Influence of phase I duration on phase II VO$_2$ kinetics parameter estimates in older and young adults

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Influence of phase I duration on phase II VO$_2$ kinetics parameter estimates in older and young adults. Am J Physiol Regul Integr Comp Physiol 301: R218–R224, 2011. First published April 13, 2011; doi:10.1152/ajpregu.00060.2011.—Older adults (O) may have a longer phase I pulmonary O$_2$ uptake kinetics (VO$_{2p}$) than young adults (Y); this may affect parameter estimates of phase II VO$_{2p}$. Therefore, we sought to: 1) experimentally estimate the duration of phase I VO$_{2p}$ (EE phase I) in O and Y subjects during moderate-intensity exercise transitions; 2) examine the effects of selected phase I durations (i.e., different start times for modeling phase II) on parameter estimates of the phase II VO$_{2p}$ response; and 3) thereby determine whether slower phase II kinetics in O subjects represent a physiological difference or a by-product of fitting strategy. VO$_{2p}$ was measured breath-by-breath in 19 O (68 ± 6 yr; mean ± SD) and 19 Y (24 ± 5 yr) using a volume turbine and mass spectrometer. Phase I VO$_{2p}$ was longer in O (31 ± 4 s) than Y (20 ± 7 s) (P < 0.05). In O, phase II rVO$_{2p}$ was larger (P < 0.05) when fitting started at 15 s (49 ± 12 s) compared with fits starting at the individual EE phase I (43 ± 12 s), 25 s (42 ± 10 s), 35 s (42 ± 12 s), and 45 s (45 ± 15 s). In Y, rVO$_{2p}$ was not affected by the time at which phase II VO$_{2p}$ fitting started (rVO$_{2p}$ = 31 ± 7 s, 29 ± 9 s, 30 ± 10 s, 32 ± 11 s, and 30 ± 8 s for fittings starting at 15 s, 25 s, 35 s, 45 s, and EE phase I, respectively). Fitting from EE phase I, 25 s, or 35 s resulted in the smallest CI rVO$_{2p}$ in both O and Y. Thus, fitting phase II VO$_{2p}$ from (but not constrained to) 25 s or 35 s provides consistent estimates of VO$_{2p}$ kinetics parameters in Y and O, despite the longer phase I VO$_{2p}$ in O.

phase II fitting; VO$_2$ kinetics; aging

THE STUDY OF OXYGEN UPTAKE kinetics permits an insightful understanding of the mechanisms regulating the rate at which oxidative phosphorylation adapts to step changes in exercise intensities and ATP requirement. In the laboratory setting, this is usually accomplished by performing step transitions from a baseline intensity to a higher work rate in either the moderate-, heavy-, or very heavy-intensity domain. Animal (6, 16–18, 22, 23) and more invasive human studies (19) have allowed for measurements of the rate of adjustment of oxidative metabolism (or in close proximity to) the active muscle (or muscle fiber) level; however, due to technical limitations and ethical issues, most of the data in humans have been reported based on measurements of gas exchange obtained at the level of the mouth (1, 7, 9, 11, 12, 14, 24, 31, 32). As such, pulmonary VO$_2$ (VO$_{2p}$) has been used as a proxy of muscle VO$_2$ kinetics. Three distinct phases can be observed when using this technique. Phase I or the cardiodynamic phase, represents the circulatory transit delay (from leg muscles to lungs) with changes in the VO$_{2p}$ occurring as a result of an increase in the pulmonary blood flow that does not reflect the increase in oxygen extraction in the active muscles. Phase II or primary component represents an exponential increase in VO$_{2p}$ related to the continued increase in pulmonary (and muscle) blood flow along with the return of deoxygenated blood (reflecting venous blood from the active muscles arriving to the lungs). This phase has been shown to closely reflect the adjustments of oxidative metabolism at the active skeletal muscle level (19, 27, 31). Phase III represents the steady-state phase of VO$_{2p}$ during moderate-intensity exercise.

Different strategies have been used in the literature to fit the exponential increase in the primary component of VO$_{2p}$ during transitions from baseline to a given work rate in the moderate-intensity domain. Usually, interpolated second-by-second data from the breath-by-breath measurements are averaged in 5-s (11–13) or 10-s (10, 20, 21, 31) bins from which the VO$_{2p}$ time constant (τVO$_{2p}$) is calculated. Frequently, the phase I VO$_{2p}$ duration has simply been assigned to last a fixed period of time (~20 s) such that phase II would consistently start at the same point for every subject (7, 9, 25, 26, 34). Although a blood transit time from exercising muscles to pulmonary capillaries of ~20 s may be an acceptable physiological assumption, it has recently been shown that the cardiodynamic phase is longer in older adults, presumably the result of age-related changes in cardiovascular function (28). According to the modeling study of Barstow et al. (2), there is an intrinsic relationship between phase I and phase II VO$_{2p}$ such that for a given rate of adjustment of muscle O$_2$ utilization (τVO$_{2m}$) a slower rate of adjustment of blood flow (i.e., larger τQ by ~10 s) at exercise onset would result in a lengthened phase I VO$_{2p}$ (by ~2 s) and, as a consequence, a smaller estimated τVO$_{2p}$ (τVO$_{2p}$ < τVO$_{2m}$). Additionally, modeling the phase II VO$_{2p}$ response using a fitting window always starting at 20 s may include data belonging to the phase I VO$_{2p}$ response, which would result in an artificial lengthening of the duration of phase II VO$_{2p}$. As such, the slower phase II VO$_2$ kinetics in older (O) compared with young (Y) adults consistently reported in the literature (1, 7, 9, 11, 12, 14, 20) has been challenged as it may (part) be the result of the fitting strategy instead of the actual physiological response as proposed elsewhere (28). Indeed, the problem of the Mezzani et al. (28) study is that the difference in the phase II VO$_2$ kinetics between the older and young individuals consistently reported in these previous studies is explained by the method used to fit the data. However, it remains unclear whether, and to what extent, a longer phase I VO$_{2p}$ would affect the fitting of the primary component VO$_{2p}$. Thus, the goals of this investigation were: 1) to experimentally estimate, using accepted gas exchange criteria, the dura-
tion of phase I \( \dot{V}O_2 \) in a group of older and young women and men during step transitions from baseline to a moderate-intensity work rate (\(-90\%\) of the estimated lactate threshold (\( \theta_L \)); 2) to compare the phase II \( \tau \dot{V}O_2 \) derived using this actual phase I duration with those estimated using different discrete start times of 15 s, 25 s, 35 s, and 45 s. It was hypothesized that 1) phase I \( \dot{V}O_2 \) duration would be significantly longer in O compared with Y adults, confirming the findings of Mezzani et al. (28); and 2) the \( \tau \dot{V}O_2 \) would remain unchanged when the starting fitting point of phase II resides within the expected values for each group (i.e., \( O = 25 – 35 \) s; \( Y = 15 – 35 \) s); and 3) a slower phase II \( \dot{V}O_2 \) kinetics in older versus younger adults would be confirmed.

**MATERIALS AND METHODS**

**Subjects.** Data were obtained from 19 O (6 women and 13 men, 68 ± 6 yr; mean ± SD) and 19 Y (9 women and 10 men, 24 ± 5 yr) adults. All procedures were approved by The University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects, and the participants provided written consent to participate. All subjects were nonsmokers, and were physically active. Additionally, no subjects were taking medications that would affect the cardiorespiratory or hemodynamic responses to exercise. Subjects had no history of cardiovascular, respiratory, or musculoskeletal diseases; the older adults were medically screened by a physician and underwent a maximal exercise stress test prior to study entry.

**Protocol.** On day 1, subjects reported to the laboratory to perform a maximal cycle ergometer ramp test (O 12–20 W/min; Y 20–25 W/min) (on a Corival 400; Lode, Groningen, Holland) for determination of \( \dot{V}O_2 \text{peak} \) and the estimated \( \theta_L \). \( \theta_L \) was defined as the \( \dot{V}O_2 \) at which CO2 production \( (\dot{V}CO_2) \) began to increase out of proportion in relation to \( \dot{V}O_2 \) with a systematic rise in minute ventilation-to-\( \dot{V}O_2 \) ratio and end-tidal \( PO_2 \), whereas minute ventilation-to-\( \dot{V}CO_2 \) ratio and end-tidal \( PCO_2 \) were stable. After this test, subjects returned to the laboratory on a different day to perform step transitions in work rate from 20 W to a moderate-intensity work rate that elicited a \( \dot{V}O_2 \) corresponding to \(-90\%\) of \( \theta_L \). Each subject performed two sets, each including two step transitions consisting of 6 min of cycling at 20 W, 6 min at 90% of \( \theta_L \), 8 min at 20 W, and another 6 min at 90% of \( \theta_L \). Cycling cadence was constrained to remain between 60–70 rpm. Each set was separated by a 30-min resting recovery while the participant was seated on a chair.

**Measurements.** Gas exchange measurements were similar to those previously described (1). Briefly, inspired and expired flow rates were measured using a low dead space (90 ml) bidirectional turbine (Alpha Technologies VMM 110), which was calibrated before each test by using a syringe of known volume. Inspired and expired gases were sampled continuously (every 20 ms) at the mouth and analyzed for concentrations of \( O_2 \), \( CO_2 \), and \( N_2 \) by mass spectrometry (model MGA-1100; Perkin Elmer) after calibration with precision-analyzed gas mixtures. Changes in gas concentrations were aligned with gas volumes by measuring the time delay (TD) for a square-wave bolus of gas passing the turbine to the resulting changes in fractional gas concentrations as measured by the mass spectrometer. Data collected every 20 ms were transferred to a computer, which aligned concentrations with volume information to build a profile of each breath. Breath-by-breath alveolar gas exchange was calculated by using algorithms of Beaver et al. (4).

**Data analysis.** \( \dot{V}O_2 \) data were removed when data points were outside 4 SD of the local mean derived from a preliminary exponential fit. The data for each transition then were linearly interpolated to 1-s intervals and time aligned such that time 0 represented the onset of exercise. Data from each transition were ensemble averaged to yield a single, averaged response for each subject. This transition was further time averaged into 10-s bins to provide time-averaged responses for each subject. The on-transient response for \( \dot{V}O_2 \) was modeled using a monoeponential of the form: \( Y(t) = Y_{Bsln} + amp[1 - e^{-\mu - TD(t)}] \), where \( Y(t) \) represents \( \dot{V}O_2 \) at any time \( t \), \( Y_{Bsln} \) is the baseline \( \dot{V}O_2 \) during 20-W cycling, amp is the steady-state increase in \( \dot{V}O_2 \) above the baseline value, \( \tau \) is the time constant defined as the time for \( \dot{V}O_2 \) to increase to 63% of the steady-state increase, and TD is the time delay, which was allowed to vary freely (to optimize accuracy of parameter estimates). This approach to data analysis explicitly disregards any data residing outside of the fitting window (i.e., data that precede the selected phase I-phase II transition), yet does not constrain the model to intersect the baseline \( \dot{V}O_2 \) at the same point in time; in essence, the TD is not used as a proxy for, nor is it synonymous with, phase I duration. Data were modeled from the beginning of phase II to 4 min (240 s) of the step transition. Four minutes were selected so data were fit for a period representing at least four time constants (>98% of the total response) during the on transient of the response, which restricted the modeling to data lying within the transient phase (8). To explore the effect of different fitting windows, the phase I-phase II transition, that is the start of phase II, was set at the EE phase I, 15s, 25 s, 35s, or 45s (representing the midpoint of the average of the 10-s binned data). Thus, for example, the fit from 25 s represents elimination of data up to 20 s (as might be expected for phase I duration in the Y group) and for the fit from 35 s, data from 0 s to 30 s were removed as phase I data [as might be expected for O, see Mezzani et al. (28)]. The model parameters were estimated by least-squares nonlinear regression (Origin; OriginLab, Northampton, MA) in which the best fit was defined by minimization of the residual sum of squares and minimal variation of residuals around the y-axis (\( y = 0 \)). The 95% confidence interval (CI) for the estimated time constant was determined after preliminary fit of the data with Bsln, Amp, and TD constrained to the best-fit values, and the \( \tau \) was allowed to vary.

**Phase I determination.** The phase I-phase II transition was determined by visual inspection of the second-by-second and 5-s averaged data as the point at which there was a sharp decrease from baseline values (20 W cycling) in both respiratory exchange ratio (RER) and end-tidal \( PO_2 \) partial pressure (\( \text{PETO}_2 \)), as previously proposed (34). The midpoint of the \( \dot{V}O_2 \) transient of the response, which restricted the modeling to data lying within the transient phase (8). To explore the effect of different fitting windows, the phase I-phase II transition, that is the start of phase II, was set at the EE phase I, 15s, 25 s, 35s, or 45s (representing the midpoint of the average of the 10-s binned data). Thus, for example, the fit from 25 s represents elimination of data up to 20 s (as might be expected for phase I duration in the Y group) and for the fit from 35 s, data from 0 s to 30 s were removed as phase I data [as might be expected for O, see Mezzani et al. (28)]. The model parameters were estimated by least-squares nonlinear regression (Origin; OriginLab, Northampton, MA) in which the best fit was defined by minimization of the residual sum of squares and minimal variation of residuals around the y-axis (\( y = 0 \)). The 95% confidence interval (CI) for the estimated time constant was determined after preliminary fit of the data with Bsln, Amp, and TD constrained to the best-fit values, and the \( \tau \) was allowed to vary.

**Statistics.** Data are presented as means ± SD. Independent \( t \)-tests, paired \( t \)-tests, and repeated-measures ANOVA were used to determine statistical significance for the dependent variables. The ANOVA model for each age group was described as \( S_{i,j} \times F_{ij} \), such that subjects (S; number of subjects) are crossed with different times for phase I (Ph; five different lengths: EE, 15 s, 25 s, 35 s, and 45 s). A Tukey post hoc analysis was used when significant differences were found for the main effects of each dependent variable. Pearson product moment correlation coefficients were used to determine the degree of association between key variables. The ANOVA and correlation coefficients were analyzed by SPSS version 15.0, (SPSS, Chicago, IL). Statistical significance was declared when \( P < 0.05 \).

**RESULTS**

Subjects’ characteristics and peak exercise values are shown in Table 1. Older adults had a higher body mass, lower \( \dot{V}O_2 \text{peak} \) and peak power output (\( \text{PO}_{\text{peak}} \)) compared with their younger counterparts (\( P < 0.05 \)). During the moderate-intensity step

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>Age, yr</th>
<th>Body Mass, kg</th>
<th>( \dot{V}O_2 \text{peak}, \text{l} \cdot \text{min}^{-1} )</th>
<th>( \text{PO}_{\text{peak}}, \text{W} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Old</td>
<td>19</td>
<td>68 ± 6</td>
<td>80 ± 10</td>
<td>2.2 ± 0.5</td>
<td>174 ± 49</td>
</tr>
<tr>
<td>Young</td>
<td>19</td>
<td>24 ± 5*</td>
<td>71 ± 12*</td>
<td>3.3 ± 0.8*</td>
<td>272 ± 67*</td>
</tr>
</tbody>
</table>

Values are means ± SD; No., number of subjects/group; \( \dot{V}O_2 \text{peak} \), peak oxygen uptake; \( \text{PO}_{\text{peak}} \), peak power output; \( \* P < 0.05 \) compared with Old.
transitions, PO was significantly lower in O (63 ± 18 W) than in Y (107 ± 37 W). The phase I VO₂p duration determined by visual inspection of RER, and PETO₂, data was longer in O (31 ± 4 s; range from 23 s to 37 s) compared with Y (20 ± 7 s; range from 8 s to 30 s) (P < 0.05). Figure 1 displays raw data used for determination of phase I in three different subjects. As shown, from these transitions from a 20-W work rate to moderate-intensity exercise, there was not always a clear
determination of the phase I-phase II transition. Nevertheless, the agreement between the two investigators for their estimates of the phase I duration was within 6 s for each individual and yielded a Pearson product moment correlation coefficient of r = 0.95.

Tables 2 and 3 describe changes in VO₂p kinetics parameters for each starting fitting point in O and Y, respectively. Figure 2 contains a comparison of the model fits starting at each phase I-phase II transition for a representative subject. Figures 3 and 4 present individual VO₂p values calculated when data were modeled from different phase II onsets in O and Y subjects, respectively. Phase II VO₂p was significantly larger (by ~4 s to 7 s; P < 0.05) in the O group when fitting started at 15 s compared with the EE phase I, 25 s, 35 s, and 45 s. No differences in VO₂p were observed in the Y group regardless of the time at which phase II VO₂p fitting started. Fitting from 15 s resulted in a significantly larger (albeit barely discernible) VO₂p amplitude (VO₂pamp) and shorter TD VO₂p compared with fitting from the EE phase I, 25 s, and 35 s in O adults. Neither VO₂pamp nor TD VO₂p was affected by fitting time in the Y group. In both O and Y groups, the CI VO₂p was smallest when fitting from the EE phase I, 25 s, and 35 s.

There was a significant correlation between phase I VO₂p duration and PO during the step transitions (r = –0.65, P < 0.05; r² = 0.42) (Fig. 5). Thus, in those working at a lower PO, there was a longer phase I VO₂p.

**DISCUSSION**

This study sought to experimentally estimate the duration of phase I VO₂p in older and young individuals and to examine the effects of using different discrete starting points (i.e., EE phase I, 15 s, 25 s, 35 s, and 45 s) for assessing phase II VO₂p kinetics parameters. The main findings were as follows: 1) fitting phase II VO₂p kinetics starting at the EE phase I, 25 s, 35 s, and 45 s in the O group and starting at the EE phase I, 15 s, 25 s, 35 s, and 45 s in the Y group did not affect the CI VO₂p, within the respective age group; however, inclusion of a substantial portion of phase I VO₂p (i.e., 20 s of data) within the phase II VO₂p fitting window resulted in longer VO₂p in O subjects (by ~7

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**Table 2. O₂ uptake kinetics parameters for older adults**

<table>
<thead>
<tr>
<th></th>
<th>Phase I, 15 s</th>
<th>Phase I, 25 s</th>
<th>Phase I, 35 s</th>
<th>Phase I, 45 s</th>
<th>Phase I EE</th>
</tr>
</thead>
<tbody>
<tr>
<td>τVO₂p, s</td>
<td>49.3 ± 12.9</td>
<td>42.9 ± 10.7*</td>
<td>42.5 ± 12.3*</td>
<td>45.2 ± 15.7*</td>
<td>43.3 ± 12.1*</td>
</tr>
<tr>
<td>VO₂pamp, 1 min⁻¹</td>
<td>0.44 ± 0.21</td>
<td>0.43 ± 0.21*</td>
<td>0.43 ± 0.21*</td>
<td>0.44 ± 0.21*</td>
<td>0.43 ± 0.21*</td>
</tr>
<tr>
<td>TD τVO₂p, s</td>
<td>7.1 ± 5.2</td>
<td>12.1 ± 5.9*</td>
<td>12.9 ± 6.0*</td>
<td>10.3 ± 9.0</td>
<td>12.1 ± 6.0*</td>
</tr>
<tr>
<td>CI τVO₂p, s</td>
<td>5.9 ± 2.9</td>
<td>5.3 ± 3.2*</td>
<td>5.4 ± 3.1*</td>
<td>5.8 ± 3.1†</td>
<td>5.3 ± 3.2‡</td>
</tr>
</tbody>
</table>

Values are means ± SD; EE, experimentally estimated; τVO₂p, phase II pulmonary VO₂ kinetics; VO₂pamp, VO₂p amplitude; TD VO₂p, time delay VO₂p; CI τVO₂p, confidence interval τVO₂p. *P < 0.05 from phase I, 15 s; †P < 0.05 from phase I, 25 s; ‡P < 0.05 from phase I, 35 s; §P < 0.05 from phase I, 45 s.

**Table 3. Oxygen uptake kinetics parameters for young adults**

<table>
<thead>
<tr>
<th></th>
<th>Phase I, 15 s</th>
<th>Phase I, 25 s</th>
<th>Phase I, 35 s</th>
<th>Phase I, 45 s</th>
<th>Phase I EE</th>
</tr>
</thead>
<tbody>
<tr>
<td>τVO₂p, s</td>
<td>31.9 ± 7.5</td>
<td>29.1 ± 9.3</td>
<td>30.7 ± 10.7</td>
<td>32.4 ± 11.1</td>
<td>30.1 ± 7.9</td>
</tr>
<tr>
<td>VO₂pamp, 1 min⁻¹</td>
<td>0.96 ± 0.42</td>
<td>0.95 ± 0.41</td>
<td>0.95 ± 0.42</td>
<td>0.96 ± 0.42</td>
<td>0.95 ± 0.42</td>
</tr>
<tr>
<td>TD τVO₂p, s</td>
<td>8.4 ± 3.3</td>
<td>11.3 ± 5.4</td>
<td>9.3 ± 7.1</td>
<td>6.0 ± 13.1</td>
<td>10.3 ± 4.6</td>
</tr>
<tr>
<td>CI τVO₂p, s</td>
<td>2.5 ± 1.0</td>
<td>2.1 ± 1.1*</td>
<td>2.3 ± 1.2</td>
<td>2.6 ± 1.11*</td>
<td>2.2 ± 1.0‡</td>
</tr>
</tbody>
</table>

Values are means ± SD; EE, experimentally estimated; τVO₂p, phase II pulmonary VO₂ kinetics; VO₂pamp, VO₂p amplitude; TD VO₂p, time delay VO₂p; CI τVO₂p, confidence interval τVO₂p. *P < 0.05 from phase I, 15 s; †P < 0.05 from phase I, 25 s; ‡P < 0.05 from phase I, 35 s; §P < 0.05 from phase I, 45 s.
s); 2) fitting \( \dot{V}_O_{2p} \) data from 25 s and 35 s after the onset of exercise resulted in the lowest CI \( \tau \dot{V}_O_{2p} \) in both O and Y subjects; and 3) O had a significantly longer phase I \( V_{O2p} \) (~30 s) duration compared with their younger counterparts (~20 s), and a significantly slower phase II \( V_{O2p} \) kinetics.

An important finding from this study is that despite the fact that older adults have a longer phase I \( V_{O2p} \), in the analysis of phase II \( V_{O2p} \), \( \tau \dot{V}_O_{2p} \) is unchanged when phase II \( V_{O2p} \) is assumed to start at 25 s (i.e., omitting data up to 20 s of the transient but a duration that is within the experimentally estimated phase I). In young subjects, \( \tau \dot{V}_O_{2p} \) is unchanged when phase I \( V_{O2p} \) duration is assumed to start anywhere in the range of 15 s to 45 s. \( \tau \dot{V}_O_{2p} \) was not different starting phase II at 25 s, 35 s, or 45 s in older, but including too much phase I data by starting phase II at 15 s did indeed lengthen the \( \tau \).

Although \( \tau \dot{V}_O_{2p} \) estimates were consistent within those values in both groups, it is important to notice that selecting the phase I-phase II transition to start at either 25 s or 35 s resulted in CI \( \tau \dot{V}_O_{2p} \) being the lowest with individual \( \tau \dot{V}_O_{2p} \) values being the closest to the line of identity (Figs. 3 and 4) in both older and younger individuals. This is not surprising because fitting \( \dot{V}_O_{2p} \) kinetics from 25 s and 35 s falls close to the values obtained for the EE phase I \( V_{O2p} \) (from the RER and P\_ETO\_2 data). These data suggest that fitting \( \tau \dot{V}_O_{2p} \) from 25 s or 35 s will result in similar outcomes for \( \dot{V}_O_{2p} \) kinetics while maximizing the confidence in the results. Additionally, when starting the phase II \( \dot{V}_O_{2p} \) fitting at a later time point than that derived from the experimentally estimated phase I \( \dot{V}_O_{2p} \) (and thus attempting to be sure all phase I data are excluded) a reliable measure of \( \tau \dot{V}_O_{2p} \) is still obtained despite the larger CI \( \tau \dot{V}_O_{2p} \); however, it is cautioned that if the amplitude of the data from 45 s into the transient is small, the model fit may be compromised (such that in the present data some attempted fits from 45 s could yield a very large time constant or a linear rather than monoeponential fit).

Recently published data by Mezzani et al. (28) found that in older adults (with an experimentally determined phase I of 31 s) using a fixed value of 20 s as the starting point for the fitting of phase II yielded a longer \( \tau \dot{V}_O_{2p} \) of 47 s versus a fit from the experimentally estimated phase I with a \( \tau \dot{V}_O_{2p} \) of 34 s. The present data with a fit from 15 s in O agree that the inclusion of phase I data in the fit can lengthen the phase II (by ~6 s). Our results differ from those of Mezzani et al. (28) as to the magnitude of the effect of inclusion of the phase I data in the phase II fit. The discrepancy between these studies resides in the strategy used for fitting phase II \( \dot{V}_O_{2p} \). In the paper of Mezzani et al. (28), although the exponential fit function included a TD it is clear that it was not allowed to vary freely; that is, the TD was actually constrained to the fixed duration assigned to the phase I \( \dot{V}_O_{2p} \) (20 s) in one model or the EE phase I \( \dot{V}_O_{2p} \) in the other model. That approach forces the
phase II exponential fit through the 20-s phase I point and resulted in a poor fit of the on transient between 20 and 60 s (see Fig. 1 in Mezzani et al. for which the estimated phase II \( \tau \) is 57 s versus the fit from 38 s in this subject giving a \( r \) of 32 s). In the present manuscript, we started the fitting of phase II \( \dot{V}_{\text{O}}2p \) at a given discrete time point but allowed the TD to vary freely (not constrained to force the model through the origin point) so that the model adjusted to fit the data points during the transition while minimizing the residuals. As such, only when the difference between the experimentally estimated and the fixed duration phase I \( \dot{V}_{\text{O}}2p \) is sufficiently large (i.e., starting the fitting of older subjects at 15 s when the estimated phase I \( \dot{V}_{\text{O}}2p \) was 31 s), will too many data points from phase I be included in the fit, thereby overestimating \( \tau \dot{V}_{\text{O}}2p \). The importance of this difference in fitting strategy (allowing TD to vary freely or fixing it at the predetermined phase I duration) cannot be overstated.

This study also showed that phase I \( \dot{V}_{\text{O}}2p \) is significantly longer in O compared with Y individuals. It has been theoretically proposed (2) and experimentally shown (28) that lengthening of phase I \( \dot{V}_{\text{O}}2p \) would affect the phase II \( \dot{V}_{\text{O}}2p \) kinetics response; that is, for a given rate of muscle O2 utilization, the longer phase I duration could result in a lowering of the \( \dot{V}_{\text{O}}2p \) time constant. If that is true, the slower \( \dot{V}_{\text{O}}2p \) kinetics (greater \( \tau \dot{V}_{\text{O}}2p \)) observed in the older compared with young individuals in some studies in which the phase I-phase II transition was not identified, but was assumed to have a fixed duration of 20 s in both groups (7, 9) may be partially the result of not accounting for the longer cardiodynamic phase that may be expected in the older group. However, the present study showed that fitting phase II \( \dot{V}_{\text{O}}2p \) starting at different discrete time points does not necessarily result in changes in the phase II \( \dot{V}_{\text{O}}2p \) parameter estimates, at least when the TD for the monoexponential fit is allowed to vary and the majority of the phase I \( \dot{V}_{\text{O}}2p \) duration is not included in the fitting of phase II \( \dot{V}_{\text{O}}2p \). In the O subjects, starting the fitting of phase II \( \dot{V}_{\text{O}}2p \), at either 35 s or 45 s did not result in a significantly slower \( \tau \dot{V}_{\text{O}}2p \) compared with the EE phase I or 25 s. The contention of Mezzani et al. (28) was that the \( \tau \dot{V}_{\text{O}}2p \) in older adults in previous papers, principally from our laboratory, may have been an overestimation caused by using a fixed duration of the phase I of 20 s for the fit. The present data show this is not the case, and in this and other data we have also explored alternate fitting strategies with an estimation of the phase II start (12, 33) and consistently find slower \( \tau \dot{V}_{\text{O}}2p \) in older adults. Mezzani et al. (28) reported a \( \tau \dot{V}_{\text{O}}2p \) of 34 s for their 60–70 year age group (not different from their young, 32 s), but acknowledged this group was habitually active and of above average cardiorespiratory fitness. \( \dot{V}_{\text{O}}2p \) kinetics are very susceptible to physical activity levels and exercise. In a recent study (29) with just 3 wk of an

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**Fig. 4.** Comparison of individual \( \dot{V}_{\text{O}}2p \) values calculated from data modeled at different phase II onsets in young subjects. \( \circ \), Individual data; \( \bullet \), group mean; error bars represent SD. No significant differences were observed among the means of fits from 15, 25, 35 or 45 s.

**Fig. 5.** Correlation between power output (PO) during the step transitions and phase I \( \dot{V}_{\text{O}}2p \). \( \bullet \), Older subjects; \( \circ \), young subjects.
exercise program the τ\(\dot{V}_\text{O}_2\) of older men was reduced from 43 s to 35 s and reached values for the untrained young in that study (34 s). Thus, healthy, community-dwelling, but untrained, older adults do in general have slower \(\dot{V}_\text{O}_2\) kinetics (with \(\tau\dot{V}_\text{O}_2\) greater than \(-40\) and up to \(-60\) s) reflecting the slower adjustment of skeletal muscle oxidative metabolism.

In relation to the duration of phase I \(\dot{V}_\text{O}_2\), it is possible that the prolonged response observed in the older individuals is a product of structural and functional changes within the vasculature. Increased age has been shown to be accompanied by an increased prevalence of varicose veins, venous hypertension (5), and increased tortuosity and branch angles in arterioles (3) that may diminish the efficiency of the muscle pump. Yet, the similar TD prior to the adjustment of muscle deoxygenation (measured using near-infrared spectroscopy) at exercise onset in older and young adults suggests that the immediate matching between the increase in muscle \(\text{O}_2\) utilization and microvascular blood flow is not diminished [i.e., the capacity of the muscle pump is well preserved with age (12, 14)]. Thus, even though the duration of the phase I \(\dot{V}_\text{O}_2\) has recently been shown to have a significant positive correlation with age (28), PO at which the moderate-intensity exercise is performed may also be a factor contributing to a lengthened phase I duration. In this regard, there was a significant negative correlation between PO during the step transitions to moderate-intensity exercise and phase I duration. A smaller PO would elicit a lower cardiac output, which may, in part, predict a longer phase I. A lower PO during the transitions could also reduce the activity of the muscle pump and result in diminished venous blood return to the lungs and thus contribute to a longer phase I duration. Indeed, Radegran and Saltin (30) demonstrated an exercise intensity-dependent hyperemic response within the first duty cycles of exercise due to muscle mechanical factors. In older individuals, a lower PO during the step transitions (reflecting a lower peak PO during the ramp incremental test) should be expected. In relation to the differences in PO between groups, faster cadences (often associated with larger PO) have been shown to affect the parameter estimates of \(\text{O}_2\) kinetics (at least during high-intensity exercise-transitions) (15). However, the fact that cadence was controlled in this study makes this possibility unlikely. Even though a longer phase I may be expected in conditions where delivery and return of blood from and to the heart is limited, a longer phase I may not be only an age-related phenomenon. Testing of older and younger subjects at the same absolute moderate-intensity domain work rates would help resolve these questions.

Although changes in gas exchange indices (i.e., RER and \(\text{PrT}_\text{O}_2\)) may provide a valid noninvasive estimate of phase I duration (and the time of the phase I-phase II transition), practical limitations may limit their usefulness in obtaining an accurate estimate of this value. In this study, determination of the cardiodynamic phase was especially challenging in older individuals (Fig. 1). It is likely that the lower amplitude in \(\dot{V}_\text{O}_2\) values observed during the step transitions in the older individuals (associated with lower PO) resulted in a lower signal-to-noise ratio such that the variability and dispersion of the data were increased. Under those conditions, larger fluctuations are seen in the RER and \(\text{PrT}_\text{O}_2\) data, thus reducing the confidence in the experimental estimation of phase I. A low signal-to-noise ratio also makes it difficult to visually identify the phase I-phase II transition from gas-exchange data during a step-transition to moderate-intensity exercise.

Another method used to identify the onset of phase II \(\dot{V}_\text{O}_2\) consists of modeling \(\dot{V}_\text{O}_2\) data by progressively adjusting the fitting window to identify the start time of phase II as the fitting sequence having the lowest \(\chi^2\) and the lowest \(\tau\dot{V}_\text{O}_2\) (10, 20, 21, 31). This method of determining the duration of phase I and start of phase II was also used in analysis of the data from this study (not presented in RESULTS). Identification of a specific time of both lowest residuals and smallest \(\tau\dot{V}_\text{O}_2\) was not always consistent, again with any noise in the data affecting the method. Thus, the phase I \(\dot{V}_\text{O}_2\) duration derived from this method was shorter than the EE phase I \(\dot{V}_\text{O}_2\) in 50% of the cases. This means that in these cases (~50%), the fits of phase II \(\dot{V}_\text{O}_2\) derived from this method would include some portion of the data that actually belonged to phase I \(\dot{V}_\text{O}_2\) (assuming, in this case, that the EE phase I provides the best estimation of phase I duration). Despite this limitation, it has to be recognized that using this methodology for determining the phase I-phase II transition at least attempts to avoid including data from phase I in a systematic manner.

In conclusion, this study showed that fitting phase II \(\dot{V}_\text{O}_2\) kinetics from the experimentally estimated phase I duration, or from 25 s to 45 s in the O group and from 15 s to 45 s in the Y group resulted in no significant changes in \(\tau\dot{V}_\text{O}_2\), and fitting \(\dot{V}_\text{O}_2\) data from the EE phase I duration or from 25 s and 35 s after the onset of exercise resulted in the lowest CI \(\tau\dot{V}_\text{O}_2\) in both O and Y subjects. Thus, fitting from 25 s or 35 s should provide reliable and similar estimates of the parameters of \(\dot{V}_\text{O}_2\) kinetics in both Y and O adults. It is also concluded that O adults had a significantly longer phase I \(\dot{V}_\text{O}_2\) and a significantly longer phase II \(\tau\dot{V}_\text{O}_2\) compared with their younger counterparts.

ACKNOWLEDGMENTS

We express our gratitude to the subjects in this study and acknowledge the assistance provided by Brad Hansen.

GRANTS

This study was supported by Natural Sciences and Engineering Research Council of Canada research and equipment grants. Additional support was provided by Standard Life Assurance of Canada. J. M. Murias was supported by a doctoral research scholarship from the Canadian Institutes of Health Research.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

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