The influence of exercise intensity on pulmonary oxygen uptake kinetics in young and late middle-aged adults

Melitta. A. McNarry\textsuperscript{1}, Michael. I. C. Kingsley\textsuperscript{1,2} and Michael. J. Lewis\textsuperscript{1}

M.A.M conceived the study and all authors assisted in its design. M.A.M collected and analysed the data. All the authors contributed to the final manuscript.

\textsuperscript{1}College of Engineering, Swansea University, Wales, UK.

\textsuperscript{2}Institute for Health and Social Science Research, CQ University, Rockhampton, Australia

**Running head:** Influence of exercise intensity on $\dot{V}O_2$ kinetics

Dr. M.A. McNarry

College of Engineering, Swansea University

Singleton Park

Swansea, SA2 8PP

Tel 01792 513069

Fax 01792 295676

Email: m.mcna@swansea.ac.uk
Abstract

It is unclear whether pulmonary oxygen uptake ($\dot{V}O_2$) kinetics demonstrate linear, first order behaviour during supra gas exchange threshold exercise. Resolution of this issue is pertinent to the elucidation of the factors regulating $\dot{V}O_2$ kinetics, with oxygen availability and utilisation proposed as putative mediators. To re-examine this issue with the advantage of a relatively large sample size, fifty young (24±4 yrs) and fifteen late middle-aged (54±3 yrs) participants completed repeated bouts of moderate and heavy exercise. Pulmonary gas exchange, heart rate (HR) and cardiac output (Q) variables were measured throughout.

The phase II $\tau$ was slower during heavy exercise in both young (Mod: 22±9; Hvy: 29±9s; $P\leq0.001$) and middle-aged (Mod: 22±9; Hvy: 30±8s; $P\leq0.001$) individuals. The HR $\tau$ was slower during heavy exercise in young (Mod: 33±10; Hvy: 44±15s; $P\leq0.05$) and middle-aged (Mod: 30±12; Hvy: 50±20s; $P\leq0.05$) participants, and the $Q\tau$ showed a similar trend (Young - Mod: 21±13; Hvy: 28±16 s; Middle-aged - Mod: 32±13; Hvy: 40±15s; $P\geq0.05$). There were no differences in primary component $\dot{V}O_2$ kinetics between age groups but the middle-aged group had a significantly reduced $\dot{V}O_2$ slow component amplitude in both absolute (Young: 0.25±0.09; Middle-aged: 0.11±0.06 l·min$^{-1}$; $P\leq0.05$) and relative terms (Young: 15±10; Middle-aged: 9±4%; $P\leq0.05$).

Thus, $\dot{V}O_2$ kinetics do not demonstrate dynamic linearity during heavy intensity exercise. Speculatively, the slower phase II $\tau$ during heavy exercise might be attributable to reduced oxygen availability. Finally, the primary and slow components of $\dot{V}O_2$ kinetics appear to be differentially influenced by middle-age.

Keywords: $\dot{V}O_2$ kinetics; cardiac output; heart rate; dynamic linearity; slow component
Introduction

In response to the onset of constant-work rate exercise, pulmonary oxygen uptake (\(\dot{V}O_2\)) rises in a near-exponential manner (the so-called phase II response), attaining a steady-state within 2-3 minutes in young, healthy adults during moderate intensity exercise (below the gas exchange threshold, GET) (64, 65). During exercise above the GET, the dynamic \(\dot{V}O_2\) response becomes appreciably more complex (40, 48, 65), with attainment of a steady state delayed, or even precluded, by the presence of a supplementary “slow component” of \(\dot{V}O_2\) (8, 65).

Irrespective of the work rate within the moderate intensity domain, \(\dot{V}O_2\) kinetics are accepted to be largely invariant (6, 26, 35). However, whether this linear, first order behaviour persists across the continuum of ‘sub-maximal’ exercise remains unclear. A linear, first order system obeys the law of superposition (25): the key response parameters (here the time constant that describes the time taken to achieve 63% of the exponential response (\(\tau\)), and the primary component gain which describes the oxygen cost per unit work rate) for a higher work rate can be predicted from the response to a lower work rate. Whether the phase II \(\tau\) is slower during heavy compared to moderate intensity exercise is controversial, with some studies reporting no difference (8, 47, 57) while others have found a significant slowing in the \(\tau\) during heavy intensity exercise (33, 36, 48). Small, heterogeneous sample sizes (e.g. 8, 22, 47, 48) and large inter-individual variability in the phase II \(\tau\) have hampered the resolution of this issue; additionally, the range of exercise intensities, modalities and modelling techniques used in different studies has limited inter-study comparison. Similarly, the primary component gain is conventionally considered to be invariant across exercise intensities (8, 48, 63) but recent studies have challenged this notion, demonstrating a significant fall in the gain with increasing exercise intensity (33, 53, 66).
Resolution of the presence (or absence) of dynamic linearity in the $\dot{V}O_2$ kinetic response across the continuum of exercise intensity domains is an important step towards elucidating the set of factors regulating $\dot{V}O_2$ kinetics (36). The rate-limiting determinant of the $\dot{V}O_2$ kinetic response continues to be a contentious issue, with oxygen delivery and oxygen utilisation both proposed as putative mediators (for thorough reviews, see 31, 49). Proponents of an oxygen delivery related limitation suggest that there is a specific point or site during the transport of oxygen from mouth to mitochondria that acts as a rate-limiter (31, 41, 59), whereas supporters of an oxygen utilisation regulator propose that the finite kinetics are attributable to an intrinsic slowness of intracellular oxidative metabolism in adjusting to the altered metabolic demand (13, 27, 33). A slowing of the phase II $\tau$ during heavy compared with moderate intensity exercise has been interpreted as reflective of a reduced oxygen availability (31). However, the metabolic properties of the recruited muscle fibres have also recently been proposed as putative mediators of a slower phase II $\tau$ and lower primary component gain during heavy compared to moderate intensity exercise (33, 66).

$\dot{V}O_2$ kinetics are highly sensitive to both advantageous (e.g. exercise training (34)) and deleterious (e.g. disease (51)) influences. Ageing is known to exert a significant slowing influence on $\dot{V}O_2$ kinetics during moderate intensity exercise (3, 12, 14, 21, 29). This slowing has primarily been attributed to age-related impairments to muscle $O_2$ delivery (12, 14, 58) or muscle $O_2$ distribution (43, 45) and diminished $O_2$ utilisation (16, 20). It is not known whether the $\dot{V}O_2$ kinetic response is similarly slowed with age during heavy intensity exercise.
In this study we sought to re-examine the dynamics of the \( \dot{V}O_2 \) response during moderate and heavy intensity exercise with the advantage of a much larger sample size than has been used previously. The specific aim of this work was to compare the \( \dot{V}O_2 \) responses in young and late middle-aged participants, at both exercise intensities. We expected to confirm that the phase II \( \tau \) is slower during heavy compared to moderate intensity exercise in young participants. We additionally hypothesised 1) that the phase II \( \tau \) would be slower during heavy relative to moderate intensity exercise in late middle-aged participants, and 2) that advancing age would be associated with slower \( \dot{V}O_2 \) kinetics, irrespective of exercise intensity.

**Methods**

**Participants**

Fifty young adults (Y: mean ± S.D. age 23 ± 3 years; body mass 71.5 ± 13.1 kg; height 1.7 ± 0.1 m; 28 male) and 15 late middle-aged adults (MA: mean ± S.D. age 54 ± 3 years; body mass 70.5 ± 11.6 kg; height 1.7 ± 0.1 m; 6 male) volunteered for the study. The participants were all recreationally active, but not highly trained. The young and middle-aged participants did not differ in absolute peak \( \dot{V}O_2 \) (Table 1), but the middle-aged participants achieved a higher age-relative percentile peak \( \dot{V}O_2 \). Because participant ‘fitness’ might confound the influence of age on oxygen uptake kinetics, further analyses were performed to compare a subgroup of young participants with the middle-aged participants, which were matched according to sex and age-relative percentile peak \( \dot{V}O_2 \) (‘percentile matched’ subgroup: male: 80\(^{th}\); female: 60\(^{th}\) percentile; (1)).

Prior to testing, participants were informed of the protocol and risks and gave written consent to participate in the study. All procedures were approved by a Swansea University ethics
committee and were conducted in accordance with the Declaration of Helsinki. Participants were asked to arrive at the laboratory in a rested state, at least two hours postprandial and to avoid strenuous exercise in the 24 hours preceding each testing session. Participants were also asked to refrain from caffeine and alcohol for 6 and 24 h before each test, respectively. All tests were performed at the same time of day (± 2 h).

Experimental Design

Participants were required to visit the laboratory on four occasions, separated by at least 24 hours recovery. Participants initially completed a ramp incremental exercise test for determination of $\dot{V}O_2^{\text{peak}}$ and GET. On each of the three subsequent visits, participants completed two bouts of moderate intensity exercise (Mod: at a work rate calculated to elicit 70% of the GET) followed by a bout of heavy intensity exercise (Hvy: at a work rate calculated to elicit a $\dot{V}O_2$ equal to the GET plus 30% of the difference between the GET and peak $\dot{V}O_2$, i.e. $\Delta30\%$). Recent studies show that prior moderate exercise bouts do not influence the response to subsequent exercise bouts (60). All exercise testing was conducted using an electronically braked cycle ergometer (Lode Excalibur, Groningen, Netherlands).

Incremental Test

Initially, participants completed 3 min of baseline cycling at 0W, after which the work rate was increased at a rate of 20-30 W·min$^{-1}$ until the limit of tolerance. The participants were asked to maintain a cadence of 70–80 rpm. Breath-by-breath pulmonary gas-exchange data were collected continuously during the incremental tests and averaged over consecutive 5-s periods (Oxycon Pro, Jaeger, Germany). The $\dot{V}O_2^{\text{peak}}$ was taken as the highest 10-s average value attained before the subject’s volitional exhaustion in the test. The GET was determined by the V-slope method (10). The work rates that would require 70% of the GET (moderate
exercise) and Δ30% were subsequently determined, accounting for the mean response time for $\dot{V}O_2$ during ramp exercise (i.e. two thirds of the ramp rate was deducted from the work rate at the GET and peak $\dot{V}O_2$ (62)).

*Step Exercise Tests*

For the determination of $\dot{V}O_2$, and $Q$ kinetics, participants completed a series of “step” tests. The protocol, which was performed three times on separate days, comprised of two moderate intensity and one heavy intensity cycle transition, each of 6-min duration. Each transition was preceded by 6 min of pedalling with no external resistance followed by an abrupt transition to the target work rate. Therefore, all participants performed a total of six bouts of moderate-intensity exercise and three bouts of heavy intensity exercise, ensuring that similar confidence levels were associated with the parameters derived for both moderate and heavy intensity exercise (Table 3).

*Measurements*

Throughout all exercise tests, participants wore a facemask and breathed through a low dead space (90 ml), low resistance (0.75 mmHg·l$^{-1}$·s$^{-1}$ at 15 l·s$^{-1}$) impeller turbine assembly (Jaeger Triple V, Hoechberg, Germany). The inspired and expired gas volumes and gas concentration signals were continuously sampled at 100 Hz, the latter using paramagnetic (O$_2$) and infrared (CO$_2$) analysers (Jaeger Oxycon Pro, Hoechberg, Germany) via a capillary line connected to the mouthpiece. These analysers were calibrated before each test with gases of known concentrations, and the turbine volume transducer was calibrated using a 3 l syringe (Hans Rudolph, Kansas City, MO). The volume and concentration signals were time aligned by accounting for the delay in capillary gas transit and analyser rise time relative to the volume signal. Breath-by-breath fluctuations in lung gas stores were corrected for by computer
algorithms (9). \( Q \) was determined noninvasively, on a beat-to-beat basis, throughout the exercise tests using a, previously validated (24, 45), thoracic bioelectrical impedance device (TaskForce, CNSystems Medizintechnik GMBH, Austria).

\( \dot{V}O_2 \) kinetics analysis

Initially, the breath-by-breath \( \dot{V}O_2 \) responses to each step transition were visually examined to remove any errant breaths caused by coughing, swallowing, sighing etc, using a 5-s moving average to identify points lying in excess of 4 standard deviations from the local mean. Subsequently, each transition was interpolated to 1-s intervals, time aligned to the start of exercise and averaged. Following baseline correction, a mono-exponential model with a time delay (Eq.1) was then applied to this averaged response:

\[
\Delta \dot{V}O_2(t) = A_1 \cdot (1 - e^{-\frac{t - \delta_1}{\tau_1}})
\]  

(Eq. 1)

where \( \Delta \dot{V}O_2 \) is the increase in \( \dot{V}O_2 \) at time \( t \) above the baseline value (calculated as the mean \( \dot{V}O_2 \) from the first 45-s of the last min of baseline pedalling), and \( A_1, \delta_1 \) and \( \tau_1 \) are the primary component amplitude, time delay (which was allowed to vary freely), and time constant, respectively. Kinetic variables (\( A_1, \delta_1 \) and \( \tau_1 \)) and their 95% confidence intervals were determined by least squares non-linear regression analysis (Graphpad Prism, Graphpad Software, San Diego, CA). A mono-exponential model was ultimately used for both moderate and heavy intensity exercise as a bi-exponential during heavy exercise was found to produce an inferior and ambiguous fit.

To investigate the effect of different fitting windows with respect to the onset of phase II, the mono-exponential derived parameters were compared when fitting started at seven different
points: 15 s, 20 s, 25 s, 30 s, 35 s, 40 s and the visually identified phase I duration (VI phase I). The VI phase I was determined as the point at which there was a sharp decrease in both the respiratory exchange ratio and the end-tidal partial pressure of oxygen, indicative of the phase I-phase II transition. This analysis was undertaken to extend the findings of a recent study by Murias et al. (46) during moderate intensity exercise to heavy intensity exercise.

Given the failure of the bi-exponential model to describe the $\dot{V}O_2$ response during heavy intensity exercise, the onset of the $\dot{V}O_2$ slow component was determined using purpose designed LabVIEW software which iteratively fits a monoexponential function to the $\dot{V}O_2$ data until the window encompasses the entire response. The resulting phase II time constants were plotted against time and the onset of the $\dot{V}O_2$ slow component identified as the point at which the phase II time constant consistently deviates from the previously “flat” profile (23, 56). The amplitude of the $\dot{V}O_2$ slow component was subsequently determined by calculating the difference between the end exercise $\dot{V}O_2$ and the sum of the primary amplitude and baseline $\dot{V}O_2$. This was expressed both in absolute terms and relative to end exercise $\dot{V}O_2$.

The functional gain of the primary $\dot{V}O_2$ response during both exercise intensities was also calculated by dividing the primary phase amplitude by the change in work rate. Finally, the mean response time (MRT) was calculated by fitting a single exponential curve to the data with no time delay from the onset of exercise to the end of exercise.

**Kinetic analysis**

To provide information on bulk O$_2$ delivery, the overall Q response to exercise was also modelled. The responses to each transition were interpolated to 1-s intervals, time aligned and averaged to produce a single data set. In accord with previous studies (5, 7, 32), the resulting responses were fitted with a mono-exponential without a time delay (Eq. 2). For
both moderate and heavy exercise, the fitting window commenced at \( t = 0 \); for heavy intensity exercise the window was constrained to the onset of the \( \dot{V}O_2 \) “slow component”.

\[
\dot{Q} = A_1 \cdot (1 - e^{-(t/\tau_1)})
\]  

(Eq.2)

where \( \Delta \dot{Q} \) is the increase in \( \dot{Q} \) at time \( t \) from the baseline (calculated as the mean from the first 45 s of the last min of baseline pedalling), and \( A_1 \) and \( \tau_1 \) are the primary component amplitude and time constant, respectively.

**Statistics**

Gaussian distribution was confirmed by the Shapiro-Wilks test. Following this, the results of the incremental ramp test were analysed to assess the influence of age using an independent samples t-test. The remaining data were analysed using a mixed ‘between-within’ analysis of variance (ANOVA), with age as a between-participant factor and exercise intensity as a within-participant factor. Post-hoc analyses for the influence of phase I duration were performed using pairwise comparisons, with Bonferroni correction. Pearson product moment correlation coefficients were used to analyse the degree of association between key variables. Inter-observer reliability between the 3 researchers who independently identified the phase I-phase II transition was calculated for both exercise intensities. All statistical analyses were conducted using PASW Statistics 18 (SPSS, Chicago, IL). All data are presented as means ± SD. Statistical significance was accepted when \( P \leq 0.05 \).

**Results**

Participants’ peak exercise values for the group (\( n=65 \)) are shown in Table 1. Age did not influence peak \( \dot{V}O_2 \) (\( P =0.23 \)), GET (\( P =0.14 \)), relative GET (GET expressed as a fraction of peak \( \dot{V}O_2 \)) (\( P =0.80 \)), or peak power (\( P =0.19 \)). Restricting the comparison to the ‘peak \( \dot{V}O_2 \)
percentile matched’ subgroup, again age did not influence peak $\dot{V}O_2$ ($P = 0.25$), GET ($P = 0.31$), relative GET ($P = 0.87$), or peak power ($P = 0.20$).

Figure 1 presents the raw data used for the identification of the phase I-phase II transition. The figure illustrates an example of where there is a clear demarcation; however, the transition point was not always so clearly discernible. Nonetheless, analysis of the between-observer repeatability of the selected transition point yielded a reliability coefficient of $R^2 = 0.72$.

There was no evidence of an interaction effect between ‘age’ and ‘exercise intensity’ on VI phase I duration ($F_{(1,63)} = 0.14, P=0.72$). In the young participants, the VI phase I duration was 28 s during moderate intensity exercise and 16 s during heavy intensity exercise, respectively. In the middle-aged participants these durations were, respectively, 36 s and 26 s. As seen in Figure 1, the VI phase I duration was significantly shorter during heavy compared with moderate intensity exercise ($F_{(1,63)} = 32.17, P < 0.001, \eta^2 = 0.373$) and was significantly shorter in young compared with middle aged participants ($F_{(1,63)} = 9.74, P < 0.01, \eta^2 = 0.153$). There was a significant correlation between the VI phase I duration and work rate during both moderate ($r = -0.33, P < 0.05$) and heavy intensity exercise ($r = -0.38, P < 0.01$). Provided a minimum phase I period of 20 s was used, the selected exclusion period did not influence phase II $\tau$ (irrespective of exercise intensity or age) ($F_{(1,63)} = 2.04, P = 0.09$). Consequently, for all subsequent analyses, a 20 s exclusion period was used to account for phase I, thereby allowing comparisons with the literature.

There was no evidence of an interaction effect between ‘age’ and ‘exercise intensity’ on phase II amplitude, phase II $\tau$, time delay or MRT ($F_{(1,63)} = 0.17-0.36, P =0.16-0.68$),
indicating an age-independent influence of exercise intensity on the $\dot{V}O_2$ dynamic responses.

As summarised in Table 2 and illustrated in Figure 2, the dynamic $\dot{V}O_2$ response was significantly influenced by exercise intensity. Heavy intensity exercise elicited a greater phase II amplitude ($F_{(1,63)} = 159.02, P < 0.001, \eta^2 = 0.72$), a slower phase II $\tau$ ($F_{(1,63)} = 27.12, P < 0.05, \eta^2 = 0.30$), a reduced phase II gain ($F_{(1,63)} = 5.76, P < 0.05, \eta^2 = 0.10$), a reduced time delay ($F_{(1,63)} = 12.74, P < 0.01, \eta^2 = 0.17$), and a reduced MRT ($F_{(1,63)} = 94.6, P < 0.001, \eta^2 = 0.61$) compared with moderate intensity exercise. Furthermore, when the analysis was restricted to the 'peak $\dot{V}O_2$ percentile matched' subgroup, as shown in Table 4, heavy exercise still provoked a greater phase II amplitude ($F_{(1,41)} = 149.48, P < 0.001, \eta^2 = 0.79$), a slower phase II $\tau$ ($F_{(1,41)} = 25.10, P < 0.001, \eta^2 = 0.38$), a reduced time delay ($F_{(1,41)} = 12.39, P < 0.001, \eta^2 = 0.23$), and a reduced MRT ($F_{(1,38)} = 81.37, P < 0.001, \eta^2 = 0.68$) compared with moderate intensity exercise. However, exercise intensity did not influence phase II gain ($F_{(1,34)} = 3.63, P = 0.065$).

In the overall group, there was no influence of age on the phase II amplitude ($F_{(1,63)} = 3.13, P = 0.08$), phase II $\tau$ ($F_{(1,63)} = 0.03, P = 0.87$), phase II gain ($F_{(1,63)} = 0.00, P = 0.95$), phase II time delay ($F_{(1,63)} = 0.07, P = 0.79$) or MRT ($F_{(1,63)} = 0.01, P = 0.92$). Furthermore, when the analysis was restricted to the 'peak $\dot{V}O_2$ percentile matched' subgroup, as shown in Table 4, there was still no influence of age on the $\dot{V}O_2$ phase II amplitude ($F_{(1,41)} = 1.52, P = 0.23$), phase II $\tau$ ($F_{(1,41)} = 0.51, P = 0.48$), phase II gain ($F_{(1,34)} = 0.19, P = 0.66$), phase II time delay ($F_{(1,41)} = 1.08, P = 0.30$) or MRT ($F_{(1,38)} = 0.05, P = 0.82$).

The influence of exercise intensity on the HR and $Q$ kinetics is summarised in Table 3. There was no evidence of an interaction effect between 'age' and 'exercise intensity' on amplitude or $\tau$ for either $Q$ or HR ($F_{(1,37)} = 0.01-0.80, P = 0.38-0.92$), indicating an age-independent
influence of exercise intensity on the \( Q \) and HR dynamic responses. Heavy intensity exercise elicited a greater amplitude response in \( Q \) \((F(1,37) = 107.02, P < 0.001, \eta^2 = 0.74)\) and HR \((F(1,40) = 164.98, P < 0.001, \eta^2 = 0.81)\). Compared with moderate intensity exercise, heavy exercise elicited a greater \( \tau \) for HR \((F(1,40) = 15.93, P < 0.001, \eta^2 = 0.29)\) but did not influence \( \tau \) for \( Q \) \((F(1,37) = 0.01, P = 0.92)\).

As shown in Table 3, age did not influence the amplitude responses of either \( Q \) \((F(1,37) = 1.12, P = 0.296)\) or HR \((F(1,40) = 2.82, P = 0.101)\) nor did age influence the \( \tau \) responses of either \( Q \) \((F(1,37) = 3.71, P = 0.06)\) or HR \((F(1,40) = 0.00, P = 0.98)\). Similarly, in the ‘peak \( \dot{V}\text{O}_2 \) percentile matched’ subgroup, age did not influence the amplitude responses of either \( Q \) \((F(1,23) = 0.984, P = 0.33)\) or HR \((F(1,29) = 2.46, P = 0.13)\) nor did age influence the \( \tau \) of the HR response \((F(1,29) = 0.12, P = 0.74)\). However, for the peak \( \dot{V}\text{O}_2 \) percentile matched subgroup (Table 4) \( Q \) \( \tau \) was faster in the young participants \((F(1,20) = 5.39, P < 0.05, \eta^2 = 0.21)\).

The \( \dot{V}\text{O}_2 \) slow component onset was similar in both young and middle-aged participants \((Y: 150 \pm 44 \text{ vs. MA: } 166 \pm 35 \text{ s, } P = 0.20)\) but the amplitude was reduced in middle-aged individuals, regardless of whether it was expressed in absolute \((Y: 0.22 \pm 0.14 \text{ vs. MA: } 0.11 \pm 0.06 \text{ l·min}^{-1}, P < 0.05)\) or relative terms \((Y: 13 \pm 8 \text{ vs. MA: } 9 \pm 4\%, P < 0.05)\). Age was significantly, but weakly, correlated with the \( \dot{V}\text{O}_2 \) slow component amplitude, in both absolute \((r = -0.28, P = 0.02)\) and relative terms \((r = -0.28, P = 0.03)\).

**Discussion**
Consistent with our hypotheses, we found that the phase II \( \tau \) was significantly slower during heavy compared to moderate intensity exercise. Our results therefore confirm the findings of earlier studies. Furthermore, we extend these observations by demonstrating that \( \dot{V}O_2 \) kinetics are similarly non-linear (as functions of exercise work load) in late middle-aged and young participants. In contrast to our hypothesis, however, the phase II \( \tau \) was not slower in the older participants; the only difference between young and middle-aged participants was that the magnitude of the \( \dot{V}O_2 \) slow component was smaller in the older group.

Across the work rates that characterise the moderate intensity domain, \( \dot{V}O_2 \) kinetics are accepted to be largely invariant (6, 26, 35). However, whether this linear (first order) behaviour, which obeys the law of superposition (25), is manifest across the continuum of supra-GET exercise intensities has been unclear from the previous literature. While some studies support the concept of dynamic linearity in the \( \dot{V}O_2 \) kinetic response between moderate and heavy intensity exercise in young people (8, 47, 57), the present results and those of Jones et al. (33), Koppo et al. (36) and Paterson et al. (48) do not. Moreover, ours is the first study to investigate the influence of exercise intensity on the dynamic \( \dot{V}O_2 \) kinetic response in a middle-aged population. Further evidence against the concept of dynamic linearity is provided by the fall in the primary component gain with increasing exercise intensity found here and elsewhere (33, 53, 66), contradicting the concept of an invariant gain with increasing exercise intensity (8, 48, 63). With regard to the gain values reported in the present study, a potential limitation to their interpretation is the use of an unloaded baseline exercise phase. This could have resulted in a non-uniform relative work load across participants, which might have influenced the primary component gain values. Nonetheless, the present results extend earlier findings, the interpretation of which was often hampered by small sample sizes (e.g. 8, 22, 47, 48). We observed a 28% and 27% slower phase II \( \tau \) during
heavy exercise in the young and middle-aged participants, respectively. This difference is
greater than that estimated in a review of studies in young healthy participants (~18%; (50))
or reported in older people (17%; (19)). The explanation for this greater phase II τ at higher
exercise intensities is presently unclear. Given the uniformity of $\dot{V}O_2$ kinetics within the
moderate intensity domain, it is unlikely to be attributable to the lower intensity of moderate
exercise used in the present study. We speculate that it might be a reflection of an inherent
variability in the response of individual participants that is of physiological origin (50).

Resolution of the debate surrounding the possible slowing of the phase II τ above the GET is
essential for elucidating the factors that regulate $\dot{V}O_2$ kinetics (36). The present study, which
refutes the theory of dynamic linearity above the GET, indicates that there is additional
complexity in the $\dot{V}O_2$ kinetics control mechanism. A slowing of the phase II τ has been
suggested to signify an oxygen delivery limitation to $\dot{V}O_2$ kinetics (e.g. 31, 41), although this
is controversial with others suggesting that any slowing is principally attributable to an
intracellular ‘metabolic inertia’ of the recruited muscle fibres (e.g. 4, 13). In the present
study, we did not measure muscle blood flow and thus we are unable to specifically address
the question of an oxygen delivery limitation. However, the slower HR and $Q$ kinetics we
observed during heavy intensity exercise, which provide an estimate of bulk muscle $O_2$
delivery (42), suggest that an oxygen delivery or distribution limitation might, at least in part,
be a contributing factor, as suggested elsewhere (15, 28). Although speculative, an
alternative (or additional) interpretation of the present data is that there is a greater
proportional contribution to muscular force production from type II muscle fibres during
heavy intensity exercise (38). Type II muscle fibres have a lower oxidative but a higher
glycolytic capacity and (at least in mouse muscle) an inherently slower $\dot{V}O_2$ response relative
to type I muscle fibres (18, 37). Therefore, a greater reliance on type II muscle fibres during
heavy intensity exercise might be anticipated to result in an overall slowing of the dynamic $\dot{V}O_2$ response. Although a slower $\dot{V}O_2$ response has previously been reported in human participants with a higher percentage of type II fibres (53), we did not assess muscle fibre type recruitment in the present study and thus further conclusions are precluded. The non-linearity observed here suggests that both oxygen delivery and oxygen utilisation might play a role in determining the $\dot{V}O_2$ kinetic response to heavy intensity exercise.

Contrary to our hypothesis, we did not observe any differences in the primary component $\dot{V}O_2$ kinetics of young and middle-aged participants during either exercise intensity. Furthermore, heavy intensity exercise was associated with a similar magnitude of slowing of the phase II $\tau$ for both age groups (28% and 27% for young and middle-aged, respectively). This finding suggests that the impairments to muscle O$_2$ delivery (39) and diminished mitochondrial oxidative function (17), to which the slower $\dot{V}O_2$ kinetics in older participants have been attributed, were not manifest in our middle-aged participants. This finding raises the interesting question regarding the progression of “ageing effects” across different parameters and the appropriate threshold age for studies investigating the influence of ageing; the late middle-aged participants of the present study were younger (54 ± 3 yrs) than the older participants in which slower $\dot{V}O_2$ kinetics have been widely reported (~65 yrs; (3, 12, 14, 21, 29)), but considerably older than the age at which reduced heart rate variability (61, 67) and aerobic fitness have been reported (2). We hypothesised that this absence of age-related differences may be partly attributable to the relative aerobic fitness of our participants: whilst the young and middle aged groups had a similar absolute peak $\dot{V}O_2$, when age is accounted for the middle-aged participants had a higher relative fitness. We therefore sought to investigate this further by comparing the $\dot{V}O_2$ kinetics in a subgroup matched according to percentile peak $\dot{V}O_2$. This analysis revealed that, in both men and women, there were still no
differences in the primary component \(\dot{V}O_2\) kinetics of young and middle-aged participants. Thus, differences in the relative peak \(\dot{V}O_2\) of the present cohorts does not appear to explain the absence of age-related effects on primary component \(\dot{V}O_2\) kinetics. Nonetheless, this apparent age-independence could be related to the considerably higher aerobic fitness of our middle-aged participants compared with levels typically reported in studies of ageing on \(\dot{V}O_2\) kinetics (19); both chronic and acute exercise improve endothelium-dependent vasodilation (30) and has been suggested to be associated with faster \(\dot{V}O_2\) kinetics in older people (44). Therefore, a high fitness of our middle-aged participants might have ameliorated the influence of age in this work. Irrespective of the origin of the similarity in \(\dot{V}O_2\) kinetics that we observed for young and middle-aged participants, this finding precluded any further investigation of the effect of an altered regulatory control on the dynamic linearity of \(\dot{V}O_2\) kinetics. Resolution of this question therefore requires further study.

In contrast to the primary component kinetics, the magnitude of the \(\dot{V}O_2\) slow component did differ significantly in young and middle-aged participants. Specifically, despite a similar time at which the \(\dot{V}O_2\) slow component became evident, the magnitude of the slow component was significantly reduced in the older participants. Interestingly, contradictory to findings in older people where a smaller absolute slow component magnitude in older people was abolished when expressed relative to end-exercise \(\dot{V}O_2\) (11, 19), the difference between the present groups persisted, indicating that this is not a reflection of the lower absolute response amplitude. Instead, the reduced slow component magnitude could be attributable to the preferential loss of type II muscle fibres reported with ageing (11). Although the aetiology of the slow component remains to be conclusively elucidated, ~90% of this component has been shown to arise from within the exercising muscle (52, 55), with the recruitment of additional (less efficient) type II muscle fibres widely purported (38, 54). Therefore, a diminished
capacity to recruit type II fibres might be expected to be associated with a reduced slow component magnitude. However, since muscle fibre type distribution and abundance was not assessed in the present study, further interpretation is beyond the scope of the current study. It is prudent to note, however, that the lower slow component amplitude observed in the present middle-aged participants might be a reflection of a slower development of this component in these individuals, i.e. the slow component might not have been fully manifest at 6 minutes in the middle-aged participants, artificially causing it to appear diminished.

A failure to appropriately exclude phase I from the subsequent phase II analysis could result in an artificial lengthening of the phase II \( \tau \) (7). The most appropriate method of avoiding such issues was recently revisited by Murias et al. (46) who concluded, in agreement with the current study, that a fixed exclusion period was advisable. This conclusion followed identification of the challenges associated with determining the phase I-phase II transition from gas exchange indices during moderate intensity exercise, challenges we similarly encountered during both moderate and heavy intensity exercise. The phase I durations observed here during moderate intensity exercise in young people were within the range of those previously reported (44), although the mean phase I duration was a little longer in the present study (26 vs. 20 s presently and in Murias et al. (44), respectively). This might be related to the lower exercise intensity used in the present study. We believe the present findings therefore provide further support for the use of a fixed point as a logical option in contrast to the uncertainties and potential bias introduced by attempting to identify an often indeterminate phase I-phase II transition.

**Perspectives and Significance**
This study re-examined the hypothesis of linear, first order dynamics as a descriptor of the \( \dot{V}O_2 \) kinetic response during supra GET exercise. In the largest sample population to date, it demonstrated that \( \dot{V}O_2 \) kinetics do not conform to this hypothesis with respect to either time- or amplitude-based components of \( \dot{V}O_2 \) kinetics. Specifically, the phase II \( \tau \) was slower and the primary component gain reduced during heavy compared to moderate intensity exercise. This study further extends these observations to a novel population, illustrating that the \( \dot{V}O_2 \) kinetics of late middle-aged participants are similar to those of the young. These findings are of significance to the continued controversy regarding the mechanistic basis of \( \dot{V}O_2 \) kinetics, and support a more complicated control mechanism during heavy intensity exercise. Although predominantly beyond the scope of the present measurements, an oxygen availability limitation to \( \dot{V}O_2 \) kinetics is suggested by the slower HR and \( Q \) kinetics that we observed. However, it is still reasonable to expect that an intracellular “metabolic inertia” within the recruited muscle fibres, possibly related to the relative contributions of different muscle fibre types to the muscular force production, exerted an influence in determining the dynamic \( \dot{V}O_2 \) response.

The present study also demonstrated a divergent influence of late middle-age on the primary- and slow components of \( \dot{V}O_2 \) kinetics. This finding provides perspective to studies in older participants with regard to the progressive manifestation of “age effects”, providing an important addition to the age and \( \dot{V}O_2 \) kinetics literature.
Grants

The development of this manuscript has been part-funded by the EU’s Convergence European Regional Development Fund through the Welsh Government's Academic Expertise for Business (A4B) programme (grant number: HE09 COL1029).
References


Table 1. Incremental ramp test derived values. Subgroup refers to the ‘peak $\dot{V}O_2$ percentile matched’ subgroup of younger participants who were compared to the middle-aged participants to account for differences in age-relative peak $\dot{V}O_2$.

<table>
<thead>
<tr>
<th></th>
<th>Young</th>
<th>Middle-aged</th>
<th>Young Subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td>$n$</td>
<td>50</td>
<td>15</td>
<td>28</td>
</tr>
<tr>
<td>Peak $\dot{V}O_2$, l·min$^{-1}$</td>
<td>3.10 ± 0.98</td>
<td>2.67 ± 1.10</td>
<td>3.06 ± 0.91</td>
</tr>
<tr>
<td>GET, l·min$^{-1}$</td>
<td>1.70 ± 0.60</td>
<td>1.42 ± 0.61</td>
<td>1.62 ± 0.57</td>
</tr>
<tr>
<td>Relative GET, %</td>
<td>54 ± 10</td>
<td>53 ± 12</td>
<td>53 ± 9</td>
</tr>
<tr>
<td>Moderate WR, W</td>
<td>38 ± 26</td>
<td>24 ± 15</td>
<td>37 ± 28</td>
</tr>
<tr>
<td>Heavy WR, W</td>
<td>159 ± 59</td>
<td>128 ± 58</td>
<td>156 ± 56</td>
</tr>
</tbody>
</table>

Values are mean ± SD. $\dot{V}O_2$, oxygen uptake; GET, gas exchange threshold; WR, work rate.

There were no significant differences between age groups.
Table 2. Oxygen uptake kinetic parameters during moderate and heavy intensity exercise in young and middle-aged participants

<table>
<thead>
<tr>
<th></th>
<th>Moderate</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Young</td>
<td>Middle-aged</td>
<td>Young</td>
<td>Middle-aged</td>
</tr>
<tr>
<td>$\dot{V}O_2$ Base, l·min$^{-1}$</td>
<td>0.65 ± 0.12</td>
<td>0.56 ± 0.11</td>
<td>0.64 ± 0.12</td>
<td>0.55 ± 0.10</td>
</tr>
<tr>
<td>$\dot{V}O_2$ Amp, l·min$^{-1}$</td>
<td>0.42 ± 0.29</td>
<td>0.28 ± 0.07</td>
<td>1.53 ± 0.6‡</td>
<td>1.29 ± 0.61‡</td>
</tr>
<tr>
<td>$\dot{V}O_2$ TD, s</td>
<td>9 ± 6</td>
<td>6 ± 7</td>
<td>11 ± 6‡</td>
<td>12 ± 7‡</td>
</tr>
<tr>
<td>$\tau$</td>
<td>21 ± 9</td>
<td>22 ± 9</td>
<td>29 ± 9‡</td>
<td>30 ± 8‡</td>
</tr>
<tr>
<td>$\tau$ 95% CI, s</td>
<td>3 ± 1</td>
<td>3 ± 1</td>
<td>3 ± 1</td>
<td>3 ± 1</td>
</tr>
<tr>
<td>$\dot{V}O_2$ MRT, s</td>
<td>28 ± 9</td>
<td>27 ± 10</td>
<td>45 ± 11‡</td>
<td>45 ± 13‡</td>
</tr>
<tr>
<td>$\dot{V}O_2$ Gain, ml·O₂·min$^{-1}$</td>
<td>11.2 ± 3.8</td>
<td>11.0 ± 3.0</td>
<td>9.7 ± 1.3‡</td>
<td>10.0 ± 1.0</td>
</tr>
<tr>
<td>$\dot{V}O_2$ End Exer, l·min$^{-1}$</td>
<td>1.05 ± 0.3</td>
<td>0.84 ± 0.13*</td>
<td>2.42 ± 0.72</td>
<td>1.95 ± 0.69*</td>
</tr>
</tbody>
</table>

Values are mean ± SD. $\dot{V}O_2$, oxygen uptake; Base, baseline; Amp, amplitude; TD, time delay; $\tau$, time constant; MRT, mean response time; CI, confidence interval; End Exer, end exercise. ‡ significant influence of exercise intensity * significant influence of age
Table 3. Cardiac output and heart rate kinetic parameters during moderate and heavy intensity exercise in young and middle-aged participants

<table>
<thead>
<tr>
<th></th>
<th>Young</th>
<th>Middle-aged</th>
<th>Young</th>
<th>Middle-aged</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Moderate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q Base, l·min⁻¹</td>
<td>10.3 ± 2.6</td>
<td>8.3 ± 1.6 *</td>
<td>11.4 ± 2.9</td>
<td>8.4 ± 2.4 *</td>
</tr>
<tr>
<td>Q Amp, l·min⁻¹</td>
<td>1.9 ± 1.0</td>
<td>1.3 ± 0.5</td>
<td>4.9 ± 1.9 ‡</td>
<td>4.1 ± 1.5 ‡</td>
</tr>
<tr>
<td>Q τ, s</td>
<td>21 ± 13</td>
<td>32 ± 13 *</td>
<td>28 ± 16</td>
<td>40 ± 14 *</td>
</tr>
<tr>
<td>Q End Exer, l·min⁻¹</td>
<td>12.0 ± 2.8</td>
<td>9.3 ± 1.9 *</td>
<td>17.1 ± 3.34</td>
<td>13.9 ± 3.2 *</td>
</tr>
<tr>
<td>HR Base, b·min⁻¹</td>
<td>89 ± 13</td>
<td>84 ± 7</td>
<td>92 ± 15</td>
<td>89 ± 12</td>
</tr>
<tr>
<td>HR Amp, b·min⁻¹</td>
<td>16 ± 14</td>
<td>10 ± 8</td>
<td>62 ± 14 ‡</td>
<td>60 ± 14 ‡</td>
</tr>
<tr>
<td>HR τ, s</td>
<td>33 ± 10</td>
<td>30 ± 12</td>
<td>44 ± 15 ‡</td>
<td>50 ± 20 ‡</td>
</tr>
<tr>
<td>HR End Exer, b·min⁻¹</td>
<td>101 ± 19</td>
<td>93 ± 13</td>
<td>159 ± 26 ‡</td>
<td>151 ± 13 ‡</td>
</tr>
</tbody>
</table>

**Heavy**

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Q Base, l·min⁻¹</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q Amp, l·min⁻¹</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q τ, s</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q End Exer, l·min⁻¹</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR Base, b·min⁻¹</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR Amp, b·min⁻¹</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR τ, s</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR End Exer, b·min⁻¹</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are mean ± SD. Q, cardiac output; Amp, amplitude; τ, time constant; End Exer, end exercise; HR, heart rate * significant influence of age ‡ significant influence of exercise
Table 4. Pulmonary $\dot{V}O_2$, $Q$ and HR kinetics in the ‘peak $\dot{V}O_2$ percentile matched’ subgroup of young participants

<table>
<thead>
<tr>
<th></th>
<th>Moderate</th>
<th>Heavy</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\dot{V}O_2$ Amp, l·min$^{-1}$</td>
<td>0.40 ± 0.26</td>
<td>1.44 ± 0.56</td>
</tr>
<tr>
<td>$\dot{V}O_2$ TD, s</td>
<td>9 ± 6</td>
<td>13 ± 6</td>
</tr>
<tr>
<td>$\dot{V}O_2$ $\tau$, s</td>
<td>20 ± 9</td>
<td>28 ± 7</td>
</tr>
<tr>
<td>$\dot{V}O_2$ MRT, s</td>
<td>28 ± 9</td>
<td>46 ± 10</td>
</tr>
<tr>
<td>$\dot{V}O_2$ Gain, ml·O₂·min$^{-1}$</td>
<td>11.0 ± 4.4</td>
<td>9.3 ± 1.3</td>
</tr>
<tr>
<td>$Q$ Amp, l·min$^{-1}$</td>
<td>1.9 ± 1.2</td>
<td>4.6 ± 1.6</td>
</tr>
<tr>
<td>$Q$ $\tau$, s</td>
<td>22 ± 7</td>
<td>27 ± 12</td>
</tr>
<tr>
<td>HR Amp, b·min$^{-1}$</td>
<td>17 ± 16</td>
<td>56 ± 13</td>
</tr>
<tr>
<td>HR $\tau$, s</td>
<td>32 ± 19</td>
<td>42 ± 14</td>
</tr>
</tbody>
</table>

Values are mean ± SD. $\dot{V}O_2$, oxygen uptake; Amp, amplitude; TD, time delay; $\tau$, time constant; MRT, mean response time; $Q$, cardiac output; Amp, amplitude; $\tau$, time constant; End Exer, end exercise; HR, heart rate; No significant influences of age.
Figure 1. Visually identified phase I-phase II transition in a representative participant during $A$) moderate and $B$) heavy intensity exercise. The solid line at time 0 represents the point at which the step transition in work rate occurred. The dotted line reflects the visually identified phase I-phase II transition. Respiratory exchange ratio (RER; clear circles); end-tidal O$_2$ partial pressure ($P_{ET_{O_2}}$; solid circles).

Figure 2. Pulmonary oxygen uptake response to a step increment in work rate from an unloaded baseline to moderate and heavy intensity exercise. Panels A and B show a representative response in young and middle-aged participants, respectively. The solid and dashed lines represent the mono-exponential model fit to the data. For clarity, data are displayed as 5-s bin averages.

Figure 3. Pulmonary oxygen uptake response to a step increment in work rate from an unloaded baseline in a representative young and middle-aged participant. Panels A and B show the responses during moderate and heavy intensity exercise, respectively. The solid and dashed lines represent the mono-exponential model fit to the data. For clarity, data are displayed as 5-s bin averages.