Speeding of \( \dot{V}_O_2 \) kinetics during moderate-intensity exercise subsequent to heavy-intensity exercise is associated with improved local O\(_2\) distribution

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Murias JM, Spencer MD, DeLorey DS, Gurd BJ, Kowalchuk JM, Paterson DH. Speeding of \( \dot{V}_O_2 \) kinetics during moderate-intensity exercise subsequent to heavy-intensity exercise is associated with improved local O\(_2\) distribution. J Appl Physiol 111: 1410–1415, 2011. First published August 11, 2011; doi:10.1152/japplphysiol.00607.2011.—The relationship between the adjustment of muscle deoxygenation (\( \Delta[Hb] \)) and phase II \( \dot{V}_O_2p \) during moderate-intensity exercise was examined before (Mod 1) and after (Mod 2) a bout of heavy-intensity “priming” exercise. Moderate intensity \( \dot{V}_O_2p \) and \( \Delta[Hb] \) kinetics were determined in 18 young males (26 ± 3 yr). \( \dot{V}_O_2p \) was measured breath-by-breath. Changes in \( \Delta[Hb] \) of the vastus lateralis muscle were measured by near-infrared spectroscopy, \( \dot{V}_O_2p \) and \( \Delta[Hb] \) response profiles were fit using a monoeponential model, and scaled to a relative % of the response (0–100%). The \( \Delta[Hb]/\dot{V}_O_2 \) ratio for each individual (reflecting the local matching of \( O_2 \) delivery to \( O_2 \) utilization) was calculated as the average \( \Delta[Hb]/\dot{V}_O_2 \) response from 20 s to 120 s during the exercise on-transient. Phase II \( \tau_{\dot{V}_O_2p} \) was reduced in Mod 2 compared with Mod 1 (\( P < 0.05 \)). The effective \( \tau^e \Delta[Hb] \) remained the same in Mod 1 and Mod 2 (\( P > 0.05 \)). During Mod 1, there was an “overshoot” in the \( \Delta[Hb]/\dot{V}_O_2 \) ratio (1.08; \( P < 0.05 \)) that was not present during Mod 2 (1.01; \( P > 0.05 \)). There was a positive correlation between the reduction in the \( \Delta[Hb]/\dot{V}_O_2 \) ratio and the smaller \( \tau_{\dot{V}_O_2p} \) from Mod 1 to Mod 2 (\( r = 0.78; P < 0.05 \)). This study showed that a smaller \( \tau_{\dot{V}_O_2p} \) during a moderate bout of exercise subsequent to a heavy-intensity priming exercise was associated with improved microvascular \( O_2 \) delivery during the on-transient of exercise, as suggested by a smaller \( \Delta[Hb]/\dot{V}_O_2 \) ratio.

\( O_2 \) extraction; muscle blood flow; near-infrared spectroscopy

FOLLOWING A STEP-INCREASE in power output, there is an instantaneous increase in the ATP requirement; however, oxygen consumption (\( \dot{V}_O_2 \)) increases exponentially toward a new steady state during the transition to moderate-intensity exercise. The rate of this exponential adjustment, which is quantitatively described by the \( \dot{V}_O_2 \) time constant (\( \tau_{\dot{V}_O_2} \)), has been suggested to be limited by either insufficient oxygen (\( O_2 \)) delivery distributed to active muscle fibers (17, 27) or a sluggish activation of enzymes and provision of substrates for mitochondrial oxidative phosphorylation (10, 27); more recently, a combination of both has been suggested (7, 14).

Previous studies have shown a significant reduction in the phase II pulmonary \( \dot{V}_O_2 \) time constant [reflecting muscle \( \dot{V}_O_2 \) (11, 30)] when moderate-intensity exercise is preceded by a bout of heavy-intensity exercise (i.e., supra-lactate threshold) "priming" exercise in older (5, 32) and younger (14, 15) subjects. That Burnley et al. (4) did not observe a significant reduction in \( \tau_{\dot{V}_O_2p} \) following heavy-intensity priming exercise has been suggested to be the result of already very fast on-transient kinetics (\( \tau_{\dot{V}_O_2p} < 20 \) s) in the absence of prior exercise. However, Gurd et al. (15) reported a reduced \( \tau_{\dot{V}_O_2p} \) in association with improved local muscle oxygenation, as well as an elevated activity of the mitochondrial pyruvate dehydrogenase (PDH) complex (14) after a heavy-intensity priming exercise. Because both local muscle \( O_2 \) delivery and mitochondrial PDH activity appear to remain elevated following heavy-intensity priming exercise, it is difficult to parse out the precise mechanisms responsible for the reduced \( \tau_{\dot{V}_O_2p} \); yet, activation of PDH by administration of dichloroacetate, in the absence of augmented \( O_2 \) delivery, has failed to demonstrate significant reductions in \( \tau_{\dot{V}_O_2p} \) during upright cycling (21, 31).

Recently, Murias et al. (24) demonstrated in both older and young men that 3 wk of endurance training resulted in significantly reduced \( \tau_{\dot{V}_O_2p} \) values. This speeding of the \( \dot{V}_O_2p \) kinetics response (from ~34 to ~22 s) was associated with improved microvascular \( O_2 \) delivery as reflected by a smaller near-infrared spectroscopy (NIRS)-derived muscle hemoglobin deoxygenation (\( \Delta[Hb] \)) to \( \dot{V}_O_2p \) ratio (i.e., reduced \( \Delta[Hb]/\dot{V}_O_2p \) throughout the exercise on-transient. More recently, in a group of young, healthy adults with a broad range of \( \tau_{\dot{V}_O_2p} \) values (~15–55 s) (26), it was demonstrated that the \( \Delta[Hb]/\dot{V}_O_2p \) was closely related to \( \tau_{\dot{V}_0} \) (\( r = 0.91 \)). Furthermore, no \( \Delta[Hb]/\dot{V}_O_2p \) “overshoot” was observed when data from those with \( \tau_{\dot{V}_O_2p} < 21 \) s were grouped. Collectively, this led to the conclusion that when \( \tau_{\dot{V}_O_2p} \) is greater than ~20 s, the rate of change of phase II \( \dot{V}_O_2p \) (muscle \( \dot{V}_O_2 \)) appears to be mainly constrained by the matching of local \( O_2 \) delivery to muscle \( \dot{V}_O_2 \).

If local muscle \( O_2 \) availability does indeed play a chief role in limiting the adjustment of \( \dot{V}_O_2p \) at the onset of moderate-intensity exercise, then reductions in \( \tau_{\dot{V}_O_2p} \) following a bout of heavy-intensity priming exercise should be expected to be accompanied by reductions in \( \Delta[Hb]/\dot{V}_O_2p \). Compared with previous papers (5, 14, 15), where the differences in \( O_2 \) delivery or the degree of deoxygenation with and without prior exercise were assessed for the baseline and amplitude (at the steady-state) of the responses, in the present analysis, the \( \Delta[Hb]/\dot{V}_O_2p \) ratio allowed examination of the relationship of the change in \( \tau_{\dot{V}_O_2p} \) and the matching of \( O_2 \) delivery to \( O_2 \) utilization during the exercise on-transient. As such, the purpose of the present study was to test the hypothesis that a bout
of heavy-intensity priming exercise would result in both a faster adjustment of \( \dot{V}O_2 \) and a reduced \( \Delta[Hb]/\dot{V}O_2 \) during the on-transient of a subsequent moderate-intensity step transition in work rate (WR) and that changes in \( \tau \dot{V}O_2 \) would be related to changes in \( \Delta[Hb]/\dot{V}O_2 \).

**METHODS**

**Subjects.** Data from 18 young male adults who had volunteered and given written consent to participate in current and previous (5, 14, 15) studies in our laboratory were combined to determine the \( \Delta[Hb]/\dot{V}O_2 \) ratio during the exercise on-transient for this study. All data included in the present study were reanalyzed for consistency. Because computation of the \( \Delta[Hb]/\dot{V}O_2 \) ratio requires data with little "noise", before any data analyses were undertaken, individual cases were examined, and only those where both the \( \dot{V}O_2 \) and \( \Delta[Hb] \) signals were of good quality were used. The previously cited papers (5, 14) that determined peak \( \dot{V}O_2 \) and \( \dot{V}O_2 \)peak (as indicated by reasonably low-confidence interval estimates for \( \tau \)). All procedures were approved by The University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects. All subjects were nonsmokers and were physically active. Additionally, no subjects were taking medications that would affect the cardiorespiratory or hemodynamic responses to exercise.

**Protocol.** Subjects reported to the laboratory on five separate occasions at approximately the same time of day for each subject. On day 1, a maximal cycle ergometer ramp test (25 W/min) was performed (on a Lode Corival 400; Lode B.V., Groningen, Holland) for determination of peak \( \dot{V}O_2 \) (\( \dot{V}O_2 \)peak) and the estimated lactate threshold (\( \dot{V}O_2 \)th). \( \dot{V}O_2 \)th was defined as the \( \dot{V}O_2 \) at which CO2 production (\( VCO_2 \)) 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 \( PCO_2 \) whereas minute ventilation-to-\( VCO_2 \) ratio and end-tidal \( PCO_2 \) were stable. From the results of this ramp test, a moderate-intensity \( \dot{V}O_2 \) was selected to elicit a steady-state increase in \( \dot{V}O_2 \) above the baseline value, \( \tau \) is the time constant defined as the duration of time for \( \dot{V}O_2 \) to increase to 63% of the steady-state increase, and TD is the time delay (such that the model is not constrained to pass through the origin). After excluding the initial 20 s of data [while not necessarily reflecting the exact duration of phase I \( \dot{V}O_2 \) in each individual, is most likely to avoid inclusion of data points from phase I \( \dot{V}O_2 \) in the fitting of phase II \( \dot{V}O_2 \) (25)], while still allowing TD to vary freely (to optimize accuracy of parameter estimates), \( \dot{V}O_2 \) data were modeled from 20 s to 4 min (240 s) of the step transition; this ensured that each subject had attained a \( \dot{V}O_2 \) steady state, yet it did not bias the model fit during the on-transient (3, 25). The model parameters were estimated by least-squares nonlinear regression (Origin, OriginLab, Northampton, MA), in which the best fit was defined by minimizing the residual sum of squares and minimal variation of residuals around the y-axis (\( \nu = 0 \)). 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 \( \tau \) allowed to vary. The NIRS-derived \( \Delta[Hb] \) data were time-aligned and ensemble-averaged to 5-s bins to yield a single response for each subject. The \( \Delta[Hb] \) profile has been described to consist of a time delay at the onset of exercise, followed by an increase in the signal with an "exponential-like" time-course (6). The time delay for the \( \Delta[Hb] \) response (TD-[\( \Delta[Hb] \)]) was determined using second-by-second data and corresponded to the time, after the onset of exercise, at which the \( \Delta[Hb] \) signal began a systematic increase. Determination of the TD-[\( \Delta[Hb] \)] was made on individual trials and averaged to yield a single value for each individual. The \( \Delta[Hb] \) data were modeled from the end of the TD-[\( \Delta[Hb] \)] to 90 s of the transition using an exponential model as described in Eq. 1. The [\( \Delta[Hb] \)] described the time course for the increase in \( \Delta[Hb] \), while the overall change of the effective [\( \Delta[Hb] \)] (\( \tau \Delta[Hb] \) = TD-[\( \Delta[Hb] \)] + \( \Delta[Hb] \)) described the overall time course of the \( \Delta[Hb] \) from the onset of exercise.

The quotient of absolute \( \Delta[Hb] \) (AU) and \( \dot{V}O_2 \) (l/min) was computed on a second-by-second basis following time alignment of the respective signals (see below for detailed description). From these profiles, an absolute \( \Delta[Hb]/\dot{V}O_2 \) baseline (60-s average prior to transition), steady-state (60-s average at end exercise), and amplitude (difference between steady-state and baseline) were derived for each of Mod 1 and Mod 2.
Table 1. Kinetics parameters for VO$_2$ in Mod 1 and Mod 2

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mod 1</th>
<th>Mod 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\tau$ VO$_2$ s</td>
<td>28.0 ± 9.4</td>
<td>21.7 ± 4.6*</td>
</tr>
<tr>
<td>VO$_2$ baseline, l/min</td>
<td>1.00 ± 0.09</td>
<td>1.16 ± 0.12*</td>
</tr>
<tr>
<td>VO$_2$ amplitude, l/min</td>
<td>0.68 ± 0.21</td>
<td>0.62 ± 0.19*</td>
</tr>
<tr>
<td>VO$_2$ steady-state, l/min</td>
<td>1.67 ± 0.24</td>
<td>1.77 ± 0.25*</td>
</tr>
<tr>
<td>CI$_{95}$ $\tau$ VO$_2$</td>
<td>3.4 ± 1.6</td>
<td>3.4 ± 1.1</td>
</tr>
</tbody>
</table>

Values are expressed as means ± SD. $\tau$, time constant of response; VO$_2$, pulmonary VO$_2$; CI$_{95}$, 95% confidence interval; *Significantly different from Mod 1 ($P < 0.05$).

The second-by-second $\Delta$[HHb] and VO$_2$ data were normalized for each subject (0%, representing the 20-W baseline value, and 100%, representing the posttransition steady state of the response). The normalized VO$_2$ was left shifted by 20 s to account for the approximate phase I-phase II transition so that the onset of exercise coincided with the beginning of phase II VO$_2$ (26), which has been previously described to coincide with muscle VO$_2$ within 10% (11, 30). Though this 20-s value may not precisely match the duration of phase I in all individuals, our laboratory has recently described the limitations and this 20-s value may not precisely match the duration of phase I in all.

Although the magnitude of the change in the absolute $\Delta$[HHb]/VO$_2$ ratio was similar in Mods 1 and 2 (i.e., same amplitude from baseline to steady state; Table 2), the rate of adjustment for $\tau$VO$_2$ was significantly slower than that of $\Delta$[HHb] in Mod 1 ($P < 0.05$) but not during Mod 2 ($P > 0.05$). Thus, whereas the steady-state reliance on O$_2$ extraction for a given VO$_2$ may have been similar, the on-transient in Mod 1 displayed an “overshoot” in the $\Delta$[HHb]/VO$_2$ ratio that was not present during Mod 2 (Fig. 1). The overall $\Delta$[HHb]/VO$_2$ ratio was calculated to derive a general description of the “excess” (relative to the steady-state values) O$_2$ extraction for a given VO$_2$ during each moderate-intensity transition. The group averages for $\Delta$[HHb]/VO$_2$ were 1.08 ± 0.09 ($P < 0.05$) and 1.01 ± 0.06 ($P > 0.05$) for Mod 1 and Mod 2, respectively [values > 1 represent a time period during the exercise transition having a greater reliance on fractional O$_2$ extraction compared with the exercise steady-state (values = 1.0), and reflects a poorer local O$_2$ delivery relative to muscle O$_2$ utilization in the area of the NIRS probe]. The overall $\Delta$[HHb]/VO$_2$ ratio was significantly greater in Mod 1 than in Mod 2. Individual data resulted in a positive correlation between the changes in the $\Delta$[HHb]/VO$_2$ ratio and the changes in $\tau$VO$_2$ from Mod 1 to Mod 2 ($r = 0.78; P < 0.05$) (Fig. 2).

**DISCUSSION**

The goal of this study was to determine whether the faster adjustment in phase II VO$_2$ after a bout of heavy-intensity priming exercise was associated with improved local O$_2$ delivery within the active muscles, as represented by a decrease in the $\Delta$[HHb]/VO$_2$ ratio. The main finding was that a better matching of local O$_2$ delivery to O$_2$ utilization was associated with a smaller $\tau$VO$_2$ during Mod 2, suggesting that improved muscle O$_2$ perfusion plays an important role in determining the rate of adjustment of VO$_2$, at least when VO$_2$ is larger than ~20 s.

We have reported previously that endurance training results in faster VO$_2$ kinetics in young and older men, and that the smaller $\tau$VO$_2$ in response to the training intervention was associated with a better matching of local O$_2$ delivery to O$_2$ utilization at the muscle level (as shown by a smaller $\Delta$[HHb]/VO$_2$).

Table 2. Kinetics parameters for $\Delta$[HHb] and $\Delta$[HHb]/VO$_2$ in Mod 1 and Mod 2

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mod 1</th>
<th>Mod 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\tau$[HHb], s</td>
<td>10.7 ± 4.5</td>
<td>17.6 ± 7.0*</td>
</tr>
<tr>
<td>$\tau$[HHb], s</td>
<td>10.6 ± 4.4</td>
<td>7.2 ± 3.3*</td>
</tr>
<tr>
<td>$\Delta$[HHb], baseline, AU</td>
<td>21.3 ± 5.1</td>
<td>24.8 ± 8.1</td>
</tr>
<tr>
<td>$\Delta$[HHb], amplitude, AU</td>
<td>−8.3 ± 4.8</td>
<td>−7.4 ± 4.7</td>
</tr>
<tr>
<td>$\Delta$[HHb], amplitude, AU</td>
<td>7.0 ± 4.0</td>
<td>9.7 ± 4.8*</td>
</tr>
<tr>
<td>$\Delta$[HHb], steady-state, AU</td>
<td>−1.3 ± 4.0</td>
<td>2.4 ± 4.8*</td>
</tr>
<tr>
<td>CI$_{95}$ $\tau$[HHb], s</td>
<td>1.6 ± 1.1</td>
<td>1.5 ± 0.7</td>
</tr>
<tr>
<td>$\Delta$[HHb]/VO$_2$ baseline, AU/l/min</td>
<td>−9.09 ± 5.22</td>
<td>−6.73 ± 3.99*</td>
</tr>
<tr>
<td>$\Delta$[HHb]/VO$_2$ amplitude, AU/l/min</td>
<td>8.32 ± 4.24</td>
<td>7.69 ± 3.33</td>
</tr>
<tr>
<td>$\Delta$[HHb]/VO$_2$ steady-state, AU/l/min</td>
<td>−0.77 ± 2.42</td>
<td>0.96 ± 2.49*</td>
</tr>
</tbody>
</table>

Normalized $\Delta$[HHb]/VO$_2$ ratio $1.08 ± 0.09$ $1.01 ± 0.06$*.

Values are expressed as means ± SD. $\tau$, time constant of response; [HHb], deoxygenated hemoglobin; TD, calculated time delay; $\tau$, effective response time ($\tau +$TD); AU, arbitrary units; $\Delta$[HHb]/VO$_2$, parameters, calculated from the second-by-second quotient of the absolute $\Delta$[HHb] (AU) and VO$_2$ (AU) over a 60-s period for the baseline and steady state. Normalized $\Delta$[HHb]/VO$_2$, ratio, calculated as the 20- to 120-s average of the normalized $\Delta$[HHb]/VO$_2$.

*Significantly different from Mod 1 ($P < 0.05$).
$\dot{V}O_2$ (24). In that study, we observed that once $\dot{V}O_2$ was $\approx 20$ s, the rate of adjustment of $V_{O_{2p}}$ matched that of $\Delta [HHb]$, and no further speeding of $V_{O_{2p}}$ kinetics was observed. Similarly, in another study (26) we showed that when $\dot{V}O_2$ was $\approx 20$ s, the adjustment of $O_2$ delivery seemed to match that of $O_2$ utilization, such that further provision of $O_2$ may not result in any speeding of $V_{O_{2p}}$ kinetics; however, a microvascular $O_2$ delivery limitation seemed responsible for a sluggish $V_{O_{2p}}$ kinetics in those with $\dot{V}O_2$ values greater than $20$ s. Data from the present investigation demonstrated an association between changes in the $\Delta [HHb]/V_{O_{2p}}$ ratio and changes in $\dot{V}O_2$ from Mod 1 to Mod 2, suggesting a role for microvascular $O_2$ delivery as a factor controlling the rate of adjustment of $V_{O_{2p}}$. Interestingly, similar to the results from our previous experiments (23, 24, 26) a $\tau\dot{V}O_2$ of $\approx 20$ s was associated with $V_{O_{2p}}$ and $\Delta [HHb]$ adjusting at a similar rate (but, note that the $\Delta [HHb]$ and $V_{O_{2p}}$ responses during the initial 20 s of exercise suggest a well-matched or perhaps even an excess of $O_2$ provision early in the on-transient). Indeed, in those subjects with a $\tau\dot{V}O_2 < 20$ s, there was virtually no change in the $\Delta [HHb]/V_{O_{2p}}$ ratio. Collectively, these data support the contention that there is a “point” beyond which the rate of adjustment for $V_{O_{2p}}$ kinetics is mostly controlled by microvascular $O_2$ delivery within the tissues, and reinforce the idea that this point occurs at $\approx 20$ s of the on-transient from baseline to moderate-intensity exercise. Unlike previously published reports (28, 29), this “point” beyond which $O_2$ provision is a burden for the rate of adjustment of $V_{O_{2p}}$ does not seem to be only age- or disease-related.

In this study, $V_{O_{2p}}$ kinetics during Mod 1 was moderately fast ($\approx 28$ s), and thus the overshoot in the $\Delta [HHb]/V_{O_{2p}}$ ratio was rather small (1.08), albeit significantly greater than 1.0. This value is consistent to those published previously for subjects with a $\tau\dot{V}O_2$ of $\approx 30$ s (26). The decrease in the $\Delta [HHb]/V_{O_{2p}}$ ratio during Mod 2 (reflecting an improved matching of local $O_2$ delivery to $O_2$ utilization) could be explained by different factors regulating blood flow distribution within the active tissues. For instance, Gerbino et al. (9) suggested that prior heavy-intensity exercise resulted in improved muscle perfusion consequent to the vasodilatory effects of metabolic acidemia. Additionally, it has been shown that acute exercise results in rapid improvements in endothelium-and flow-mediated vasodilation (16), so that blood flow distribution (i.e., delivery to active fibers) within the exercising muscles could be enhanced. It is unknown how much of the constraint imposed by $O_2$ delivery would be overcome had the $\Delta [HHb]/V_{O_{2p}}$ ratio during Mod 1 been larger; however, it is interesting that, at least when the overshoot in the $\Delta [HHb]/V_{O_{2p}}$ ratio is modest, a single bout of heavy-intensity priming exercise resulted in a “perfect” matching in the rate of adjustment of $V_{O_{2p}}$ and $\Delta [HHb]$ during the subsequent bout of moderate-intensity exercise. It should be noticed that in this...
study, the average Δ[HHb]/VO₂ ratio for a given period of time (similar to considering the area under the curve) was considered. Taking into account that the duration of the overshoot contributes to the “average” magnitude of the overshoot in the calculation of the overall ΔHHb/VO₂ ratio, it is likely that if the duration of the overshoot is short compared with the entire period of time, the contribution of the overshoot to the average value may not be properly quantified (i.e., would be underestimated), even though its amplitude is significant. As such, this approach could be considered as rather “conservative” in the sense that more data points from well-matched Δ[HHb] and VO₂ signal are likely to be included.

Previous studies have suggested that, unlike older adults (5, 32), young healthy subjects did not speed phase II VO₂ kinetics after a bout of high-intensity priming exercise (4, 5). However, more recently Gurd et al. (14, 15) demonstrated that, in young individuals, heavy-intensity priming exercise resulted in smaller τ VO₂ during the second bout of moderate-intensity exercise compared with the first one. In these later studies, those subjects that had the slower rate of adjustment for VO₂ kinetics were the ones displaying the largest reduction in τ VO₂. This would indicate that the initial τVO₂ will play a role in determining whether or not and to what extent the rate of adjustment of VO₂ is sped in the second moderate-intensity bout. The discrepancies in the results among different studies could be related to the characteristics of each group being tested and not to aging per se. For instance, in the study from Burnley et al. (4), phase II τVO₂ was less than 20 s, even before the bout of heavy-intensity priming exercise. Under these circumstances, it is difficult to think of an intervention that could result in speeding of VO₂ kinetics. Data from our previous studies (26) and from the present investigation support the notion that improving microvascular O₂ delivery within the active tissues may eliminate the main constraint to the rate of adjustment of VO₂ kinetics when τVO₂ is ~20 s; however, to produce further reductions in τVO₂, it would appear that some intracellularly controlled mechanism has to be modified. In this regard, Gurd et al. (14) examined the effects of PDH activity on τVO₂ from a moderate-intensity exercise transition that was followed by a heavy-intensity priming exercise bout. They suggested that an elevated PDH activity during Mod 2 could have contributed to the smaller τVO₂ compared with Mod 1; however, the association between the increased PDH activity and the reduced τVO₂ in Mod 2 was weak.

It is important to notice that even if one accepts that when τVO₂ is larger than ~20 s, the majority of the constraint for oxidative phosphorylation is related to maldistribution of blood flow within the active tissues, there is still a limitation that remains to be explained. It is likely that during the first ~20 s of activity, the locus of control of VO₂ kinetics resides mainly intracellularly and is explained by the ability to provide substrates other than O₂ to the mitochondria. To that end, the intracellular mechanisms, which likely represent the fundamental limitation in the rate of adjustment of oxidative phosphorylation, have been described by Meyer (22) as a simple RC circuit [where R relates to the mitochondrial redox potential and C relates to the total Cr content (TCr = PCr+Cr)]. Furthermore, it has been shown that in single fiber preparations, the kinetics for the fall in intracellular PO₂ (analogous to VO₂ transients) was markedly faster when creatine kinase (CK) was knocked out compared with a control condition. This suggests that CK-catalyzed breakdown of phosphocreatine at the onset of exercise limits the rise in ADP concentration such that activation of oxidative phosphorylation is attenuated (19, 33). Indeed, a recent study has shown a significantly shorter VO₂ (8 s vs. 16 s) in a dog model under acute CK inhibition (12). Additionally, competition for the binding site of cytochrome-c oxidase in the mitochondria between vascular released NO and O₂ has been shown to contribute to the rate of adjustment of VO₂ kinetics (18, 20). Also, substrate supply (provision of acetyl groups and NADH) has been thought to be one of the mechanisms controlling VO₂ kinetics (13, 14). Although these “intracellular” factors will alter phosphorylation and/or redox potential (17) and affect the driving of oxidative phosphorylation, it is possible that once the initial delay in the activation and time course of the increase of oxidative phosphorylation is overcome (i.e., ~20 s likely due to intracellular control), all of the substrates required to drive oxidative metabolism but O₂ are present in saturating amounts, such that further increases in any of them will not necessarily result in an altered time course of adjustment. In this light, factors related to both O₂ utilization and O₂ delivery are likely involved in the regulation of VO₂ kinetics, yet it seems that when τVO₂ > ~20 s, the rate of adjustment of VO₂ is primarily “limited” by provision of O₂.

In conclusion, this study demonstrated that a reduced τVO₂ during a moderate bout of exercise subsequent to a heavy-intensity priming exercise was associated with improved microvascular O₂ delivery during the on-transient of exercise, as suggested by a smaller Δ[HHb]/VO₂ ratio. Even though our data do not exclude the possibility that the fundamental control to VO₂ kinetics (i.e., initial 20 s) may be explained by intracellular factors that were not measured in this study, they further support the contention that microvascular O₂ distribution within the active tissues is mainly responsible for the faster rate of adjustment in VO₂ following heavy-intensity priming exercise, at least when τVO₂ is greater than ~20 s.

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DISCLOSURES

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

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