a further increase in $\dot{V}_E$ and pulmonary gas exchange;[3,12] however, we do not know if the $\dot{V}O_2$ Φ_2 on-transient response to exercise intensity below estimated lactate threshold (below $\hat{\theta}_L$) and above $\hat{\theta}_L$ (above $\hat{\theta}_L$) ($S_{UBMAXIMAL}$) could be modelled differently in old men by the empirical exponential mathematical models already tested in young men.[5,8]

In the search for determinant mechanisms of this $\dot{V}O_2$ kinetic response and for "simplicity" we decided to assess in this study the Φ_2 $\dot{V}O_2$ on-transient kinetic ($\Phi_2\dot{V}O_2$ time constant)[5] response in old men. We addressed the following questions:

- Is there any exponential mathematical model that fitted statistically best $\Phi_{2postulated}\dot{V}O_2$ on-transient $S_{UBMAXIMAL}$ response?
- Which exponential mathematical model fitted either statistically or physiologically (or both) best the $\Phi_2\dot{V}O_2$ into the entire $\dot{V}O_2$ on-transient $S_{UBMAXIMAL}$ ($\Phi_{2\ Isolated}\dot{V}O_2$) response?
- Are the $\Phi_2\dot{V}O_2$ time constant values, from best fitting models, different from each other?

Hypothesis

If the exponential phase two $\dot{V}O_2$ on-transient response to $S_{UBMAXIMAL}$, is similarly modelled by different fitting models like the single monoexponential function, one-two-, and 3-component models in terms of time constant duration, thus these $\Phi_2\dot{V}O_2$ kinetic parameter ($\tau\Phi_2\dot{V}O_2$) estimated values from best fitting models should not be significantly different from each other, in old adults.

MATERIAL AND METHODS

The cardiopulmonary methodology used in this study has been already described somewhere else.[5,8] However, in brief as follows:

- ***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 (Beaver, et al., 1981). Inspired and expired air was sampled continuously (1 mL•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.[5] The electrocardiograph (Harco, Sauborn Model 500-1100) measures the bioelectric potentials of the heart, inputs the ECG signals into a computerized oscilloscope (Perking Elmer EM 530 B), and records these voltages in a microcomputer.[5] All the input signals were stored on a hard disc system for later analyses.
- ***Testing 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-braqued 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[8] for the determination of the $\hat{\theta}_L$, peak O_2 uptake ($\dot{V}O_{2peak}$), heart rate peak and maximal work rate.[8]
- ***$\dot{V}O_{2peak}$:*** The $\dot{V}O_2$ averaged over the final 15 s of the incremental test prior to fatigue was taken as $\dot{V}O_{2peak}$.
- ***Estimated lactate threshold ($\hat{\theta}_L$):*** The $\hat{\theta}_L$ as a non-invasive method was expressed as a percentage of the $\dot{V}O_2$max. The $\hat{\theta}_L$ was defined as the $\dot{V}O_2$ at which there was a systematic increase in the ventilatory equivalent for $\dot{V}_E/\dot{V}O_2$ and end-tidal PO_2, with no concomitant increase in the $\dot{V}_E/\dot{V}CO_2$, or decrease in the end-tidal PCO_2.[2,13-15] The $\dot{V}O_2$ corresponding to the time of the $\hat{\theta}_L$ was calculated as Wasserman, et al.;[16] as well as, the work rate corresponding to the $\dot{V}O_2$ at 80% and 120% $\hat{\theta}_L$ was calculated.[5] For example,[5] from the $\dot{V}O_2$ corresponding to the time of the $\hat{\theta}_L$ (*$\hat{\theta}_L\dot{V}O_2$ 1875, mL•min^{-1} 52.1%$\dot{V}O_{2max}$*) it was calculated the work rate corresponding to both the:

i) *80% $\hat{\theta}_L\dot{V}O_2$ expected (mL•min^{-1}) $\hat{\theta}_L\dot{V}O_2$ • 0.8 1875 • 0.8 1650, mL•min^{-1}*, and the
ii) *120% $\hat{\theta}_L\dot{V}O_2$ expected (mL•min^{-1}) $\hat{\theta}_L\dot{V}O_2$ • 1.2 1875 • 1.2 2220, mL•min^{-1}*; evermore, since the $\dot{V}O_2$ *equivalent (mL•min^{-1}) (10•Watts$_{BaseLine}$) + $\dot{V}O_{2BaseLine}$ (10 • 20) + 500 700, mL•min^{-1}*, then *the 100% $\hat{\theta}_L\dot{V}O_2$ equivalent (power in Watts) ($\hat{\theta}_L\dot{V}O_2$ - $\dot{V}O_2$ equivalent) / 10 (1875 - 700) / 10 117.5, W*; consequently, the
iii) *80% $\hat{\theta}_L\dot{V}O_2$ equivalent (W) [($\hat{\theta}_L\dot{V}O_2$ • 0.8) - $\dot{V}O_2$ equivalent] / 10 (1650 - 700) / 10 95, W*, and the
iv) *120% $\hat{\theta}_L\dot{V}O_2$ equivalent (W) [($\hat{\theta}_L$ $\dot{V}O_2$ • 1.2) - $\dot{V}O_2$ equivalent] / 10 (2220 - 700) / 10 152, W.*

- ***Submaximal constant-load leg cycling exercise tests ($S_{UBMAXIMAL}$):*** 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 $M_{ODERATE}$ or H_{EAVY}.[4,16] Three different intensities of $S_{UBMAXIMAL}$ were studied to determine $\dot{V}O_2$ on-transient kinetics and consisted in square waves of 50 W (absolute power output, $M_{ODERATE}$Abs), power outputs corresponding to 80% $\hat{\theta}_L$ (relative power output, $M_{ODERATE}$Rel) and 120% $\hat{\theta}_L$ (relative power output, H_{EAVY}Rel), with each subject performing all three exercise intensities during the curse of the study. The protocol began with 6 min loadless cycling, followed by a step increase in power output lasting 6 min in duration, and ending with a step decrease in power output back to loadless cycling. Changes in power output were initiated without warning the subject. Each subject performed 4-6 transitions for the $M_{ODERATE}$ protocols (Abs and Rel), and two to four repetitions for the H_{EAVY}Rel protocol. During each test, subjects pedalled while breathing to measure the ventilation and gas exchange calculated breath-by-breath[14] by a computer based programme.[5]

- ***Data analysis:*** The breath by breath $M_{ODERATE}$ and H_{EAVY} data were interpolated to 1 s interval, and each repetition was time aligned and assemble averaged to provide a single response for each subject for determining the kinetics of the $\dot{V}O_2$ on-transient response to $S_{UBMAXIMAL}$.[5] We determined in Φ_3 the magnitude of the $\Delta\dot{V}O_2$ data as the difference between the $\dot{V}O_2$ at the end exercise and the $\dot{V}O_2$ at 3 min of exercise ($\Delta\dot{V}O_{2(6\text{-}3min)}$). The $\dot{V}O_2$ at 3 min ($\dot{V}O_{2\_3min}$) was taken as mean between 2.75 and 3.15 min, and the end exercise $\dot{V}O_2$ ($\dot{V}O_{2\_6min}$) was taken as the mean $\dot{V}O_2$ during the last 0.25 min exercise. We also calculated the slope subthreshold $\dot{V}O_2$ - power relationship and the $\dot{V}O_2$ during loadless pedalling cycling.[5,8].
- ***Modelling:*** The breath-by-breath $\dot{V}O_2$ on-transient single response from each subject was modelled by using the 1C, 2C and 3C exponential mathematical expressions with eight different fitting models as follows.[5] The $M_{ono}E_{xponential}F_{unction}$ of the form $\dot{V}O_2(t)\quad a_{mplitude0} + a_{mplitude} \bullet [1-e^{-(t/\tau)}]$; presented as $\dot{V}O_2$(t) is the mass rate of change per unit of time ($d\dot{V}O_2 \bullet dt^{-1}$) assuming $T_{ime}D_{elay}\quad 0$; $a_{mplitude0}$ is the baseline; $a_{mplitude}$ is the $\dot{V}O_2$ distance value from $a_{mplitude0}$ to the $\dot{V}O_2$ required, or the difference between unloaded pedalling and end-exercise $\dot{V}O_2$ response ($\dot{V}O_{2EE}$); $1-e^{-(t/\tau)}$ is the negative exponential distribution,[17] $e^{-(t/\tau)}$ is the die-away factor with the time constant τ, for an exponential on-transient $\dot{V}O_2$ response increase, t is the time in which the transient $\dot{V}O_2$ response is gradually (exponentially) dying away; when t $\quad\tau$ it means that the time required for the transient $\dot{V}O_2$ response to die away to e^{-1} part ($e^{-1}\quad 1/2.71828\quad 0.3678$) of its original value, thus, $\tau\quad 1 - 0.3678\quad 0.63$, and $e\quad 2.718281\quad [(1 + n^{-1})]^n$, $n \geq 10$ and 'e' is incommensurable with 1. This single $M_{ono}E_{xponential}F_{unction}$ models with three parameters (3P: $a_{mplitude0}$, $a_{mplitude}$, and τ) (1C,3P). The 1C is the $M_{ono}E_{xponential}F_{unction}$ with the inclusion of $T_{ime}D_{elay}$ (named onecomponent)[7] that it brought about the 1C with 4P ($a_{mplitude0}$, $a_{mplitude}$, $T_{ime}D_{elay}$, and τ),[5,18,19], expressed as follows (1C,4P): $\dot{V}O_2(t)\quad a_{mplitude0} + a_{mplitude} \bullet [1-e^{-[(t-TimeDelay)/\tau]}]$.
  The 2C consists in a doble $M_{ono}E_{xponential}F_{unction}$ with $T_{ime}D_{elay}1$ and $T_{ime}D_{elay}2$ included, and for this reason it models two gapped exponential transient periods of time with 7P ($a_{mplitude0}$, $a_{mplitude1}$, $T_{ime}D_{elay}1$, $\tau1$, $a_{mplitude2}$, $T_{ime}D_{elay}2$, and $\tau2$),[6,20,21] expressed as follows (2C,7P): $\dot{V}O_2(t)\quad a_{mplitude0} + a_{mplitude1} \bullet [1-e^{-[(t-TimeDelay1)/\tau1]}] + a_{mplitude2} \bullet [1-e^{-[(t-TimeDelay2)/\tau2]}]$.
  The 3C consists in a triple $M_{ono}E_{xponential}F_{unction}$ with $T_{ime}D_{elay}1$, $T_{ime}D_{elay}2$ and $T_{ime}D_{elay}3$ included, and for this reason it models three gapped exponential transient periods of time with 10P ($a_{mplitude0}$, $a_{mplitude1}$, $T_{ime}D_{elay}1$, $\tau1$, $a_{mplitude2}$, $T_{ime}D_{elay}2$, $\tau2$, $a_{mplitude3}$, $T_{ime}D_{elay}3$, $\tau3$,),[6] expressed as follows (3C,10P): $\dot{V}O_2(t)\quad a_{mplitude0} + a_{mplitude1} \bullet [1-e^{-[(t-TimeDelay1)/\tau1]}] + a_{mplitude2} \bullet [1-e^{-[(t-TimeDelay2)/\tau2]}] + a_{mplitude3} \bullet [1-e^{-[(t-TimeDelay3)/\tau3]}]$.
  When 3C,10P is constrained to $T_{ime}D_{elay}2\quad T_{ime}D_{elay}3$ then the threecomponent model is identified as 3C,9P (constrained 3C,10P).[22] The Φ_2 $\dot{V}O_2$ τ estimate parameter of the response was compared together with a statistical analysis of how well each model fit the $\dot{V}O_2$. We specifically addressed:

  - The effect of incorporating the analysis of Φ_1 $\dot{V}O_2$ data within a model to physiologically isolate Φ_2.
  - The effect of incorporating the analysis of Φ_3 $\dot{V}O_2$ data within a model to physiologically isolate Φ_2 and to statistically isolate Φ_2, based on Fisher test.[23]
  - Differences between fitting entire $\dot{V}O_2$ on-transient response *versus* a fitting window for Φ_2 $\dot{V}O_2$ on-transient data.

  The acceptability of the fitting models were also assessed primarily on whether the information provided by the models was consistent with current understanding of the $\dot{V}O_2$ on-transient response ($\Phi_{2\_PhysBestFit}$ $\dot{V}O_2$); as well as, statistical merits ($\Phi_{2\_StatBestFit}$ $\dot{V}O_2$). In addition to this, data were placed into discrete time-bins of 10 s (10-s bins $\dot{V}O_2$ data) to be modelled using 1C exponential mathematical expression. Eight fitting models were expressed as follows: $1C,4P_{0\ 3333 \to 3\ min}$, $1C,4P_{0.3333 \to 6\ min}$, and $2C,7P_{BL2 \to 3\ min}$ (BL2, two min baseline) to estimate $\tau\Phi_{2postulated}$; $2C,7P_{BL2 \to 6\ min}$, $3C,9P_{BL2 \to 6\ min}$, and $3C,10P_{BL2 \to 6\ min}$ to estimate τ from an isolated Φ_2 ($\tau\Phi_{2\ Isolated}$) with the second exponential term of these multi-component fitting models. These multi-component fitting models were used to assess the best physiological ($\Phi_{2\ IsolatedPhysBestFit}$), statistical ($\Phi_{2\_StatBestFit}$) and both ($\Phi_{2\ Isolated\_PhysStat\ BestFit}$) fit of Φ_2 $\dot{V}O_2$ on-transient response to submaximal exercise. The $1C,4P_{BL2 \to 6\ min}$ and $1C,3P_{BL2 \to 6\ min}$ that fitted the entire on-transient $\dot{V}O_2$ data set, were used to assess the best fit compared to multiple component models. The kinetic analysis of phase two $\dot{V}O_2$ was assessed in terms of the $\tau\Phi_2$ ($\tau2$, time constant two).
- ***Statistical analyses:*** The goodness of fit for each fitting model was assessed using the lowest residual sum of squares (RSS values) from a computerized nonlinear regression technique:[24]

$$F = ((SS_1 - SS_2)/(df_1 - df_2))/(SS_2/df_2)$$

Where *SS* is the residual sum of squares of each fit, df is the number of degrees of freedom, the suffixes *1* and *2* refer to the models being compared where suffix 1 refers to the model with the fewest parameters. 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, the deviations within- models mean square) 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).[5,23,25] The number of circular permutations for model comparisons (nP´x) was calculated according to Zar[25] and expressed as a factorial function:[5]

$$nP'x = n! / [(n - x)!(x)]$$

Were nP´x is the number of different ways of arranging two out (x 2) of n (n 8) mathematical models in circular "arrangement". For example,[5,23,25] on the assessment of the:

i) 2C,7P $_{BaseLine\_0\ to\ 6\ min\ for\ Hvy}$ (data: RSS_1 19743532, NDP_1 360, NP_1 7, df_1 360 - 7 353) *versus* 3C,10P$_{from\ MinBaseLine_0\ to\ 6\ min\ for\ Hvy}$ (data: RSS_2 11826244; NDP_2 360, NP_2 10, df_2 360 - 10 350) with $F_{valueRSS}$ $[(RSS_1 - RSS_2) / (df_1 - df_2)] / (RSS_2 / df_2)$ $[(19743532_1 - 11826244_2) / (353_1 - 350_2)] / (11826244_2 / 350_2)$, $F_{valueRSS}$ *(21.3)* resulted significantly high compared $F_{tab,1\alpha}$ (1.10, P < 0.05); consequently, complex model (3C,10P) statistically best fitted $\dot{V}O_2$ on-transient experimental data for heavy intensity exercise.[5] On the assessment[5,23,25] of the
ii) 1C,4P$_{from\ 0.3333\ to\ 3\ min\ for\ ModAbs}$ (data: MSE_1 280528, NDP_1 160, NP_1 4, df_1 160 - 4 156) *versus* 2C,7P$_{from\ BaseLine_0\ to\ 6\ min\ for\ ModAbs}$ (data: MSE_2 1348; NDP_2 360, NP_2 10, df_2 360 - 7 353) with $F_{valueMSE}$ $[(MSE_1 - MSE_2) / (df_1 - df_2)] / (MSE_2 / df_2)$ $[(280528_1 - 1348_2) / (156_1 - 353_2)] / (1348_2 / 353_2)$, $F_{valueMSE}$ *(371.1)* resulted significantly high compared $F_{tab,1\alpha}$ (1.23, P < 0.05); consequently, complex model (2C,7P) statistically best fitted $\dot{V}O_2$ on-transient experimental data for moderate absolute intensity exercise.[5] The eight exponential mathematical fitting models used in this study were four simple (1C,4P$_{0.3333 \to 3\ min}$, 1C,4P$_{0\ 3333 \to 6\ min}$, 1C,3P$_{BL2 \to 6\ min}$, 1C,4P$_{BL2 \to 6\ min}$) and four complex (2C,7P$_{BL2 \to 3\ min}$, 2C,7P$_{BL2 \to 6\ min}$, 3C,9P$_{BL2 \to 6\ min}$ and,3C,10P$_{BL2 \to 6\ min}$) models. Data treatment consisted of group analyses performed using either a ANOVA with Student-Newman-Keuls and Tukey *post-hoc* analyses or Kruskal-Wallis ANOVA on Ranks procedure Dunns' 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.[25] Student t-test was used to assess for significant differences between the estimated parameter means from two groups with the same number of parameters.[25] The probability level denoted significance at p ≤ 0.05. Except where otherwise stated, the estimated parameters are presented as mean ± $s_{TANDARD}d_{EVIATION}$.

RESULTS

Physical characteristics and ramp exercise test

The physical characteristics, maximal cardiorespiratory and $\hat{\theta}_L$ values are presented in table 1. The $\dot{V}O_{2End\ Exercise}$, exercise intensity expressed as absolute power output ($M_{ODERATE}$Abs) and relative ($M_{ODERATE}$Rel, H_{EAVY}Rel) to the $\hat{\theta}_L$ (% $\hat{\theta}_L$) are presented in table 2. The power output (W), significantly lasted $M_{ODERATE}$ low compared H_{EAVY} (Table 2). The square wave test $\dot{V}O_{2End\ Exercise}$, significantly lasted {$M_{ODERATE}$ lower than H_{EAVY}} (Table 2) different from $\dot{V}O_{2\ \hat{\theta}L}$ (except $M_{ODERATE}$) (Table 1). The $\dot{V}O_2$ relative exercise intensity the $\hat{\theta}_L$ (% $\hat{\theta}_L$) lasted $M_{ODERATE}$ low compared H_{EAVY} (Table 2). The W relative exercise intensity the $\hat{\theta}_L$, calculated as $W_{\_intensity\ exercise}$ / $W_{\_\hat{\theta}L}$, lasted (%): $M_{ODERATE}$Abs (82.2 ± 16.3) lower than-$M_{ODERATE}$Rel (57.0 ± 4.6) lower than H_{EAVY}Rel (143.2 ± 4.7) (F_{ratio} 29, P < 0.0001). The $\dot{V}O_{2\_6min}$ on-transient significantly lasted $M_{ODERATE}$ low compared H_{EAVY} (F_{ratio}

Table 1. Anthropometric, maximal ramp test and estimated lactate threshold cardiorespiratory data in nine old men.

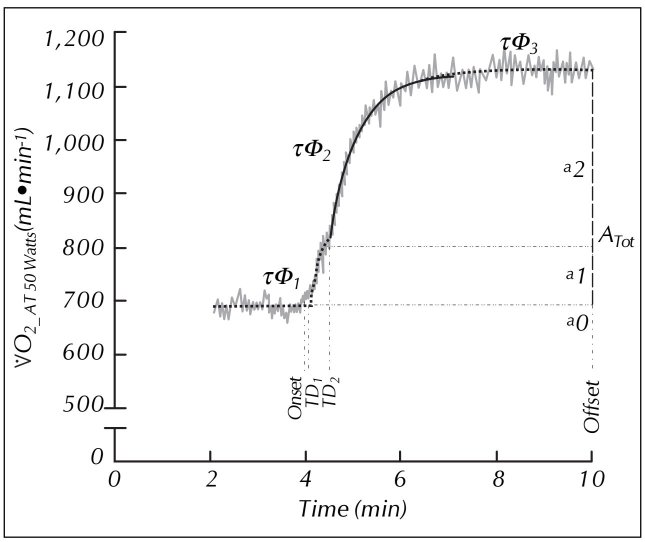
Age (years)	Height (cm)	Total Body Mass (kg)	Work Rate (Watts)	$\dot{V}O_2$peak (L•min-1)	$\dot{V}O_2$peak (mL•kg-1•min-1)	Heart Rate Experimental (beats•min-1)	Heart Rate 220 Age (beats•min-1)	$E_{stimated}$ L_{actate} $T_{hreshold}$ (mL•min-1)	$E_{stimated}$ L_{actate} $T_{hreshold}$ (% $\dot{V}O_2$peak)
70.7 ± 4.7	173.9 ± 5.5	79.8 ± 10	128.4 ± 20.8	2.2 ± 0.4	28.3 ± 7.2	158.3 ± 14.9	149.3 ± 4.7	1,333 ± 139	61.7 ± 8.0

Numeric values are mean ± sd.

Table 2. Data for exercise at the same absolute power output (PO), and during relative intensity exercise below (moderate) and above (heavy) the estimated lactate threshold ($\hat{\theta}_L$) in nine old men.

Absolute PO (50 Watts)[e]			Moderate Relative(80% $\hat{\theta}$)				Heavy relative (120% $\hat{\theta}$)				
$\dot{V}O_2$ (mL•min-1)	% $\hat{\theta}_L$	% $\dot{V}O_2$peak	PO (W)	$\dot{V}O_2$ (mL•min-1)	% $\hat{\theta}_L$	% $\dot{V}O_2$peak	PO (W)	$\dot{V}O_2$ (mL•min-1)	% $\hat{\theta}_L$	% $\dot{V}O_2$peak	$\hat{\theta}_L$ (W)
1180[a] ± 145	89[i] ± 15	56[k] ± 15	37[e,g] ± 11	1050[a,c] ± 198	79[i] ± 12	49[k] ± 11	90[f] ± 17	1,770[b] ± 333	121[j] ± 17	81[l] ± 14	63[h] ± 14

Numeric values are mean ± sd. Significant differences between means with different letter, allocated by ANOVA procedure Tukey test: a≠b;c≠dF_{ratio} = 19.5, P < 0.001 (included differences from mean $\dot{V}O_2$ $\dot{V}_ET$ = 1333 ± 139[a,d], mL•min-1); Kruskal Wallis ANOVA based on Ranks: e≠f;g≠hH_{ratio} = 26.8, P < 0.001; Student Newman Keuls test: i≠jF_{ratio} = 35.6, P < 0.001; Student Newman Keuls test: k≠lF_{ratio} = 12, P < 0.001 (included differences from mean $\dot{V}O_2$ $\dot{V}_ET$ % $\dot{V}O_2$peak = 62 ± 7.8[k], %). % $\dot{V}_ET$ calculated as ($\dot{V}O_2$ exercise intensity) / $\dot{V}O_2\dot{V}_ET$) • 100. % $\dot{V}O_2$peak calculated as ($\dot{V}O_2$ exercise intensity)/$\dot{V}O_2$peak) • 100.



Experimental data
1C,4P0.3333→3 min: τΦ2P = 36 s
2C,7PBL2→6 min: τΦ2Iso_Phys = 41 s

Figure 1. *Oxygen uptake ($\dot{V}O_2$) time course during the on transient of moderate intensity (50 W) exercise. Exercise onset (start) is at six min. Exercise offset (end) is at six min. The best intra phase two data fit for the postulated (p) phase two ($\Phi_{2postulated}$) $\dot{V}O_2$ was $1C,4P_{0.3333 \rightarrow 3\ min}$ ($\Phi_{2postulated}$) fitting model. The best physiologically (Phys) fit for the isolated phase two (Φ_{2Iso}) $\dot{V}O_2$ was the $2C,7P_{BL2 \rightarrow 6\ min}$ (Φ_{2Iso_Phys}) fitting model ($2C,7P_{Baseline\_Onset\ to\ Offset}$). Estimates for the time required to reach 63% of final amplitude (τ) are with reference to phase two ($\tau\Phi_{2postulated}$; $\tau\Phi_{2Iso\_Phys}$). The characteristic seven parameters (7P) of a twocomponent exponential model (2C) describing this $\dot{V}O_2$ time course data are as followed: a_0 is the baseline $\dot{V}O_2$ (2C model started fitting from 2 min baseline, BL2, before the onset to the offset of the exercise); a_1 and a_2 (long dashed lines) are the increases in the amplitude of $\dot{V}O_2$ above the baseline value; $\tau 1$ and $\tau 2$ are the time constants; TD_1 and TD_2 are the time delays; and $A_{Tot} = a_1 + a_2$. The $2C,7P_{BL2 \rightarrow 6\ min}$ Phys differentiates Φ_2 $\dot{V}O_2$ from both Φ_1 $\dot{V}O_2$ and Φ_3 $\dot{V}O_2$ on transient entire response data.*

7.5, P < 0.0001) (Table 2), and the $\dot{V}O_{2\_3min}$ on-transient also lasted as followed (mL•min-1): {$M_{ODERATE}$Abs (1119 ± 153) similar $M_{ODERATE}$Rel (1022 ± 193)} lower than H_{EAVY}Rel (1574 ± 235) (F_{ratio} 13, P < 0.0001). Finally, only H_{EAVY}Rel showed $\dot{V}O_{2\_6min}$ (mL•min-1) on-transient significantly (F_{ratio} 4, P < 0.03) higher (1770 ± 333) than $\dot{V}O_{2\_3min}$ on-transient (1574 ± 235), confirming that this exercise intensity was below $\hat{\theta}_L$ ($\Delta\dot{V}O_{2(6\text{-}3min)}$ 197 ± 70).

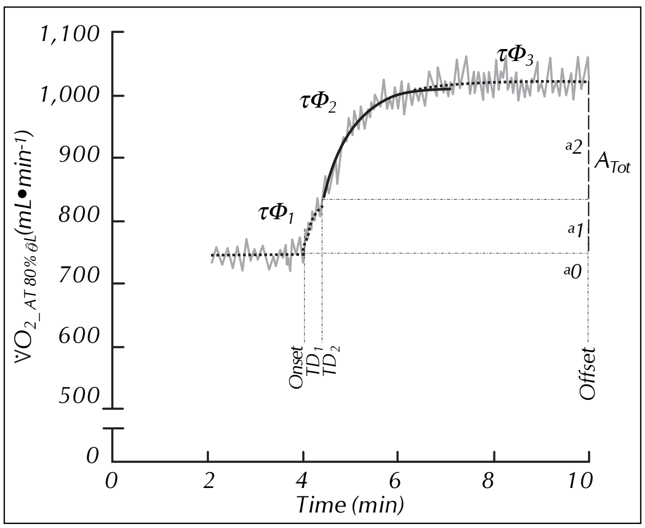
$\dot{V}O_2$ linear regression

The slope (coefficient) of the $M_{ODERATE}$ $\dot{V}O_2$ - power output relationship and the $\dot{V}O_2$ during loadless cycling (constant) were: $\dot{V}O_2$ $M_{ODERATE}$ 569.53 + (12.43 • W), n 18, R 0.98, P < 0.001 and $\dot{V}O_{2\_loadless}$ 751 ± 127 mL•min-1.

Mathematical Modelling

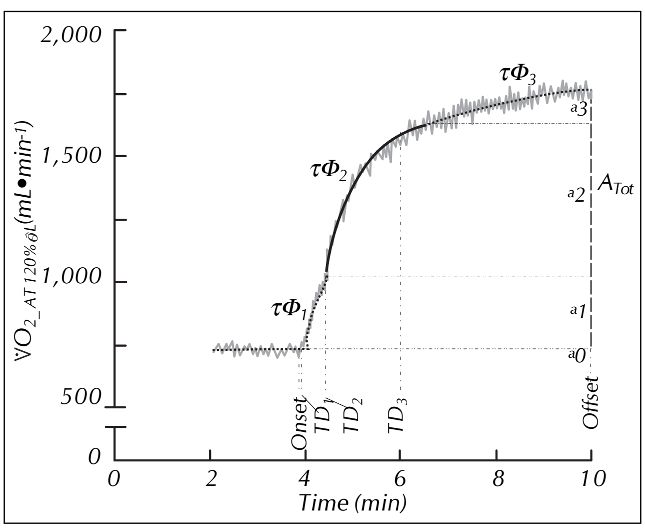
We have compared estimates of on-transient phase two pulmonary O_2 uptake time constant (Φ_2 $\dot{V}O_2$ τ) by eight empirical exponential mathematical fitting models of $\dot{V}O_2$ data during moderate- and heavy-intensity exercise in old men. For $M_{ODERATE}$, the most convenient best intra- Φ_2 $\dot{V}O_2$ fit was provided by a onecomponent exponential model, which omitted Φ_1 $\dot{V}O_2$ data, that fitted from 20 s after the exercise onset to a presumed steady-state at 3 min and underestimated T_{ime}Delay2. The estimate of Φ_2 $\dot{V}O_2$ τ provided by onecomponent exponential model was similar to that provided by the best physiologically Φ_2 $\dot{V}O_2$ fit, a two exponential model, that fitted from baseline_exercise onset to exercise offset. Both models (1C and 2C) had physiological significance as they focussed, $1C,4P_{0.3333 \rightarrow 3\,min}$ modelling intra-Φ_2 $\dot{V}O_2$ and $2C,7P_{BaseLine\_Onset\ to\ Offset}$ modelling into the entire data and also physiologically isolating Φ_2 $\dot{V}O_2$, upon the area of the on-transient data which reflected working muscle $\dot{V}O_2$. For H_{EAVY}, $\dot{V}O_2$ was best modelled with a threecomponent exponential model that was fit throughout the entire data set. The $3C,10P_{BaseLine\_Onset\ to\ Offset}$ modelling H_{EAVY} response data was both statistically best compared $2C,7P_{BaseLine\_Onset\ to\ Offset}$ and physiologically best compared $1C,4P_{0\ 3333 \rightarrow 3\,min}$, $2C,7P_{BaseLine\_Onset\ to\ Offset}$ and $3C,9P_{BaseLine\_Onset\ to\ Offset}$. These more convenient ($1C,4P_{0.3333 \rightarrow 3\,min}$ modelling $S_{UBMAXIMAL}$ response data) and best physiological fitting models ($2C,7P_{BaseLine\_Onset\ to\ Offset}$ modelling $M_{ODERATE}$ response data or $3C,10P_{BaseLine\_Onset\ to\ Offset}$ modelling H_{EAVY} response data) showed on-transient Φ_2 $\dot{V}O_2$ τ estimated values similar in older men, that seem to be correct in order to kinetically compare the on-transient pulmonary Φ_2 $\dot{V}O_2$ data (Φ_2 $\dot{V}O_2$ τ) of submaximal exercise in young *versus* old men. Our research on this topic is guaranteed.

An example of the $\dot{V}O_2$ time course for $M_{ODERATE}$Abs, $M_{ODERATE}$Rel and H_{EAVY}Rel tests are presented in figures 1-3 respectively. Examples of the best fitting models for $\Phi_{2postulated}$ with $1C,4P_{0.3333 \rightarrow 3\,min}$ and Φ_{2Iso} with $2C,7P_{BL2 \rightarrow 6\,min}$



Experimental data
$1C,4P_{0.3333 \rightarrow 3\,min}$: $\tau\Phi_{2P}$ = 37 s
$2C,7P_{BL2 \rightarrow 6\,min}$: $\tau\Phi_{2Iso\_Phys}$ = 44 s

Figure 2. *Oxygen uptake ($\dot{V}O_2$) time course during the on transient of moderate intensity (80% $\hat{\theta}_L$) exercise. Exercise onset (start) is at six min. Exercise offset (end) is at six min. The best intra phase two data fit for the postulated (p) phase two ($\Phi_{2postulated}$) $\dot{V}O_2$ was $1C,4P_{0.3333 \rightarrow 3\,min}$ ($\Phi_{2postulated}$) fitting model. The best physiologically (Phys) fit for the isolated phase two (Φ_{2Iso}) $\dot{V}O_2$ was the $2C,7P_{BL2 \rightarrow 6\,min}$ (Φ_{2Iso_Phys}) fitting model ($2C,7P_{Baseline\_Onset\ to\ Offset}$). Estimates for t (time required to reach 63% of final amplitude) are with reference to phase two ($\tau\ \Phi_{2postulated}$; $\tau\ \Phi_{2Iso\_Phys}$). $\hat{\theta}_L$, estimated lactate threshold.*



Experimental data
$1C,4P_{0.3333 \rightarrow 3\,min}$: $\tau\Phi_{2P}$ = 45.48 s
$3C,10P_{PBL2 \rightarrow 6\,min}$: $\tau\Phi_{2Iso\_Phys\&Stat}$ = 43.59 s

Figure 3. *Oxygen uptake ($\dot{V}O_2$) time course during the on transient of heavy intensity (120% $\hat{\theta}_L$) exercise. Exercise onset (start) is at six min. Exercise offset (end) is at six min. The best intra phase two data fit for the postulated (p) phase two ($\Phi_{2postulated}$) $\dot{V}O_2$ was $1C,4P_{0.3333 \rightarrow 3\,min}$ ($\Phi_{2postulated}$) fitting model. The best both physiologically (Phys) and statistically (Stat, based on Fisher' test) fit for the isolated phase two (Φ_{2Iso}) $\dot{V}O_2$ was the $3C,10P_{BL2 \rightarrow 6\,min}$ ($\Phi_{2Iso\_PhysStat}$) fitting model ($3C,10P_{Baseline\_Onset\ to\ Offset}$). Estimates for τ (time required to reach 63% of final amplitude) are with reference to phase two ($\tau\ \Phi_{2postulated}$; $\tau\ \Phi_{2Iso\_p}$). The characteristic ten parameters (10P) of a threecomponent exponential model (3C) describing this $\dot{V}O_2$ time course data are as followed: a_0 is the baseline $\dot{V}O_2$ (3C model started fitting from 2 min baseline, BL2, before the onset to the offset of the exercise); a_1, a_2 and a_3 (long dashed lines) are the increases in the amplitude of $\dot{V}O_2$ above the baseline value; $\tau1$, $\tau2$ and $\tau3$ are the time constants; TD_1, TD_2 and TD_3 are the time delays; and $A_{Tot} = a_1 + a_2 + a_3$. The $3C,10P_{BL2 \rightarrow 6\,min}$ Phys differentiates Φ_2 $\dot{V}O_2$ from both Φ_1 $\dot{V}O_2$ and Φ_3 $\dot{V}O_2$ on transient entire response data. $\hat{\theta}_L$, estimated lactate threshold.*

are presented in figures 1 and 2 for $M_{ODERATE}$. Examples of the best fitting models for $\Phi_{2postulated}$ with $1C,4P_{0.3333 \rightarrow 3\ min}$ are shown in figures 3 and 4 and for $\Phi_{2\ Isolated}$ are also presented in figure 3 with $3C,10P_{BL2 \rightarrow 6\ min}$ ($\Phi_{2\ Isolated\_PhysStat\ BestFit}$) and figure 4 with $3C,9P_{BL2 \rightarrow 6\ min}$, $\Phi_{2\text{"Isolated"}\_Stat\ BestFit}$ for H_{EAVY}.

The RSS and MSE estimates for kinetic analysis of $\dot{V}O_2$ during the on-transient of steady-state $S_{UBMAXIMAL}$ as estimated by eight different fitting models are presented in table 3. The mathematical model permutations of 1C, 2C and 3C comparisons for the on-transient $\dot{V}O_2$ $S_{UBMAXIMAL}$ responses are presented in table 4. The amplitude and the parameter estimates determined from kinetic analyses of $\dot{V}O_2$ during the on-transient of steady-state exercise, as estimated by the best fitting models from these study, are presented in table 4 for $M_{ODERATE}$ and H_{EAVY}. Amplitudes from $\Phi_{2\ Isolated}\dot{V}O_2$ and $\Phi_3\dot{V}O_2$ during the on-transient of steady-state H_{EAVY} were different in model $3C,9P_{BL2 \rightarrow 6\ min}$ compared to model $3C,10P_{Bl2 \rightarrow 6\ min}$ (Table 5).

Onecomponent fitting model comparisons

Both $1C,4P_{BL2 \rightarrow 6\ min}$ and $1C,3P_{BL2 \rightarrow 6\ min}$ were not physiologically useful for fitting $\dot{V}O_2$ on-transient entire response data to characterize Φ_2 $\dot{V}O_2$ for $S_{UBMAXIMAL}$. The simple one model $1C,4P_{0.3333 \rightarrow 3\ min}$ fitted (Figures 1-3)

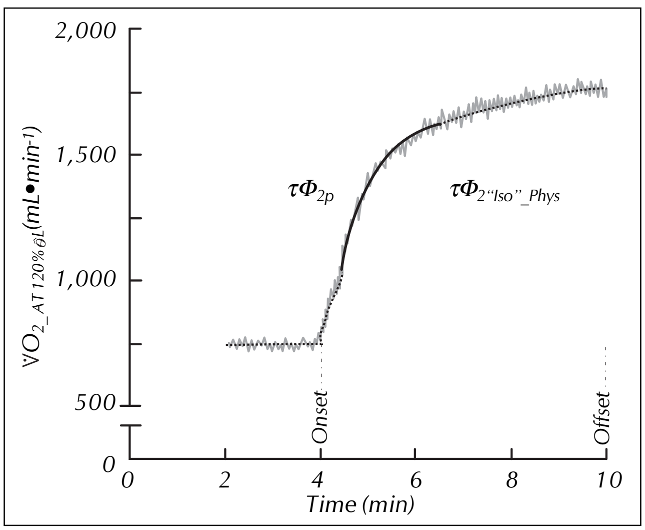


Figure 4. *Oxygen uptake ($\dot{V}O_2$) time course during the on transient of heavy intensity (120% θ_L) exercise. Exercise onset (start) is at six min. Exercise offset (end) is at six min. The best fit for the postulated (p) phase two ($\Phi_{2postulated}$) $\dot{V}O_2$ was the simple $1C,4P_{0.3333 \rightarrow 3\ min}$ ($\Phi_{2postulated}$) fitting model. The best statistically fit for "isolated" phase two (Φ_2) $\dot{V}O_2$ was the restricted ($T_{ime}D_{elay2} = T_{ime}D_{elay3}$) 3C or $3C,9P_{BL2 \rightarrow 6\ min}$ ($\Phi_{2\text{"Iso"}\_Stat}$) fitting model ($3C,9P_{Baseline\_Onset\ to\ Offset}$). Estimates for τ (time required to reach 63% of final amplitude) are with reference to phase two ($\tau\Phi_{2postulated}$; $\tau\Phi_{2\text{"Iso"}\_Phys}$). The $3C,9P_{BL2 \rightarrow 6\ min}$ Phys differentiates Φ_2 $\dot{V}O_2$ from Φ_1 $\dot{V}O_2$ but not from Φ_3 $\dot{V}O_2$ on transient entire response data. θ_L, estimated lactate threshold.*

Table 3. Residual sum of squares and mean square error estimates for kinetic analysis of $\dot{V}O_2$ during the on transient of steady state submaximal exercise as estimated by eight different exponential mathematical models in nine old men.

	Work Rate					
			Estimated Ventilatory Threshold			
	50 Watts		80%		120%	
Fitting Model	RSS (x10^5)	Mean Square Error	RSS (x10^5)	Mean Square Error	RSS (x10^5)	Mean Square Error
$1C,4P_{0.3333 \rightarrow 3\ min}$	2.07 ± 0.64	1324 ± 408	3.07 ± 2.70	1965 ± 1731	6.31 ± 8.31	4050 ± 5332
$1C,4P_{0.3333 \rightarrow 6\ min}$	4.73 ± 1.75	1409 ± 522	6.29 ± 4.60	1870 ± 1369	14.85 ± 20.15	4420 ± 5997
$1C,3P_{BL2 \rightarrow 6\ min}$	7.61 ± 3.47	1536 ± 619	7.77 ± 5.61	1787 ± 1155	18.96 ± 23.76	3612 ± 3902
$1C,4P_{BL2 \rightarrow 6\ min}$	6.77 ± 2.61	1402 ± 504	7.12 ± 5.30	1643 ± 1094	17.65 ± 21.12	3707 ± 4436
$2C,7P_{BL2 \rightarrow 3\ min}$	3.79 ± 1.50	1294 ± 512	4.61 ± 2.86	1666 ± 1118	8.82 ± 9.37	3010 ± 3198
$2C,7P_{BL2 \rightarrow 6\ min}$	6.43 ± 2.61	1359 ± 552	6.98 ± 5.05	1657 ± 1103	15.86 ± 20.68	3503 ± 4350
$3C,9P_{BL2 \rightarrow 6\ min}$	It did not fit these data		It did not fit these data		15.97 ± 19.93	3391 ± 4231
$3C,10P_{BL2 \rightarrow 6\ min}$	It did not fit these data		It did not fit these data		17.70 ± 17.83	3035 ± 3030

Numeric values are mean ± sd. **RSS:** Residual Sum of Squares and is expressed as RSS x 10^5. 1C, 2C, and 3C are the onecomponent, twocomponents, and threecomponents exponential mathematical models. **3P:** three parameters. **4P:** four parameters. **7P:** seven parameters. **9P:** nine parameters. **10P:** ten parameters. **BL2:** two min baseline. **→:** fitting period of time window: 0.3333 → 6 min, from 20 s after start to end exercise; BL2 → 6 min, from two min baseline to end exercise.

Table 4. The best statistical fit from the two out mathematical model permutations of onecomponent, twocomponent and threecomponent mathematical exponential models for the on transient $\dot{V}O_2$ submaximal exercise in nine old men.

Number of Permutations	Fitting Model "S_{imple}" (S_i)	*versus* "C_{omplex}" (C_o)	50 Watts F_{value}Calculated[a] F_{RS}	F_{MSE}	Estimated Lactate Threshold 80% F_{RSS}	F_{MSE}	120% F_{RSS}	F_{MSE}
Onecomponent model *vs.* Onecomponent model.								
1	$1C,3_{PBL2 \to 6\ min}$	$1C,4P_{BL2 \to 6\ min}$	$42^*,C_o$		$28^*,C_o$		$17^*,C_o$	
2	$1C,3P_{BL2 \to 6\ min}$	$1C,4P_{0.3333 \to 6\ min}$		$1.33^*,C_o$		$0.01,S_i$		$0.21,S_i$
3	$1C,3P_{BL2 \to 6\ min}$	$1C,4P_{0.3333 \to 3\ min}$		$0.01,S_i$		$0.01,S_i$		$0.07,S_i$
4	$1C,4P_{0.3333 \to 3\ min}$	$1C,4P_{0.3333 \to 6\ min}$		$0.08,S_i$		$0.04,S_i$		$0.17,S_i$
5	$1C,4P_{0.3333 \to 3\ min}$	$1C,4P_{BL2 \to 6\ min}$		$0.06,S_i$		$0.71,S_i$		$0.01,S_i$
6	$1C,4P_{0.3333 \to 6\ min}$	$1C,4P_{BL2 \to 6\ min}$		$0.17,S_i$		$0.77,S_i$		$0.74,S_i$
Onecomponent model *vs.* {Twocomponent model / Threecomponent mode}].								
1	$1C,4P_{0.3333 \to 3\ min}$	$2C,7P_{BL2 \to 3\ min}$		$0.03,S_i$		$0.44,S_i$		$0.76,S_i$
2	$1C,4P_{0.3333 \to 3\ min}$	$2C,7P_{BL2 \to 6\ min}$		$0.03,S_i$		$0.07,S_i$		$0.14,S_i$
3	$1C,4P_{0.3333 \to 3\ min}$	$3C,9P_{BL2 \to 6\ min}$	The three components model did					$0.24,S_i$
4	$1C,4P_{0.3333 \to 3\ min}$	$3C,10P_{BL2 \to 6\ min}$	not fit moderate exercise intensity					$0.28,S_i$
Twocomponent model *vs.* Twocomponent model.								
1	$2C,7P_{BL2 \to 3\ min}$	$2C,7P_{BL2 \to 6\ min}$		$0.09,S_i$		$0.03,S_i$		$0.14,S_i$
Twocomponent model *vs.* Threecomponent model.								
1	$2C,7P_{BL2 \to 3\ min}$	$3C,9P_{BL2 \to 6\ min}$	The three components model did					$0.06,S_i$
2	$2C,7P_{BL2 \to 6\ min}$	$3C,9P_{BL2 \to 6\ min}$	not fit moderate exercise intensity				$45^*,C_o$	
3	$2C,7P_{BL2 \to 3\ min}$	$3C,10P_{BL2 \to 6\ min}$						$0.02,S_i$
4	$2C,7P_{BL2 \to 6\ min}$	$3C,10P_{BL2 \to 6\ min}$					$14^*,C_o$	
Threecomponent model *vs.* Threecomponent model.								
1	$3C,9P_{BL2 \to 6\ min}$	$3C,10P_{BL2 \to 6\ min}$						$0.13,S_i$

Fisher's test (F_{value}, at 0.05 level of significance and one tailed*: $F_{tabulated}0.05\ (1\alpha) = 1.15$). If $F_{calculated} > F_{tabulated}$ then C_o model fits best; if $F_{calculated} < F_{tabulated}$ then "Simple" model fits best. C: component; P: parameters.

Table 5. Amplitude and parameter estimates determined for kinetic analysis of $\dot{V}O_2$ during the on transient of steady state submaximal exercise as estimated by the best fit exponential mathematical models in nine old men.

$W_{ork}\ R_{ate}$	Fitting Model	Estimated parameters Baseline (a_0, mL•min-1)	$A_{mplitude}\Phi_1$ (a_1,mL•min-1)	$A_{mplitude}\Phi_2$ (a_2,mL•min-1)	$A_{mplitude}\Phi_3$ (a_3,mL•min-1)	$A_{mplitudeTotal}$ (mL•min-1)
$50W_{atts}$	$1C,4P_{0.3333 \to 3\ min}$	[860.4 ± 131.6]	–	299 5 ± 52.5	–	–
	$2C,7P_{BL2 \to 6\ min}$	741.5 ± 129.8	192.6 ± 55.1	245 2 ± 51.5	–	438.7 ± 52 5
80% $\hat{\theta}_L$	$1C,4P_{0.3333 \to 3\ min}$	[824.9 ± 143.6]	–	210.6 ± 111.0	–	–
	$2C,7P_{BL2 \to 6\ min}$	750.6 ± 130.6	138.3 ± 63.6	142.7 ± 94.3	–	281 5 ± 150.4
120% $\hat{\theta}_L$	$1C,4P_{0.3333 \to 3\ min}$	[969.2 ± 143.4]	–	700.0 ± 204.7	–	–
	$3C,9P_{BL2 \to 6\ min}$	740.4 ± 112.2	368.5 ± 171.2	338.1 ± 78.5[a]	366 8 ± 236.5[c]	1073.4 ± 315.2
	$3C,10P_{BL2 \to 6\ min}$	744.0 ± 115.9	299.8 ± 103.8	592.7 ± 209.1[b]	175 3 ± 139.8[d]	1067 8 ± 325.5

		Φ_1TD1(s)	Φ_2TD2(s)	Φ_3TD3(s)	$\Phi_1\tau$1(s)	$\Phi_2\tau$2(s)	$\Phi_3\tau$3(s)	MRT_{exp}(s)	RSSx10^5	MSE	$B_{est}F_{it}T_{ype}$
50W	$1C,4P_{0.3333 \to 3\ min}$	–	[5.53 ± 6]	–	–	33.00 ± 5	–	–	2.07 ± 1	1324 ± 408	Φ_2p $\dot{V}O_2$
	$2C,7P_{BL2 \to 6\ min}$	0.10 ± 4	27.23 ± 4	–	17.74 ± 7	51.90 ± 13	–	52.57 ± 9	6.43 ± 3	1359 ± 552	Φ_2P $\dot{V}O_2$
80% $\hat{\theta}_L$	$1C,4P_{0.3333 \to 3\ min}$	–	[-3.01 ± 8]	–	–	51.77 ± 19	–	–	3.07 ± 3	1965 ± 1731	Φ_2p $\dot{V}O_2$
	$2C,7P_{BL2 \to 6\ min}$	-1.08 ± 12	26.09 ± 7	–	21.20 ± 9	61.69 ± 16	–	52.59 ± 11	6.98 ± 5	1657 ± 1103	Φ_2P $\dot{V}O_2$
120% $\hat{\theta}_L$	$1C,4P_{0.3333 \to 3\ min}$	–	[-0.63 ± 3]	–	–	45.19 ± 8	–	–	6.31 ± 8	4050 ± 5332	Φ_2p $\dot{V}O_2$
	$3C,9P_{BL2 \to 6\ min}$	-3.07 ± 4	22.83 ± 3	22.83 ± 3	19.11 ± 103	4.12 ± 17	164.41 ± 2	86.82 ± 15	215.97 ± 2	3391 ± 4231	Φ_2*S$\dot{V}O_2$
	$3C,10P_{BL2 \to 6\ min}$	-0.78 ± 7	23.37 ± 5	152.04 ± 41	14.58 ± 10	40.16 ± 7	111.21 ± 38	81.64 ± 18	17.70 ± 18	3035 ± 3030	Φ_2PS$\dot{V}O_2$

: No estimated parameter value. **$\hat{\theta}_L$:** Estimated lactate threshold. $a \neq b$ ($t = 9$) and $c \neq d$ ($t = 57$) Student $t_{\alpha 0.05}$, $p < 0.05$. **Φ:** Phases of the increase in $\dot{V}O_2$ during the on transient of submaximal exercise. **[ ]:** "virtual" either baseline $\dot{V}O_2$ or TD2. **TD:** time delay. **τ:** time constant. **MRT_{exp}:** exponential mean response time (the time required for the transient $\dot{V}O_2$ response to reach 63% of final amplitude): $MRT_{exp}\ 1C = TD + \tau\ \dot{V}O_2$; $MRT_{exp}\ 2C = [a_1 / (a_1 + a_2)] \bullet (TD1 + \tau 1) + [a_2 / (a_1 + a_2)] \bullet (TD2 + \tau 2)$; $MRT_{exp}\ 3C = [a_1 / (a_1 + a_2 + a_3)] \bullet (TD1 + \tau 1) + [a_2 / (a_1 + a_2 + a_3)] \bullet (TD2 + \tau 2) + [a_3 / (a_1 + a_2 + a_3)] \bullet (TD3 + \tau 3)$. 1C, 2C, and 3C, One , two , and three component exponential mathematical model. **RSS:** residual sum of squares and is expressed as RSS x 10^5. **MSE:** mean square error. **p:** postulated. **S:** statistical best. **P:** physiological best. ***:** no physiological sense.

best intra $\Phi_2\dot{V}O_2$ data ($\Phi_{2postulated}\dot{V}O_2$) for $S_{UBMAXIMAL}$ (Table 4).

One-, two-, and three-component fitting model comparisons

The $2C,7P_{BL2 \rightarrow 6\ min}$ showed physiological best fit $\Phi_2\dot{V}O_2$ on-transient response data to $M_{ODERATE}$ (Table 4, Figures 1 and 2); $\Phi_{2\ Isolated\_PhysBestFit}\dot{V}O_2$). The 3C model (3C,9P, $3C,10P)_{BL2 \rightarrow 6\ min}$ fitted statistically better (based on Fisher's test) than $2C,7P_{BL2 \rightarrow 6\ min}$ (Table 4) the $\Phi_2\dot{V}O_2$ on-transient response data for H_{EAVY}. The $3C,9P_{BL2 \rightarrow 6\ min}$ was neither physiologically nor statistically better than $3C,10P_{BL2 \rightarrow 6\ min}$ (Tables 4 and 5, Figure 4) on fitting $\Phi_2\dot{V}O_2$ on-transient response data for H_{EAVY}. The $3C,10P_{BL2 \rightarrow 6\ min}$ showed physiological sense in terms of amplitude and temporal parameter estimates of the three $\dot{V}O_2$ phases of response data for H_{EAVY} and allowed us to physiologically characterize the $\Phi_2\dot{V}O_2$ (Table 5, Figure 3) response data for H_{EAVY}.

Phase Two $\dot{V}O_2$ On-Transient Kinetics ($\tau\ \Phi_2\dot{V}O_2$)

The $1C,4P_{0.3333 \rightarrow 3\ min}$ characterized $\tau\Phi_{2postulated}\dot{V}O_2$ on-transient data for $M_{ODERATE}$Abs ($\tau\Phi_{2postulated}$ 33 ± 4.95 s),

Table 6. Parameter estimated by the best fit onecomponent mathematical model from kinetic analysis of $\dot{V}O_2$ data placed into discrete time bins of 10 s during the on transient of steady state submaximal exercise in nine old men.

Work Rate	Baseline(a_0) (mL•min^{-1})	AmplitudeΦ_2(a_2) (mL•min^{-1})	Φ_2T$_{ime}$D$_{elayed}$(TD2) (s)	$\Phi_{2postulated}$ τ(τ2) (s)	± 95 (confidence interval)
50 Watts	[740 ± 137]	438 ± 55	[10.32 ± 12]	42.61 ± 9.1	3 ± 0.9
80% $\hat{\theta}_L$	[727 ± 87]	293 ± 134	[7.94 ± 8.8]	42.73 ± 4.83	6 ± 2.2
120% $\hat{\theta}_L$	[741 ± 112]	922 ± 260	[7.08 ± 5.5]	43.70 ± 7.8	2 ± 0.7

$\hat{\theta}_L$: estimated lactate threshold. Φ_2: refers to phase 2 of the increase in $\dot{V}O_2$ during the on transient of submaximal exercise. a_0: represents the baseline $\dot{V}O_2$ prior to the transition to submaximal exercise. The a_0 shown in square brackets is the $\dot{V}O_2$ corresponding to 0.3333 min (20 s) with the exercise transient, and thus represents a "virtual" baseline $\dot{V}O_2$. Data was fitted with onecomponent exponential mathematical model of four parameters (a_0,a_2,TD2, τ2). Fitting window 20 s from exercise onset to either end exercise (MOD: 50 Watts, 80% $\hat{\theta}_L$) or phase 2 3 transition (HVY: 120% $\hat{\theta}_L$). The T$_{ime}$D$_{elay}$2 shown in square brackets represent a "virtual" TD2. τ: time constant. $\Phi_{2postulated}\dot{V}O_2$ started 20 s after de onset of the exercise and end al 3 min on transient response to submaximal exercise.

Table 7. Final summary best fit exponential mathematical models that characterized the Phase two $\dot{V}O_2$ during the on transient of steady state moderate intensity (50 W, 80% $\hat{\theta}_L$) and heavy intensity (120% $\hat{\theta}_L$) exercise, respectively, in nine old men.

Exponential Mathematical Model	Fitting Model	$\tau\ \Phi_2\dot{V}O_2$ Comments
	Submaximal Exercise	
$\dot{V}O_2(t) = a_{0(virtual)} + a_1 \bullet [1\ e^{-[(t-TD1)/\tau 1]}]$	$1C,4P_{0.3333 \rightarrow 3\ min\ Exercise}$	$\tau\Phi_{2\ postulated}$ (Practical Phys $\tau\Phi_2\dot{V}O_2$)
	Moderate-Intensity Exercise	
$\dot{V}O_2(t) = a_0 + a_1 \bullet [1\ e^{-[(t-TD1)/\tau 1]}] + a_2 \bullet [1\ e^{-[(t-TD2)/\tau 2]}]$	$2C,7P_{Baseline \rightarrow End\ Exercise}$	"Φ_1", $\tau\Phi_{2Phys\ Isolated}$, Φ_3 $\therefore \Phi_{2\ Isolated}\dot{V}O_2(t) = a_0 + a_2 \bullet [1\ e^{-[(t-TD2)/\tau 2]}]$
	Heavy-Intensity Exercise	
$\dot{V}O_2(t) = a_0 + a_1 \bullet [1\ e^{-[(t-TD1)/\tau 1]}] + a_2 \bullet [1\ e^{-[(t-TD2)/\tau 2]}] + a_3 \bullet [1\ e^{-[(t-TD2)/\tau 2]}]$	$3C,10P_{Baseline \rightarrow End\ Exercise}$	"Φ_1", $\tau\ \Phi_{2Phys\ Isolated}$, Φ_3 $\therefore \Phi_{2\ Isolated}\dot{V}O_2(t) = a_0 + a_2 \bullet [1\ e^{-[(t-TD2)/\tau 2]}]$

$\rightarrow$: Fitting period of time arrow. On transient, the output of a system from the onset to the offset of the exercise; Onset and Offset, the start and the end, respectively, of an application of an ergometric forced function. $\hat{\theta}_L$: Ventilatory threshold. Phys: physiological sense (it differentiated $\Phi_2\ \dot{V}O_2$ from both $\Phi_1\ \dot{V}O_2$ and $\Phi_3\ \dot{V}O_2$). $\dot{V}O_2$: Pulmonary oxygen uptake. $\dot{V}O_2(t)$: Mass rate of change per unit of time ($d\dot{V}O_2 \bullet dt^{-1}$), mL•min^{-1}. **TD:** Time delay, s. a_0: Baseline (the $\dot{V}O_2$ at the start of the model). **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 τ (s), for an exponential increase (on transient $\dot{V}O_2$ response). **t:** The time in which the transient $\dot{V}O_2$ response is gradually (exponentially) dying away, when t = τ 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, τ = 1 0.3678 = 0.63, and e = 2.718281 = $[(1 + n^{-1})]^n$, n ≥ 10 and 'e' is incommensurable with 1. Onecomponent (1C), TD1: Twocomponents (2C), TD1 and TD2; Threecomponents (3C), 2C and TD3. **4P:** Four parameters (a_0, a_1, TD1, τ1). **7P:** Seven parameters (*4P*, a_2, TD2, τ2). **10P:** Ten parameters (7P, a_3, TD3, τ3).

$M_{ODERATE}Rel$ ($\tau\Phi_{2postulated}$ 51.77 ± 18.75 s) ($\Phi_{2postulated}\dot{V}O_2$ τ $M_{ODERATE}$ 42.38 ± 16 s) and $H_{EAVY}Rel$ ($\tau\Phi_{2postulated}$ 45.19 ± 8.15 s) responses (Table 5) that kinetically characterized this submaximal exercise-intensity ($\tau\Phi_{2postulated}$ for $S_{UBMAXIMAL}$ 46.34 ± 14.87 s) (Figures 1-3). The $\Phi_{2\ Isolated}\dot{V}O_2$ characterized from entire on- transient data showed that model 2C,7$P_{BL2 \rightarrow 3\ min}$ did not properly fit the $\dot{V}O_2$ on- transient entire H_{EAVY} data. Thus, it followed that the physiological best fitting model for $M_{ODERATE}$ was 2C,7$P_{BL2 \rightarrow 6\ min}$ (Table 5) because it fitted three $\dot{V}O_2$ phases and kinetically characterized $\tau\Phi_{2\ Isolated}$ (Table 5), in agreement with the morphology of the $\dot{V}O_2$ entire response data for the $M_{ODERATE}$ response (Figures 1 and 2). Thus $\tau\Phi_{2\ Isolated\_PhysBestFit}$ for $M_{ODERATE}$ was 53.68 ± 15.59 s.

The 3C,10$P_{BL2 \rightarrow 6\ min}$ kinetically characterizing $\Phi_{2\ Isolated}$ $\dot{V}O_2$ (Table 5) from entire on-transient data showing a $\tau\Phi_{2\ Isolated\_PhysBestFit}\dot{V}O_2$ for H_{EAVY} equal to 40.16 ± 7.35 s (Figure 3). These $\dot{V}O_2$ $\tau\Phi_{2postulated}$ $S_{UBMAXIMAL}$, $\tau\Phi_{2\ Isolated\_PhysBestFit}$ $M_{ODERATE}$, and $\tau\Phi_{2\ Isolated\_PhysBestFit}$ H_{EAVY} values from those best fitting models were not significantly different from each other and, gave an overall $\tau\Phi_2\dot{V}O_2$ value of 46 ± 15 s in our old group of men. The $\tau\Phi_{2\ data\ of\ \dot{V}O2\ 10\text{-}s\ bins}$ value (43 ± 7 s) (Table 6) was not significantly different from $\tau\Phi_2\dot{V}O_2$. Table 7 showed the final summary of all these best fitting models characterizing phase two $\dot{V}O_2$ on-transient response to moderate- and heavy- intensity ($S_{UBMAXIMAL}$) exercise.

DISCUSSION

Physical characteristics, ramp exercise test, and constant load tests

The physical characteristics, maximal cardiorespiratory and $\hat{\theta}_L$ values from all of our subjects were above average fitness.[26] In this study the observations were that subject showed low power output and low square wave test $\dot{V}O_{2End\ Exercise}$ for $M_{ODERATE}$ compared to H_{EAVY}. Subjects showed $M_{ODERATE}$Abs $\dot{V}O_2$ (% $\hat{\theta}_L$) similar to $\dot{V}O_{2\ \hat{\theta}L}$. $M_{ODERATE}$ Rel $\dot{V}O_2$ (% $\hat{\theta}_L$) resulted low compared $\dot{V}O_{2\ \hat{\theta}L}$ and they were lower that the H_{EAVY}Rel $\dot{V}O_2$ (% $\hat{\theta}_L$). However, these differences in the numeric values of these variables, showed $\Phi_2\dot{V}O_2$ τ values not to be kinetically different between the work rates of $M_{ODERATE}$. Our study showed the well known observation that cycle exercise resulted in a linear increase in $\dot{V}O_2$ of approximately 10 mL•min^{-1} (this study 12 mL•min^{-1} for $M_{ODERATE}$) for every one W increase in work rate.[27] The H_{EAVY} showed a positive on-transient $\Delta\dot{V}O_{2(6\text{-}3min)}$ value because the metabolic requirement for performance of this heavy work rate, is known to be over and above that predicted from below $\hat{\theta}_L$ $\dot{V}O_2$ - work rate relationship.[4]

Mathematical Modelling

- ***Onecomponent fitting model comparisons:*** The 1C fitting models 1C,4$P_{0.3333\ min\ to\ Offset}$, 1C,4$P_{BaseLine_Onset\ to\ Offset}$, and 1C,3$P_{BaseLine_Onset\ to\ Offset}$ oversimplifying the $\dot{V}O_2$ response data for $M_{ODERATE}$ and H_{EAVY},[28] they poorly fitted in terms of large MSE through the phase due to an increase in pulmonary blood flow[15,19,27] followed by a further exponential increase in pulmonary $\dot{V}O_2$ that reflects muscle $\dot{V}O_2$,[29,30] and they showed also no physiological sense of the estimates of $\Phi_1\dot{V}O_2$ τ. All these observations are in agreement with those ones observed in a similar study done with young adults.[8,9] Thus, from 1C fitting model comparisons, the most convenient best intra-fit $\Phi_{2postulated}$ $\dot{V}O_2$ on-transient response data to $S_{UBMAXIMAL}$ in terms of both τ2 value and physiological meaning, was the 1C,4$P_{0\ 3333 \rightarrow 3\ min}$, in agreement with previous observations in young adults.[8,9] The fact that 1C,4$P_{0.3333 \rightarrow 3\ min}$ physiologically best intra-fitted Φ_2 $\dot{V}O_2$ on-transient response data to $S_{UBMAXIMAL}$ compared to either 2C,7P for $S_{UBMAXIMAL}$ or 3C for H_{EAVY}, is explained because this Φ_2 $\dot{V}O_2$ is an exponential transient response[7] and also because the shorter the period of time modelled the better both the fit and the simple the mathematical model.[8,23]
- ***Twocomponent fitting model comparisons:*** We fit the same $S_{UBMAXIMAL}$ data set with three different 2C fitting models (2C,7$P_{BaseLine_Onset\ to\ 3\ min}$, and 2C,7$P_{BaseLine_Onset\ to\ Offset}$) which varied mainly in their fitting window and consideration of the phases of increase in $\dot{V}O_2$ in our group of old men. Taking in consideration that the $\dot{V}O_2$ response data during the on-transient of $M_{ODERATE}$, culminating in a steady-state value, is less complicated relative to the response during the on-transient of H_{EAVY}; the 2C,7$P_{BaseLine_Onset\ to\ 3\ min}$ omitted Φ_1 $\dot{V}O_2$ and arbitrary limits of 3 min the Φ_2 $\dot{V}O_2$ end, had the inconvenient, that it did not neither physiologically differentiate nor isolate Φ_2 $\dot{V}O_2$ from the $M_{ODERATE}$ entire data in young[5,8,9] and old men in this study. Thus, the 2C,7$P_{BaseLine_Onset\ to\ Offset}$ fitting models was physilogically best fit in old men for the $M_{ODERATE}$ $\Phi_{2\ Isolated}$ $\dot{V}O_2$ on-transient entire response data, because this model included a baseline when it differentiated this $\Phi_{2\ Isolated}$ $\dot{V}O_2$ with its second exponential term from the three phases of this entire $M_{ODERATE}$ $\dot{V}O_2$ on-transient response.[5,8,9] If $M_{ODERATE}$ $\Phi_1\dot{V}O_2$ were and exponential response, then the fitting model 2C,7$P_{BaseLine_Onset\ to\ Offset}$ would probably perfectly match the entire $\dot{V}O_2$ morphology of this $M_{ODERATE}$ response data. Nevertheless, 2C,7$P_{BaseLine_Onset\ to\ Offset}$ supported in both physiological and kinetical terms the isolation

of the $M_{ODERATE}$ $\Phi_2\dot{V}O_2$ ($\Phi_{2\ Isolated\_Phys}$ $\dot{V}O_2$ τ) response data to constant-load leg cycling. In consequence, we preferred $2C,7P_{BaseLine\_Onset\ to\ Offset}$ to characterize $\tau\Phi_{2\ Isolated}$ $\dot{V}O_2$ on-transient response data to $M_{ODERATE}$ in old men, because it properly fitted with double exponential functions (with twocomponent included: TD1 and TD2)[7] the cardiodynamic (Φ_1), exponential (Φ_2), and steady state (Φ_3) $\dot{V}O_2$ responses to $M_{ODERATE}$.[31] These observations are in agreement with the fact that Mod being less complicated response thus it may be described adequately by relatively less complex (2C instead 3C) mathematical models. In consequence, the $2C,7P_{BaseLine\_Onset\ to\ Offset}$ fitting model was physiologically best fit in old men for the $M_{ODERATE}$ $\Phi_{2\ Isolated}$ $\dot{V}O_2$ on-transient entire response data, because it differentiated this $\Phi_{2\ Isolated}$ $\dot{V}O_2$ with its second exponential term from the three phases of this entire $M_{ODERATE}\dot{V}O_2$ on-transient response data.[8]

- ***Threecomponent fitting model comparisons:*** The 3C models fitted statistically better than $2C,7P_{BaseLine\_Onset\ to\ Offset}$ for H_{EAVY} constant-load leg cycling, because the superimposed morphology of the slow component in the H_{EAVY} Φ_2 $\dot{V}O_2$ on-transient response data cannot be properly fitted by 2C models.[8,9,32,33] These assessments lead us from the physiological system, $\dot{V}O_2$ on-transient $S_{UBMAXIMAL}$, to a mathematical formulation, modelling Φ_2 $\dot{V}O_2$, with the best fitting exponential mathematical models, and to the physiological interpretation of the results in terms of Φ_2 $\dot{V}O_2$ τ.
- ***Phase Two $\dot{V}O_2$ On-Transient Kinetics ($\tau\Phi_2$ $\dot{V}O_2$):*** The $1C,4P_{0.3333\ \rightarrow\ 3\ min}$ kinetically (τ) characterized $S_{UBMAXIMAL}$ $\Phi_{2\ postulated}$ $\dot{V}O_2$ on-transient response data to constant-load leg cycling, because this $S_{UBMAXIMAL}$ Φ_2 $\dot{V}O_2$ on-transient response data is an exponential one[7] and also because by fitting the period of time from 20 s after the onset of the exercise to 3 min exercise, we were mainly modelling in the whole Φ_2 experimental data, as well as because the probability of kinetic influences on $\Phi_2\dot{V}O_2$ from both Φ_1 $\dot{V}O_2$ and Φ_3 $\dot{V}O_2$[6] were minimized; in particular Φ_3 $\dot{V}O_2$ that it has been considered to overlap Φ_2 $\dot{V}O_2$ during H_{EAVY} constant-load leg cycling.[6,9] In consequence, the $1C,4P_{0.3333\ \rightarrow\ 3\ min}$ fitting model seems to be closely implying dependence in nature, because there is a high probability that this $\Phi_{2\ postulated}$ $\dot{V}O_2$ on-transient kinetic ($\Phi_{2\ postulated}$ $\dot{V}O_2$ τ) response data to $S_{UBMAXIMAL}$ is related at peripherical level (energy- metabolism kinetics) in terms of $\dot{V}O_{2\_comsumption}$ τ and PCr τ (cause) and Φ_2 $\dot{V}O_{2\_pulmonary\ uptake}$ τ (effect).[34]

We preferred $2C,7P_{BaseLine\_Onset\ to\ Offset}$ to kinetically characterize $S_{UBMAXIMAL}$ $\Phi_{2\ Isolated}$ $\dot{V}O_2$ on-transient response data, because it showed also physiological sense as a fitting model that isolated the $M_{ODERATE}$ Φ_2 $\dot{V}O_2$ on-transient response data ($\Phi_{2\ Isolated\_PhysBestFit}$) to constant-load leg cycling. This $2C,7P_{BaseLine\_Onset\ to\ Offset}$ properly fits with double exponential functions (with $T_{ime}D_{elay}1$ and $T_{ime}D_{elay}2$ included)[7] the cardiodynamic (Φ_1), exponential (Φ_2), and steady state (Φ_3) $\dot{V}O_2$ responses to $M_{ODERATE}$.[31] The $T_{ime}D_{elay}2$ from both the$M_{ODERATE}$Abs (26 s) and the $M_{ODERATE}$Rel (27 s), were different from that assumed prior to phase two of approximately 20 s for fitting model $1C,4P_{20s\ \rightarrow\ 3\ min}$,[28] because Φ_1 $\dot{V}O_2$ on-transient response data finished approximately 20 s after the onset $M_{ODERATE}$ but individual variability and the intensity of the $M_{ODERATE}$ test may be responsible for small significant differences like those observed of 6 s for $M_{ODERATE}$Abs and 7 s for $M_{ODERATE}$Rel power output. If Φ_1 $\dot{V}O_2$ were and exponential response to $M_{ODERATE}$, then the fitting model $2C,7P_{BaseLine\_Onset\ to\ Offset}$ would probably perfectly match the entire $\dot{V}O_2$ morphology of response to $M_{ODERATE}$. Nevertheless, $2C,7P_{BaseLine\_Onset\ to\ Offset}$ supported in physiological and in kinetical terms the isolation of the M-$_{ODERATE}$ Φ_2 $\dot{V}O_2$ ($\Phi_{2\ Isolated\_PhysBestFit}$ $\dot{V}O_2$ τ) response data.

The $3C,10P_{BaseLine\_Onset\ to\ Offset}$ showed both statistical merits and physiological sense in kinetically characterizing the isolated H_{EAVY} Φ_2 ($\tau\Phi_{2\ Isolated\_\ PhysStat\ BestFit}$) $\dot{V}O_2$ on-transient response data to constant-load leg cycling. The $3C,10P_{BaseLine\_Onset\ to\ Offset}$ kinetically characterized with its second exponential term the H_{EAVY} $\Phi_{2\ Isolated\_PhysStat\ BestFit}$ $\dot{V}O_2$ on-transient response data to constant-load leg cycling.[4,7,9,28] The $3C,9P_{BaseLine\_Onset\ to\ Offset}$ did not model in physiological terms the estimated parameters (i.e., τ) of the entire $\dot{V}O_2$ on-transient response data to H_{EAVY}, because it was $3C,10P_{BaseLine\_Onset\ to\ Offset}$ restricted to $T_{ime}D_{elay}2$ $T_{ime}D_{elay}3$. Evermore, during H_{EAVY} both the amplitude Φ_2 and amplitude Φ_3 $\dot{V}O_2$ were different in $3C,9P_{BaseLine\_Onset\ to\ Offset}$ compared to $3C,10P_{BaseLine\_Onset\ to\ Offset}$; and these amplitude value differences, particularly the one from the slow component (amplitude Φ_3 $\dot{V}O_2$), is one of the reasons for the lack of physiological sense in the way of modelling entire $\dot{V}O_2$ on-transient response data to H_{EAVY} by the fitting model $3C,9P_{BaseLine\_Onset\ to\ Offset}$.[5,8,9] These no sense in the estimated values of the temporal parameters, is explained because the Φ_3 $\dot{V}O_2$ on-transient response data to H_{EAVY}, elicited no steady- state ($\Delta\dot{V}O_{2(6\text{-}3min)}$ positive, slow component).[4] In $M_{ODERATE}$, not only is $\Phi_1\dot{V}O_2$ a non exponential response[7] but the Φ_3 $\dot{V}O_2$ has been questioned of whether this slow component is or not an exponential response data to H_{EAVY}.[9] Nevertheless and since we were interested for this study in kinetically characterizing Φ_2 $\dot{V}O_2$ only, then 3C,10P$_{BaseLine_Onset\ to\ Offset}$ characterized H$_{EAVY}$ $\Phi_{2\ Isolated\_PhysBestFit}$ $\dot{V}O_2$ τ response data to constant-load leg cycling. When modelling the Φ_2 $\dot{V}O_2$ on-transient response data to M$_{ODERATE}$, it is useful to use the fitting model 1C,4P$_{20\ s\ \rightarrow\ 3\ min}$[28] as we did in this study, 1C,4P$_{0.3333\ \rightarrow\ 3\ min}$, and did also previously[5,8,9] as a general reference of τ values of the postulated on-transient Φ_2 $\dot{V}O_2$ to feedback the kinetic (τ) values from the isolated Φ_2 $\dot{V}O_2$ with either 2C,7P$_{BaseLine_Onset\ to\ Offset}$ for S$_{UBMAXIMAL}$ or 3C,10P$_{BaseLine_Onset\ to\ Offset}$ for H$_{EAVY}$; these $\tau 2$ values should be similar to each other, as it was observed in young adults[5,8,9] and in this study for S$_{UBMAXIMAL}$ as well.

The Φ_2 $\dot{V}O_2$ on-transient data of response to S$_{UBMAXIMAL}$ is very important from the kinetically and physiologically points of view because they allow us to study the oxygen mass rate of change per unit of time during a non steady-state condition response to exercise, in terms of mathematical modelling of this response, to assess the dynamics of the blood,[35] cardiovascular and energy metabolism[4,18] in human beings. The τ for expired ventilation exceeds that of $\dot{V}O_2$ by some 50-70%.[3] This kinetic dissociation of expired ventilation from $\dot{V}O_2$[3] has been explained as a transient hypoxemia during phase two of a constant-load exercise, and it has been demonstrated.[20,36] Interestingly, pulmonary τ Φ_2 $\dot{V}O_2$ uptake seems to be similar to the kinetics of $\dot{V}O_2$ consumption by the exercising body mass.[29,37] Finally, whether the rate of increase in oxidative phosphorylation is limited by the adaptation of oxygen utilization or oxygen transport mechanisms, is motive of debate.[30,34,38,39] In consequence, there is a need for a consensus in the way to model the oxygen uptake on-transient kinetics of the response to different intensities of exercise, in search of a cause- effect relationship, underlaying the mechanisms of the non steady- state response in exercise physiology, to match the mathematical model with the physiological one to come. Finally, these findings in old men seem to be correct in order to kinetically compare them properly with those from young men.

CONCLUSIONS

The simple (practically) onecomponent, four parameters, exponential mathematical model (1C,4P), conveniently best intramodelled and fitted $\dot{V}O_2$ on-transient data and allowed us to kinetically characterize the estimated $\dot{V}O_2$ on-transient time constant for postulated phase two $\dot{V}O_2$ on-transient data of submaximal exercise (fitting model 1C,4P$_{from\ 0.3333\ \rightarrow\ 3\ min\ exercise}$). The complexes twocomponent seven parameters (2C,7P) and threecomponent, ten parameters (3C,10P) exponential mathematical models, were physiologically and statistically best fit, respectively, on kinetically characterizing the estimated $\dot{V}O_2$ on-transient time constant for the isolated phase two $\dot{V}O_2$ on-transient data, for moderate-intensity exercise with the fitting model 2C,7P$_{from\ baseline_start\ to\ end\ exercise}$ and for heavy exercise intensity with the fitting model 3C,10P$_{from\ baseline_start\ to\ end\ exercise}$. These 2C,7P and 3C,10P fitting models differentiated from the three $\dot{V}O_2$ phases of the entire on-transient data and kinetically characterized, the estimated $\dot{V}O_2$ on-transient time constant for phase two of response by intra modelling the phase two $\dot{V}O_2$ into the entire on-transient data with their second exponential term. The phase two $\dot{V}O_2$ on-transient time constant estimated values from these one-, two- and three-component best fitting models of the $\dot{V}O_2$ on-transient response data to submaximal exercise, were similar to each other.

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Solicitud de sobretiros:
Javier Padilla P. MD, MSc
Fisiología del Ejercicio,
Escuela Superior de Medicina 3º Piso
Instituto Politécnico Nacional,
Casco de Santo Tomás, DMH,
C.P. 11340, México, D.F.
Tel.: (55) 5729-6300, Ext/Fax: 62733
Correo electrónico: japadillap@ipn.mx