Age-related slow fundamental recovery VO\textsubscript{2} kinetics during submaximal exercise

Abstract
We studied, the fundamental (Φ\textsuperscript{2}) pulmonary oxygen uptake recovery ([off]-Φ\textsuperscript{2} VO\textsubscript{2} response) to submaximal exercise in terms of Φ\textsuperscript{2}, time constant two. We assessed healthy male volunteers eight young (YG=8) and nine old (OG=9) if [off]- Φ\textsuperscript{2} VO\textsubscript{2} response to submaximal exercise show [off]-asymmetry in the Φ\textsuperscript{2} VO\textsubscript{2} kinetics (t\textsubscript{2}, t\textsubscript{1}) from the YG vs OG characterised from the best exponential fitting models. Subjects (YG=25.2±2.9; OG=71.0±4.3) completed an initial incremental ramp test (YG=25 W\textsubscript{min}^{-1}, OG=15 W\textsubscript{min}^{-1}) to volitional fatigue from which the ventilatory threshold (V\textsubscript{cT}) and work rates corresponding to 80% V\textsubscript{cT} (ModRel) and 120% V\textsubscript{cT} (HvyRel) were identified, and an “absolute” work rate of 50W (AbsMod) (submaximal exercise) was selected. The [off] step-transitions in work rate were initiated from a baseline without warning to the subject. Each [off]-transition lasted 6 min (entire [off]-VO\textsubscript{2}) and 4 to 6 transitions were performed at each sub maximal exercise intensity. The VO\textsubscript{2} [off]-response was measured breath-by-breath at one min baseline and throughout each transition. Data were interpolated to 1-s intervals and ensemble-averaged to yield a single response profile for each subject and intensity were filtered. The averaged response for each subject was fitted with a two- [2C for Mod], and three-component (3C for Hvy) exponential model by using entire [off]-VO\textsubscript{2} fitting windows. Parameter estimates (i.e., t\textsubscript{c, t}) were determined for each component. Our best statistically and/or physiologically fitting model showed significant slow τ\textsubscript{2}, age-related (τ\textsubscript{2}, τ\textsubscript{1}=19.8s, t=7.3P,0.001) independent of the level of exercise intensity. There was an age-related slow fundamental recovery exercise VO\textsubscript{2} kinetics (long t\textsubscript{1}) during submaximal exercise in old adult men.

Keywords: O\textsubscript{2} uptake kinetics, [off]-phase two O\textsubscript{2}, time constant, young and old men.

Introduction
Physical exercise requires the interaction of physiological control mechanisms to enable the blood-cardiovascular and respiratory systems to couple their functions to support the increased energy metabolism in terms of oxygen (O\textsubscript{2}) consumption (VO\textsubscript{2}) and carbon dioxide production (VCO\textsubscript{2}) of the contracting muscles.\textsuperscript{1} The exercise recovery pulmonary O\textsubscript{2} uptake ([off]-VO\textsubscript{2}) and their kinetics ([off]-VO\textsubscript{2} kinetics) are currently characterized by empirical mathematical models that are a weighted sum of an offset and delayed exponentials.\textsuperscript{2,4} Because of the different mechanisms in ATP regeneration have different effects on gas exchange\textsuperscript{2} study of the pulmonary gas exchange (VCO\textsubscript{2}/VO\textsubscript{2}) responses to exercise can reveal information regarding the kinetics of the relative contributions of aerobic respiration, phosphocreatine hydrolysis, and anaerobic glycolysis to the total bioenergetic response, it is specially important to study the VO\textsubscript{2} kinetics that reflects the skeletal muscle VO\textsubscript{2} during physical exercise\textsuperscript{6,8} (Φ\textsubscript{2} VO\textsubscript{2} transient phase two VO\textsubscript{2}). Moreover, during recovery from moderate and heavy exercise the estimated muscle capillary blood flow kinetics have been observed biphasic.\textsuperscript{6,7} Exercise tests in which gas exchange is determined realistically evaluate the ability of these systems to promote their common major function, which is support of cellular respiration and allows the investigator to search for mechanisms to distinguish between a young adult an and old human response characteristic of the ageing processes, grade the adequacy of the coupling mechanisms, and assess the effect of therapy on a diseased organ system.\textsuperscript{6} The moderate-to-heavy aerobic exercise off-transient O\textsubscript{2} response, shows an initial rapid decline, similar to recovery from light exercise, named the off-transient phase one VO\textsubscript{2} response ([off]- Φ\textsuperscript{2} VO\textsubscript{2} followed by a more gradual decline to baseline resting levels, the [off]-transient phase two VO\textsubscript{2} response (off)- Φ\textsuperscript{2} VO\textsubscript{2}.\textsuperscript{1,2} Evermore, the recovery kinetics may be able to reflect the exercise capacity of people and provide the prognostic information about mortality for particular disease group.\textsuperscript{3}

The exercise transient (on)- Φ\textsuperscript{2} VO\textsubscript{2} kinetics in terms of its time constant τ\textsubscript{1} (on)- Φ\textsuperscript{2} VO\textsubscript{2} are slowed with aging (long t\textsubscript{c}, numeric value)\textsuperscript{9} but whether the slowed (on)- Φ\textsuperscript{2} VO\textsubscript{2} kinetics observed in older adults during whole body large muscle mass exercise, such as cycling is due to an inability to increase muscle blood flow and O\textsubscript{2} delivery and/or a reduced capacity to utilize O\textsubscript{2}, has not been clearly established.\textsuperscript{1,11} Nevertheless, information on the Φ\textsuperscript{2} VO\textsubscript{2} kinetics during end recovery submaximal exercise ([off]-transient Φ\textsuperscript{2} VO\textsubscript{2} in older adults was limited.\textsuperscript{10} Thus, the two components (2C,7P) and the three component (3C,10P) exponential mathematical models\textsuperscript{11,12} for moderate intensity exercise and heavy intensity exercise respectively were constructed. The 2C, 7P and the 3C, 10P models have been statistically and/or physiologically assessing were used to get the best fit data from the end recovery submaximal exercise ([off]-transient Φ\textsuperscript{2} VO\textsubscript{2} t\textsuperscript{1,12} JustificationIn the absence of a modeling evaluation and its kinetics of aging, of response of oxygen uptake of submaximal exercise, it was decided to perform this study using mathematical modeling and its kinetics to offer a new approach that could contribute to obtain a deeper insight into the mechanisms of recovery related to age. This can be useful in future research to compare kinetically between different conditions
such as growth, development and disease status and rehabilitation.\textsuperscript{13} Thus, the purpose of this research was to compare the [off]-transient $\Phi_{\text{VO}_2 \tau}$ of young men and older adults using the best exponential mathematical models of statistical and/or physiological adjustment such as the two component model (2C,7P) and three component model (3C,10P) for moderate intensity exercise and heavy intensity exercise, respectively.\textsuperscript{12,13}

**Hypothesis**

If aging affects the fundamental kinetics of submaximal exercise recovery then the duration of the transient recovery time [off]-transient $\Phi_{\text{VO}_2 \tau}$ of submaximal exercise should be longer (slow $t_\tau$) in older men compared to men young adults. If the hypothesis is corroborated, this would not affect the clinical method used by a physician and its collaborators, but it would have a kinetic approach, among other approaches, that reflects in a more objective way the status of the patients themselves diagnosing the degree of affect of their homeostasis and also allow the feedback of the physiotherapeutic methods of their rehabilitation. Of course there is also the possibility of going deeper into the causality of the kinetics of oxygen consumption in the promotion of health and physical activity and aging.

**Material and methods**

**Subjects**

The subjects in this study were eight healthy men with an average (mean±SD) age of 25.2±2.9 years (YG) and nine healthy elderly (OG) with an average age of 71.0±4.3 years. The data was obtained from the studies carried out under control conditions in our laboratory for several years. The subjects performed seated in a cycle ergometer exercise of both moderate intensity and intense intensity.

**Ethical approval**

The Review Board for Research with Human Subjects provided ethical approval and each subject gave their informed consent.

**Testing procedures**

The determination of the maximum pulmonary uptake of oxygen (VO$_2$max) and the VO$_2$ was measured using a bidirectional turbine (VMM110, Alpha technologies) previously calibrated. Respired gases were sampled continuously (1 mAs$^{-1}$) at the mouth and analysed for concentrations of $O_2$, $CO_2$ and $N_2$ by mass spectrometry (MGR 9N, Airspec 2000 after calibration with precision-analysed gas mixtures. Changes in gas concentration were aligned with gas volumes by measuring the time delay for a bolus of gas to pass the turbine to the resulting changes in fractional gas concentrations as measured by the mass spectrometer. Breath-by-breath alveolar gas exchange was calculated using previously described algorithms\textsuperscript{12} and data were interpolated to 1 s intervals and to improve the signal-noise ratio each subject performed a number of repetitions of the exercise protocol (constant-load exercise tests): 6-8 for Mod 2 (2-4 transitions A visit\textsuperscript{1}) and 2-3 for HvyRel (one transition A visit\textsuperscript{1}). The interpolated data were then averaged for each individual to yield a single overlaid response from 50W, 80% VeT and 120% VeT data that was used for determining the kinetics of the VO$_2$ [off]-transient responses to submaximal exercise.

**Models**

The data for VO$_2$ [off]-transients were constructed with our previously assessed best fitting models. For moderate-intensity exercise, an exponential model with the twocomponent and seven Parameters\textsuperscript{12,13} were fitted to the data. For heavy-intensity exercise exponential model with threecomponent and 10 Parameters\textsuperscript{12,13} were fitted to the data.The double empirical mathematical model of 2C is adjusted to a transient temporal course of the transient response curve [off]-$O_2$ from a resting baseline ($A_0$) to a steady state, with consecutive transitory periods and exponentials of time with 7 parameters; $7P=\{A_0, A_1, \delta_1, \tau_1; A_2, \delta_2, \tau_2\}$, expressed as 2C,7P:\textsuperscript{12,13}

$$[\text{Off}]-\Phi_{\text{VO}_2}(t)=A_0\cdot \left(1-\exp\left(-\left(1/t_\tau-1\right)\right)\right)-A_0\cdot \left(1-\exp\left(-\left(t-\tau_2\right)/\tau_2\right)\right);$$

also, the 3C empirical triple exponential mathematical model was performed, it fits a transient temporal course of the transient response curve [off] - VO$_2$ from a resting baseline ($A_0$) to a steady state, with consecutive periods transient and exponential time with 10 parameters; $10P=\{A_0, A_1, \delta_1, \tau_1; A_2, \delta_2, \tau_2; A_3, \delta_3, \tau_3\}$, expressed as 3C,10P:\textsuperscript{12,13}

$$[\text{Off}]-\Phi_{\text{VO}_2}(t)=A_0\cdot \left(1-\exp\left(-\left(1-t_\tau\right)/\tau_1\right)\right) - A_0\cdot \left(1-\exp\left(-\left(t-\delta_3\right)/\tau_3\right)\right) - A_0\cdot \left(1-\exp\left(-\left(t-\delta_2\right)/\tau_2\right)\right);$$

where $t_\tau$ is the time on the x-axis of the graph. $A_0$ is the value [Off]-VO$_2$ (ml·min$^{-1}$) from $A_0$ to [Off]-VO$_2$, expressed as 3C,10P.\textsuperscript{12,13} $A_0$ is the gain in the model of a component or in phase one. $A_0$ is the gain in the two-component model or in phase two. $A_0$ is the gain in the three-component model or in phase three. $1-\exp\left(-t/\tau\right)$ is the exponential distribution.\textsuperscript{19,20} $\delta(t)$ is the disappearance factor with the time constant $t$. $\tau$ is the time in which the transient response [Off]-VO$_2$ induced decays exponentially; when $t=\tau$, which means the time required for the transient response of

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Data were modelled using these multi-component models mentioned above using non-linear least squares regression techniques,\(^{16}\) and the best fit defined by the minimisation of the residual sum of squares. We used initial estimates of phases' (from one up to three) time delay: \(\Phi_1\), \(\delta_1\), \(\delta_0\); \(\Phi_2\), \(\delta_0\), \(\delta_2\); \(\Phi_3\), \(\delta_0\), \(\delta_3\), \(\delta_2\), \(\delta_1\) and \(\delta_0\); and from one up to three time constant: \(\Phi_1\), \(\delta_0\), \(\delta_2\), \(\delta_1\), \(\delta_0\), 180s; and from one up to three component model or in phase three. \(\delta_0\) is the delay in time delay in the three-component model or in phase three.

Amplitudes both from \(\Phi_1\) (the fundamental \(A_1\)) and from \(\Phi_2\) (\(A_2\)) were also expressed in terms of functional gain (\(G=\Delta VO_2/\Delta WorkRate\)) from models 2C,7P (BL1 to ERE) (\(G_2\)); and 3C,10PP (BL1 to ERE) (\(G_3\)). The kinetic analyses of VO\(_2\) transient response recovery from the submaximal exercise ([off]) was assessed in terms of the [off]-\(\Phi_1\)-VO\(_2\) kinetics (\(\tau_1\)).\(^{15}\) 

**Statistical analysis**: Estimated values of the \(\Phi_1\)-VO\(_2\) (i.e., \(\tau_1\), \(\delta_1\), \(A_1\)) and from the different models used were compared, young versus old data group, using two-way analysis of variance all pair wise multiple comparison procedures (Holm-Sidak method) with repeated measures.\(^{16}\) The Student’s t-test was used to determine if the mean values of the two groups were significantly different.\(^{10}\) The probability level of 0.05 was chosen as the criterion for acceptance of statistical significance.

**Results**

General physical characteristics, except age, were similar between YG and OG but there were age-related low cardiorespiratory fitness and age-related high ventilatory threshold

Old subjects compared young subjects were not significantly different in physical characteristics. However, in age (years) YG resulted (25.16±2.95) low compared OG (71.02±4.73) (t=24, P≤.001), in height (cm) YG was (179.6±5.7) was not significantly different to OG (174.1±5.5), in total body mass (kg) YG was (79.2±9.3) was not significantly different to OG (79.9±9.9) and in body mass index (kg m\(^{-2}\)) YG was (24.5±2.3) was not significantly different to OG (26.4±3). OG resulted significantly low in cardio-respiratory fitness compared the YG (except ‘cT’ that was conversely) (Figure 1).

**Figure 1** Groups’ maximal cardiorespiratory fitness data from a ramp test.

*Student t-test significant differences (P<0.05) between young and old subjects for work rate, \(t=7.2\); pulmonary oxygen uptake (VO\(_2\)), \(t=6.0\); heart rate, \(t=4.6\) and; ventilatory threshold (VeT), \(t=3.4\).

Age-related low submaximal work rate intensity exercise

The subjects [off]-transient pulmonary oxygen uptake response profiles to AbsMod (recovery from 50W); ModRel (80% ‘cT’): recovery from 84.2±14 W(YG) and recovery from 36.6±11.3 W(OG) and; HvyRel (120% ‘cT’): recovery from 160.3±24 W (YG) and recovery from 90.0±16.5 W (OG) square wave exercise is shown in Figure 2. As expected, analyses showed significant (P<0.001) aged-low ModRel (YG\(_{max}\) - OG\(_{max}\)=47.6W, \(t=7\)) and HvyRel (YG\(_{max}\) - OG\(_{max}\)=70.3W, \(t=10.3\)) work rate intensity.

**[Off]-estimated temporal parameters baseline1min (A0, ml min\(^{-1}\))**

Analyses showed that \(A_0\) for groups times intensity exercise AbsMod (YG=1188.8±33.6, OG=1180.0±50.4) ModRel (YG=1630.0±81.5, OG=1049.0±65.5) and HvyRel (YG=2783.1±162.1, OG=1633.1±121.3)
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OG=1773.0±109.3) resulted in a statistically significant interaction for relative work rate exercise only; in other words, ModRel A_{2} in the OG resulted in 581 ml·min^{-1} low compared YG (t=4, P<0.001), and HvyRel A_{2} in the OG resulted in 1010 ml·min^{-1} low compared YG (t=8, P<0.001). The end-exercise VO_{2} (ml·min^{-1}) in YG (1182±87) resulted similar compared OG (1180±145) (t=3, P≤0.05).

**Age-related low fundamental gain (G_{A2}, ml·min^{-1}·W^{-1}), age-related slow time delayed (δ_{2}, s) and age-related slow time constant (τ_{2}, s)** did not depend on the level of exercise intensity.

Analyses showed between groups significant (t=5, P<0.001) low G_{A2} age-related (YG-OG=2.1). Analysis showed significant (t=4.5, P<0.001) slow δ_{2}, age-related (OG-YG=7) and, significant slow τ_{2}, age-related (OG-YG=19.8, t=7.3, P<0.001) (Figure 3) but all of them were not dependent on the level of exercise intensity. In other words, gain, time delayed, and time constant from phase two [off] resulted numerically similar between ModRel and HvyRel exercise intensity but the mentioned parameters were significant low in the OG compared YG.

**Discussion**

This study sought to experimentally estimate the duration of phase [off]-transient Φ_{2} kinetics from submaximal exercise modelled with two component (phase two) and three component exponential (phase two) mathematical models. G_{A2} refers to the decrease in oxygen uptake during phase two in response to a simultaneous decrease in work rate. Phase 2 referred to the period following the offset of exercise when the mixed venous blood gas concentrations decrease to change because of changes in the effluent from the exercising muscles. Phase two [off] reflects the “kinetic phase” of the gas exchange that begins at the end of phase one [off] and continues until a recovery steady state is obtained. [Off] refers to end exercise recovery transient response; δ_{2}, refers to the latency when phase two [off] first become apparent τ_{2}, refers to the time required for phase two [off] to reach it’s 63% of the response. *Significant differences (P<0.001) between young and old subjects for gain (G_{A2}), time delayed (δ_{2}) and time constant (τ_{2}).

**Physical characteristics and ramp exercise test**

In spite of the different age between the OG and YG, we observed both lacks of significant differences in physical characteristics for height, total body mass, and body mass index and also a significantly high eT in the OG compared the YG. We explain these observations as indicators that the old subjects were in good physical fitness in terms of their general anthropometry and estimated ventilatory threshold, specially because the response to ramp test exercise is an essential component of the physiological evaluation of subjects across the entire spectrum of fitness and physical activity; from elite athletes to patients with a variety of disease states.

**Submaximal exercise test**

Since it has been observed aged low-on-transient VO_{2} response profiles to submaximal exercise previously\(^9,10,21\) and aging is associated...
with progressive declines in resting and energy expenditure and total energy expenditure it was not a surprise, that the young and old subjects [off]-transient VO₂ response profiles to ModRel recovery from 80% eT, and HvyRel recovery from 120% eT were significant aged-low work rate intensity. resulting differences from both the ModRel OG-YG=47.6 W and the HvyRel OG-YG=7.3 W.

However, this aged-low submaximal exercise was multifactorial in origin. Moreover, for moderate exercise condition, the O₂ deficit represented the energy equivalent to the depletion of high-energy phosphates (Creatine phosphate and ATP) and O₂ stored in the body at the start of the exercise. For heavy exercise condition, the O₂ deficit included the energy equivalent of the anaerobic. Therefore, the estimation of the O₂ deficit during heavy exercise transitions could also be considered the slow component of VO₂ as an additional deficit component with delayed start. Nevertheless, we considered that it did not affect the differences in O₂ deficit previously observed between YG and OG for heavy exercise condition. The high O₂ age-related deficit observed for the moderate absolute- intensity exercise was mainly because ageing was associated with poor muscle function that yielded slow VO₂ kinetics and a large O₂ deficit but the causes of lactate threshold production are a matter of debate.

[Off]-estimated temporal parameters

The [off]-transient (post-exercise VO₂ recovery) responses to the exercise tests for 50 W, absolute moderate exercise; relative moderate exercise and; for relative heavy exercise (submaximal exercise) constant [off]-loadless ([off]-transient) cycling were analysed with best statistically and/or physiologically exponential mathematical fitting models that characterised the [off]- Φ VO₂ kinetics ([off]-τΦ VO₂) for this submaximal exercise in young healthy adult and old men. Nevertheless, the aged-low submaximal exercise observations are multifactorial in origin.

Baseline l min (Ao, ml min⁻¹)

The VO₂A₀ values from the YG and OG resulted similar to each other, probably because these AbsMod work were performed without a lactic acidosis by our subjects. In this condition, the O₂ flow through the muscles is adequate to supply all of the O₂ needed for the aerobic regeneration of ATP in the steady state, and the patterns of VO₂ and VCO₂ increase reaching the steady-state exercise baseline without lactic acidosis. In contrast, our analyses showed that VO₂A₀ values from young and old groups times intensity exercise (ModRel and HvyRel) resulted in a statistically significant interaction for relative work rate exercise only, and probably this is due to the fact that by applying two different relative exercise intensities, 80% eT and 120% eT, our subjects performed these tests at different energy level intensity. In consequence, the VO₂A₀ values (ml·min⁻¹) in the YG were 581 and 1010 high compared OG for ModRel and HvyRel intensity exercise, respectively.

Age-related low [off]-Φ VO₂ functional gain (GA₀;ml min⁻¹ W⁻¹)

Analyses showed between groups significant low [off]- Ψ VO₂A₀ age-related; in the OG the [off]- Ψ VO₂A₀ was 2.1 ml·min⁻¹ W⁻¹ low compared YG and thus, the decrease in pulmonary oxygen uptake in response to a simultaneous decrease in work rate resulted diminished in the OG probably due to less efficiency for muscular work.

Age-related slow [off]-Φ VO₂ time delay (δ)

The δΦ VO₂ [off]- transient response in the OG was 6.95 s longer than that in the YG from submaximal exercise [off]-response. Slow [off]-transient Φ VO₂ time delay (δₘ) age-related, can be explained by an inertia of both the feedforward of ventilation and the time needed for down blood to flow from working muscles to lungs related with temporal physiological considerations modulating muscle efficiency indicating that it is necessary to take account of this transient delay “from muscle to mouth” if pulmonary OVVO₂ kinetics are to be used to estimate the end recovery exercise kinetics of muscle VO₂ consumption also.

Age-related slow [off]-Φ VO₂ kinetics (τₘ)

Our finding of long fundamental [off]-time constant age-related from submaximal exercise, not dependent on the level of exercise intensity, is in partial agreement with the previous observation that during high-intensity leg exercise in humans where exercise mode had no discernible effect on the kinetics of VO₂ in a subsequent recovery phase. In this study the [off]- Φ VO₂ kinetics resulted in 19.8 s prolonged in the OG compared the YG and this observation in older adults, probably means that the [off]- Φ VO₂ kinetics may be limited by a slow adaptation of muscle blood flow and O₂ delivery, due to the fact that in various studies have been observed increased total peripheral resistance, reduced capillary density, endothelial dysfunction, sarcopenia and altered capillary hemodynamics, which suggest that the convective delivery of O₂ to working muscle during exercise may be reduced in OG compared with YG, postulating that muscle O₂ delivery may limit VO₂ kinetics in older adults. Therefore, potential differences in the physical properties of the muscle vascular system could account, at least in part, for the age-related slow VO₂ [off] kinetics. In brief, in this work we observed a significant low fundamental gain, long fundamental both time delayed and time constant age-related in a subsequent recovery phase that was not dependent (except the fundamental gain) on the level of exercise intensity.

Conclusion

There was a slow kinetics (τ₂ of prolonged duration) related to age during VO₂ in phase two of age-related recovery of submaximal exercise, markedly influenced by the dynamics of VO₂ during submaximal muscle exercise in adult men.

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Conflict of interest

Author declares that there is no conflict of interest.
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