Effects of prior heavy exercise on heterogeneity of muscle deoxygenation kinetics during subsequent heavy exercise

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Submitted 23 January 2009; accepted in final form 11 June 2009

The balance between muscle O2 uptake (m\(\dot{V}{O_2}\)) and muscle O2 delivery (m\(\dot{Q}{O_2}\)) by capillary blood flow, i.e., the ratio m\(\dot{V}{O_2}/\)m\(\dot{Q}{O_2}\), is reflected by the level of muscle oxygenation (14, 19, 25, 27, 32). Thus the profile of muscle oxygenation can provide important information concerning the adequacy of the vascular response and the O2 pressures essential for driving blood-muscle O2 flux.

Prior heavy exercise has been used as an experimental intervention to alter m\(\dot{Q}{O_2}\) and elucidate the mechanisms of the m\(\dot{V}{O_2}\) kinetics following the onset of exercise (3, 7–11, 15, 16, 22–24, 30–33, 39, 42, 44, 47, 51–53, 55). Collectively, previous studies reported that prior exercise in the upright position does not alter the phase II time constant of pulmonary O2 uptake (p\(\dot{V}{O_2}\) response in the subsequent bout of heavy exercise (3, 7–11, 22, 30, 32, 44, 47, 52), with a few exceptions (16, 46, 53). The net amplitude of phase II is unaltered in some studies using 6- to 8-min recovery between heavy exercise bouts (7, 10, 44, 52) and increased in other studies in which the recovery duration is 10 min or longer (up to ~45 min) (3, 8, 9, 11, 47). In contrast, the amplitude of the slow component (SC) is routinely diminished (3, 7–11, 17, 22, 24, 30, 32, 39, 42–44, 47, 52). The likely mechanistic bases for the changes in p\(\dot{V}{O_2}\) kinetics induced by prior heavy exercise involve increased muscle O2 utilization and/or increased O2 delivery to muscle mediated by a residual vasodilatation and/or a right shift in the oxyhemoglobin dissociation curve (6, 9, 16, 22–24, 32, 44).

Several studies have suggested that the effects of the prior heavy exercise on p\(\dot{V}{O_2}\) responses in the subsequent heavy exercise might be related to the homogeneity of m\(\dot{Q}{O_2}\) distribution and matching to m\(\dot{V}{O_2}\) (1, 15, 16, 24, 32, 33). Thus reduced heterogeneity of the matching of m\(\dot{Q}{O_2}\) and m\(\dot{V}{O_2}\) is a possible, yet undetermined, mechanism to explain the effects of prior heavy exercise on p\(\dot{V}{O_2}\) kinetics.

The effects of prior heavy exercise on muscle deoxygenation kinetics are controversial. In the upright (16, 32) or prone (33) position, there are no significant differences in muscle deoxygenation kinetics [mean response time (MRT) of the primary phase] between the first and second bouts of heavy exercise. In contrast, Marles et al. (44) found that the MRT of muscle deoxygenation was faster in the second bout than in the first heavy-exercise bout. These studies assumed a homogeneous response of muscle deoxygenation within muscle regions and among different portions of the exercising muscle based on either single channel near-infrared spectroscopy (NIRS) (16, 32, 33) or an average of eight channels (44). However, we have recently shown appreciable heterogeneity in the kinetics of muscle deoxygenation across 10 sites of the working quadriceps during heavy exercise (38). The effects of prior exercise on the spatial heterogeneity of muscle deoxygenation kinetics during subsequent heavy exercise have not been described.

The purpose of this study was to investigate the effects of prior heavy cycling exercise on the spatial heterogeneity of the rectus femoris muscle deoxygenation kinetics during subsequent heavy exercise. We hypothesized that 1) the spatial heterogeneity in the dynamic matching of muscle microvascular m\(\dot{V}{O_2}/m\dot{Q}{O_2}\) would be reduced after prior heavy exercise, and 2) the anticipated reduction in the SC of p\(\dot{V}{O_2}\) response would be correlated with the reduction in the spatial heterogeneity during a subsequent bout of exercise.

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METHODS

Subjects. Seven healthy men (age, 23.7 ± 5.5 yr; height, 172.4 ± 7.1 cm; body mass, 62.1 ± 2.7 kg; means ± SD) participated in this study, which was approved by the Human Subjects Committee of Kobe Design University. After explanation of all procedures and possible risks and benefits of participation, each subject signed an informed consent form.

Protocol. All testing was completed in a well-ventilated laboratory maintained at 25.3 ± 1.5°C and 55.5 ± 11.6% humidity. The subjects came to the laboratory on three occasions within 3 wk to establish their peak \( pV\dot{O}_2 \) and perform repeated bouts of heavy cycling exercise on an electronically braked cycle ergometer (232C-XL; Combi Wellness, Tokyo, Japan) in an upright position. The subjects were asked to avoid caffeine and alcohol ingestion and strenuous exercise for 12 h before the test.

In the first visit to the laboratory, height and body mass were measured, and the subjects performed a ramp-incremental cycling exercise test to determine peak \( pV\dot{O}_2 \), gas exchange threshold (GET), and work rates for the constant work rate tests. The protocol, which was designed to produce volitional exhaustion within 10–15 min, consisted of 4 min of unloaded exercise, followed by work rate increases of 30 W/min until the limit of tolerance. Pedaling frequency was held constant at 50 rpm for all exercise bouts with the aid of an audible metronome, and the pedaling rate was monitored using an inductive revolution meter fitted to the ergometer. The peak \( pV\dot{O}_2 \) was defined as the highest \( pV\dot{O}_2 \) achieved during the test averaged over a 20-s interval. The GET was estimated from gas exchange measurements using the V-slope method, ventilatory equivalents, and end-tidal gas tensions (5). The work rates for heavy exercise were calculated to elicit 40% of the difference between the GET \( pV\dot{O}_2 \) and peak \( pV\dot{O}_2 (\Delta 40 pV\dot{O}_2 = GET pV\dot{O}_2 + 0.4(peak pV\dot{O}_2 - GET pV\dot{O}_2)) \).

Over the next two visits, repeated bouts of heavy cycling exercise were performed twice at approximately the same time of day, with 3 days between visits. The cycling exercise protocol consisted of 1 min of rest and 4 min of unloaded exercise, followed by two 6-min bouts of heavy exercise separated by 6 min of unloaded exercise.

Measurements. Throughout the experiment, pulmonary gas exchange and ventilation were measured breath by breath (37, 38). Subjects breathed through a low-resistance hot-wire flowmeter for measurement of inspiratory and expiratory flows. The flowmeter was calibrated by inputting known volumes of room air at various mean flows and flow profiles. Respired gases obtained from samples drawn continuously from the mouthpiece were analyzed using a gas analyzer (a paramagnetic O\(_2\) analyzer and an infrared CO\(_2\) analyzer; Aeromonitor AE-300S; Minato Medical Science, Osaka, Japan). Precision-analyzed gas mixtures were used for calibration. Data collected every 13 ms were transferred to a computer, and gas volume and concentration signals were time-aligned by accounting for the delay in the sampling tube and the analyzer rise time relative to the volume signal. Alveolar gas exchange variables were calculated breath by breath (4).

The changes in the concentrations of oxy (\( \Delta\text{oxy-[Hb+Mb]} \)-) and deoxygenymoglobin/myoglobin (\( \Delta\text{deoxy-[Hb+Mb]} \)) were measured simultaneously throughout the experiment at 10 different sites on the rectus femoris muscle by near-infrared spectroscopy (NIRS; NIRO-200 oxygenation monitor; Hamamatsu Photonics K. K., Shizuoka, Japan) using a multifiber adapter system (C9866). The details of the NIRS system were reported in our previous study (38). TheNIRO-200 monitor uses continuous-wave spectroscopy to provide standard measurements of the relative changes in the concentrations of Hb and Mb (18, 45). Two fiber optical bundles for light irradiation carried the near-infrared light produced by the laser diodes to the tissue of interest, whereas eight fiber optical bundles for light collection returned the transmitted light from the tissue to avalanche photodiodes in the system. Three different wavelength laser diodes (775, 810, and 850 nm) provided the light source. The intensity of transmitted light was measured continuously at 0.5 Hz, and the concentration changes from the resting baseline were calculated. The emitters were set at a distance of 5 cm on a plastic board; the receptors were placed near the emitters, at a distance of 3 cm. After the subject’s thigh was shaved and cleaned, the probes were placed around the rectus femoris muscle, and the most distal probe was placed on the muscle 9–12 cm above the knee joint, using double-sided adhesive tape and surgical tape. Probe position was similar across visits as established by pen-marked determination of probe placement when the first NIRS measurements were made. Zero point of gain was set when the subject was at rest in a seated position.

Data analysis. The breath-by-breath pulmonary gas exchange data were interpolated to 1-s intervals, filtered for aberrant data points, and then ensemble-averaged to yield a single response for each subject. For each subject, the data sets for the two visits were time-aligned and averaged.

The response curve of \( pV\dot{O}_2 \) was fit by a three-term exponential function that included amplitudes, time constants, and time delays, using nonlinear least-squares regression techniques. The computation of best-fit parameters was chosen by the program to minimize the sum of the squared differences between the fitted function and the observed response (2, 35–37, 42, 53). The first exponential term (phase I, cardiodynamic component) started with the onset of exercise and the second (phase II, primary component) and third (slow component, SC) terms began after independent time delays.

\[
pV\dot{O}_2(t) = pV\dot{O}_2_{\text{baseline}} + A_i [1 - e^{-t/TD_i}] + A_p [1 - e^{-t/TD_p}] + A_S [1 - e^{-t/TD_S}]
\]

where \( pV\dot{O}_2(t) \) represents \( pV\dot{O}_2 \) at a given time \( t \); \( pV\dot{O}_2_{\text{baseline}} \) represents the baseline \( pV\dot{O}_2 \) data before starting the heavy exercise; \( A_i, A_p, \) and \( A_S \) are the asymptotic amplitudes for the exponential terms; \( T_1, T_p, \) and \( T_S \) are the time constants; and \( TD_i, TD_p, \) and \( TD_S \) are the time delays.

The phase I \( pV\dot{O}_2 \) at the start of phase II (i.e., at \( TD_p \)) was assigned the value for that time \( (A_i) \).

\[
A'_i = A_i \times (1 - e^{-TD_i/T_D})
\]

The physiologically relevant amplitude of the primary exponential component during phase II \( (A^*_p) \) was defined as the increase in \( V\dot{O}_2 \) from baseline to the asymptote of the primary component (i.e., net amplitude as the sum of \( A'_i \) and \( A_p \)). The absolute amplitude of the primary component was defined as the sum of baseline and \( A^*_p \). Concerns of investigators regarding the validity of using the extrapolated asymptotic value for the SC \( (A_S) \) for comparisons, we used the value of the slow exponential function at the end of exercise, defined as \( A_S^* \).

To evaluate the overall mean response time (MRT\(_t\)), the \( pV\dot{O}_2 \) data during heavy exercise were fitted using the technique described above, with a single-exponential function of the form

\[
pV\dot{O}_2(t) = pV\dot{O}_2_{\text{baseline}} + A [1 - e^{-t/TD}] + A [1 - e^{-t/TD_S}]
\]

where \( A, TD, \) and \( \tau \) represent the amplitude, time delay, and time constant of the overall response during the heavy exercise bout, respectively. From this, a summary statistic for the kinetics (MRT\(_t\)) was calculated.

Individual responses of the \( \Delta\text{deoxy-[Hb+Mb]} \) during the baseline-to-exercise transitions for each of the 10 sites in each subject were time-interpolated to 1-s intervals. For each subject, the data sets for the two visits were time-aligned and averaged. The \( \Delta\text{deoxy-[Hb+Mb]} \) signals for each site at the onset of both the first and second bouts of heavy cycling exercise were normalized such that the unloaded exercise baseline values were adjusted to zero, and thus the \( \Delta\text{deoxy-[Hb+Mb]} \) data are presented as the relative change from the baseline to the end-exercise values. The time (TD) to the onset of an increase in \( \Delta\text{deoxy-[Hb+Mb]} \) was determined as the first point greater than one standard deviation above the mean of the baseline (14–16, 26). Subsequently, \( \Delta\text{deoxy-[Hb+Mb]} \) data were fit with a monoexponential model from the time of initial increase in \( \Delta\text{deoxy-[Hb+Mb]} \) to 60 s, to determine the rate of adjustment of muscle deoxygenation.

\[ \text{MRT}_t = TD + \tau \]

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The calculated model for all parameters of \( \dot{V}O_2 \) and \( [\text{deoxy-Hb} + \text{Mb}] \) reached 95% level of the primary component in 60 s (i.e., 10-s time delay plus 4 time constants) during heavy exercise (16, 19, 25, 32, 38, 44).

\[
\Delta \text{deoxy-[Hb+Mb]}(t) = \Delta \text{deoxy-[Hb+Mb]}_{\text{baseline}} + A(1 - e^{-|t|/\tau})
\]

where \( \Delta \text{deoxy-[Hb+Mb]}(t) \) represents \( \Delta \text{deoxy-[Hb+Mb]} \) at a given time \( t \); \( \Delta \text{deoxy-[Hb+Mb]}_{\text{baseline}} \) represents the baseline data before the beginning of heavy cycling exercise; and \( A \), TD, and \( \tau \) represent the amplitude, time delay, and time constant of the primary component, respectively. The TD and \( T_{\text{MRT}} \) of the \( \Delta \text{deoxy-[Hb+Mb]} \) response over the “fundamental” phase of the response were summed (MRT) to provide an indication of the overall response dynamics in the absence of any “slow component” (32, 38).

**Statistical analysis.** The means and SD of the subject data were calculated for all parameters of \( \dot{V}O_2 \) and \( \Delta \text{deoxy-[Hb+Mb]} \). Intersite coefficient of variation [CV (%)] = 100 × SD/mean of the 10 site values) for each subject was calculated as an index of spatial heterogeneity of the \( \Delta \text{deoxy-[Hb+Mb]} \) primary component kinetics (TD, \( \tau \), and MRT). Furthermore, as a measure of “data point-by-data point” intersite heterogeneity of the \( \Delta \text{deoxy-[Hb+Mb]} \), root mean square error (RMSE) for each subject at a given time was calculated as follows:

\[
\text{RMSE}(t) = \sqrt{\frac{\sum(X_i - X_{\text{ave}})^2}{n}}
\]

where \( X_i \), \( X_{\text{ave}} \), and \( n \) are individual responses at each site, the mean of the 10 site values, and the number of sites (i.e., 10), respectively. Differences between the first and second bouts were analyzed using a paired \( t \)-test. Statistical significance was accepted at \( P < 0.05 \).

**RESULTS**

All of the subjects participated in daily exercise, and thus the average peak \( \dot{V}O_2 \)/body mass value was higher than that typically reported for sedentary subjects (56.8 ± 6.2 ml·min⁻¹·kg⁻¹). The work rate at the GET + \( \Delta \text{deoxy} \) was 227 ± 21 W.

**Pulmonary \( O_2 \) uptake kinetics.** The kinetics of \( \dot{V}O_2 \) responses during heavy cycling exercise are shown in Fig. 1. The kinetic parameters of \( \dot{V}O_2 \) at the onset of the first and second bouts of heavy cycling exercise are presented in Table 1. Before the second bout of exercise, the baseline was significantly increased compared with that before the first bout (\( P < 0.05 \)). There were no significant differences in the \( \tau_p \) and \( A_p \) values of the \( \dot{V}O_2 \) kinetics between the first and second bouts of heavy cycling exercise; however, the overall MRT and \( A_p \) values in the second bout were significantly reduced compared with those in the first bout (\( P < 0.01 \)).

**Deoxy-[Hb+Mb] kinetics and their spatial heterogeneity.** Figure 2 shows the mean \( \Delta \text{deoxy-[Hb+Mb]} \) values across all sites, and sites following the onset of each bout of heavy cycling exercise. During the initial component following the onset of exercise, there was a pronounced decrease of \( \Delta \text{deoxy-[Hb+Mb]} \) at the majority of sites, indicating that the increase in \( O_2 \) delivery occurred at a faster rate than that of \( \dot{V}O_2 \), whereas other sites evidenced a constant rate of \( \Delta \text{deoxy-[Hb+Mb]} \) before the subsequent exponential increase.

The means and SD of the average \( \tau_p \), \( \tau_p \), and MRT of the primary component for the seven subjects across all 10 sites at the onset of the two bouts of heavy cycling exercise are presented in Table 2. The average TD value for the second bout was significantly shorter than that for the first bout (\( 1st \) bout vs. \( 2nd \) bout: 13.5 ± 1.3 vs. 9.3 ± 1.4 s, \( P < 0.01 \)). In contrast, both the \( \tau \) and the MRT values for the second bout were significantly slower than those for the first bout (\( \tau \): 9.3 ± 1.3 vs.

**Table 1. Parameters of pulmonary \( \dot{V}O_2 \) kinetics at the onset of two sequential bouts of heavy cycling**

<table>
<thead>
<tr>
<th></th>
<th>1st Bout</th>
<th>2nd Bout</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL, l/min</td>
<td>0.44±0.06</td>
<td>0.52±0.04*</td>
</tr>
<tr>
<td>TDp, s</td>
<td>22.4±3.1</td>
<td>16.6±2.7†</td>
</tr>
<tr>
<td>( \tau_p ), s</td>
<td>19.1±1.8</td>
<td>20.7±5.7</td>
</tr>
<tr>
<td>( A'_p ), l/min</td>
<td>2.18±0.20</td>
<td>2.26±0.18</td>
</tr>
<tr>
<td>( A_a ), l/min</td>
<td>2.62±0.21</td>
<td>2.78±0.21*</td>
</tr>
<tr>
<td>TDa, s</td>
<td>115.1±25.3</td>
<td>130.5±29.7</td>
</tr>
<tr>
<td>( A'_a ), l/min</td>
<td>0.37±0.12</td>
<td>0.11±0.12‡</td>
</tr>
<tr>
<td>MRTa, s</td>
<td>45.2±6.1</td>
<td>36.4±4.8§</td>
</tr>
</tbody>
</table>

Values are means ± SD. \( \dot{V}O_2 \), \( O_2 \) uptake; BL, baseline; TDp, time delay in phase II; \( \tau_p \), time constant in phase II; \( A'_p \), amplitude in phase I + phase II, not including BL; \( A_a \), absolute primary amplitude (BL + \( A'_p \)); TDa, time delay in phase III (slow component); \( A'_a \), amplitude in phase III; MRTa, overall mean response time (TD + \( \tau_p \)). *\( P < 0.05 \); † \( P < 0.01 \) compared with 1st bout.

**Fig. 1.** Pulmonary \( O_2 \) uptake responses to the first (solid line) and second (dotted line) bouts of heavy cycling exercise. Data are means of all subjects; standard deviations (SD) were omitted for clarity.

**Fig. 2.** Time courses of the changes in the concentration of deoxymyoglobin/myoglobin (\( \Delta \text{deoxy-[Hb+Mb]} \)) response at the onset of 2 sequential bouts of heavy cycling exercise. The y-axis indicates the relative change from the baseline to the first minute values of the muscle deoxygenation. Symbols indicate mean values for the first (■) and second bouts (○), respectively. SD were omitted for clarity.
Table 2. Kinetics of Δdeoxy-[Hb+Mb] across all 10 sites and intersite CV for the primary component at the onset of two bouts of heavy cycling

<table>
<thead>
<tr>
<th></th>
<th>1st Bout</th>
<th>2nd Bout</th>
</tr>
</thead>
<tbody>
<tr>
<td>TD, s</td>
<td>13.5±1.3</td>
<td>9.3±1.4†</td>
</tr>
<tr>
<td>τ, s</td>
<td>9.3±1.3</td>
<td>17.8±1.0†</td>
</tr>
<tr>
<td>MRT, s</td>
<td>22.7±1.8</td>
<td>27.1±1.9†</td>
</tr>
<tr>
<td>CV of TD, %</td>
<td>21.7±10.4</td>
<td>33.3±9.4</td>
</tr>
<tr>
<td>CV of τ, %</td>
<td>26.6±11.8</td>
<td>13.7±5.6†</td>
</tr>
<tr>
<td>CV of MRT, %</td>
<td>16.6±11.2</td>
<td>15.1±5.8</td>
</tr>
</tbody>
</table>

Values are means ± SD. ΔDeoxy-[Hb+Mb], change in concentration of deoxyhemoglobin/myoglobin; CV, intersite coefficient of variation. †P < 0.01 compared with 1st bout.

To our knowledge, this study is the first to report the effects of previous heavy exercise on the spatial heterogeneity of muscle deoxygenation kinetics during subsequent heavy cycling exercise. Consistent with our first hypothesis, we found that the spatial heterogeneity of muscle deoxygenation kinetics (i.e., the intersite CV of the primary component τ and the RMSE) during subsequent heavy exercise was reduced compared with prior heavy exercise. However, in contrast to our second hypothesis, the decrease in the heterogeneity of the muscle deoxygenation kinetics (the primary component τ as the major response) was not correlated with the reductions in the SC (and thus the MRT₁) of pVO₂ response during subsequent heavy exercise in these moderately aerobically fit subjects.

**Effect of prior exercise on muscle deoxygenation kinetics.** The Δdeoxy-[Hb+Mb] kinetics at the onset of the second bout of heavy cycling exercise revealed a significantly shorter TD combined with a much slower τ, and thus longer MRT, for the second bout compared with the first bout. To elucidate underlying mechanisms of the muscle deoxygenation responses during exercise transitions, we adopted efficient computerized curve-fitting techniques for precise characterization of the kinetics into discrete components (TD and τ), in addition to the overall MRT information. A novelty of the present study is that the shortening of TD during subsequent heavy cycling exercise was observed at multiple NIRS measurement sites within and among the muscles. After prior exercise, the shortening of the TD is consistent with single-muscle fiber PO₂ (28), isolated muscle microvascular PO₂ (6), and human muscle Δdeoxy-[Hb+Mb] (based on either single-channel or an 8-channel array).

![Fig. 3. Data point-by-data point root mean square error (RMSE) changes following the onset of the 2 bouts of heavy cycling exercise (means and SD for 7 subjects). Symbols indicate the mean values for the first (▲) and second bouts (●), respectively. *P < 0.05; **P < 0.01 compared with first bout.](http://ajpregu.physiology.org/)
average NIRS; Refs. 15, 16, 33, 44). However, the present finding of a slower $\tau$ of the primary component during subsequent heavy exercise is not consistent with previous studies that found a similar $\tau$ for bout 1 vs. bout 2 (16, 32, 33, 44).

It remains unclear exactly how the microvascular blood flow (mQ) is distributed following the onset of exercise. Since the muscle pump and mechanically induced vasodilatation likely increase bulk phase I mQ within a muscle without regard for the metabolic requirements of the individual fibers, a microvascular mismatching of mQO2 with respect to mVO2 is likely to occur in some intramuscular regions; i.e., hyperperfusion in areas of the muscle that are inactive (13, 14, 29, 43). As exercise is continued, negative-feedback control of local vascular responses (phase II mQ) progresses toward some more “optimal” matching of mVO2/mQO2. Consistent with this notion, regions that are hyperperfused by the muscle pump early into exercise (high amplitude of phase I mQ and faster kinetics in relation to mVO2) may have a late emergence of the subsequent increase in mQ (phase II), leading to a long TD and rapid $\tau$ of deoxy-[Hb+Mb]. On the other hand, a rapid appearance of phase II of mQ would occur in regions where the early increase in mQ closely matches the dynamics of mVO2 (i.e., constant deoxy-[Hb+Mb]), and thereby a short TD would be followed by a slower $\tau$ (20). The results in the present study support the latter scenario, thus suggesting that the performance of prior heavy exercise would promote the convective delivery of O2 (phase II mQ) to multiple sites of the muscles, improving the adequacy of mVO2/mQO2 matching at the onset of the subsequent bout of exercise (7, 9, 15, 16, 22, 23, 44).

Another interpretation for the results is that O2 utilization was improved by the intervention. The shorter TD indicates that the balance between O2 delivery and demand was disturbed earlier following the onset of the subsequent bout of exercise, possibly as a consequence of a priming of the intramuscular oxidative metabolic machinery (see below), which enabled increased O2 extraction to commence earlier (33). The slower subsequent $\tau$ implies that more O2 was available such that extraction for the second bout did not need to increase as rapidly across the transient.

The shortening of TD observed at multiple sites of the muscle in the present study is in accordance with the work of Behnke et al. (6) and Hogan et al. (28). They demonstrated the TD before the decrease in microvascular (rat spinotrapezius muscle; Ref. 6) and intracellular PO2 (frog isolated single myocyte; Ref. 28) following onset of contractions was reduced by a prior bout of contractions. For the isolated myocyte preparation (28), the O2 availability was uniform around the fiber, suggesting that VO2 increased faster during the second contractile period (see DISCUSSION in Ref. 44). Collectively, the significantly shorter TD and slower $\tau$ of $\Delta$deoxygen-[Hb+Mb] kinetics suggest that at multiple NIRS measurement sites among the muscles, the prior heavy exercise tightened the matching of muscle O2 availability to O2 utilization during subsequent heavy exercise.

**Heterogeneity of muscle deoxygenation kinetics and mVO2 kinetics.** Previous studies reported that the $\tau_p$ of pVO2 kinetics did not differ significantly between prior and subsequent heavy exercise in the upright position (3, 7–11, 22, 30, 32, 44, 47, 52), with a few exceptions (16, 46, 53), whereas the amplitude of the SC and the MRT were consistently decreased during subsequent heavy cycling exercise. Our results are consistent with the majority of these previous studies.

In contrast to our second hypothesis, the significant reductions in the spatial heterogeneity of muscle deoxygenation kinetics ($\tau$) and the RMSE were not correlated with altered pVO2 kinetics during subsequent heavy exercise (as either the unaltered $\tau_p$ or the reductions in either the SC or the MRT).

It is well known that there is substantial heterogeneity in muscle blood flow within an active muscle (e.g., 34, 48, 54). The reduction of the dynamic spatial heterogeneities of muscle deoxygenation by the prior heavy exercise suggests an improved (more homogeneous) distribution of local blood flow and matching of mQO2 to mVO2 within the active muscle (as reflected in the shorter TD and slower $\tau$ of $\Delta$deoxygen-[Hb+Mb] kinetics). If the intra- and intermuscular heterogeneity of the dynamics of muscle oxygenation contribute to slow the kinetics of phase II pVO2 (i.e., O2 delivery limitation to VO2 kinetics), these variables should have been directly and positively related. However, the reduction in the heterogeneity did not improve the phase II pVO2 kinetics during a subsequent bout of heavy exercise. The present study suggests that the heterogeneity of microvascular mQO2 (in relation to mVO2) might not lead to O2 delivery limitation of the primary phase of mVO2 kinetics during heavy exercise, i.e., this condition lies to the right of the “tipping point,” where mVO2 kinetics are independent of mQO2 (12, 38, 50). However, caution is required to interpret this notion. That mQO2 was not an initial limitation might, in part, have been due to the subjects’ fitness as evidenced by the faster phase II pVO2 kinetics in the present study compared with untrained subjects. An mQO2 distribution limitation has been suggested for those with the slower kinetics, and the potential to speed kinetics in those subjects with
faster kinetics is limited (26). In those subjects with phase II pVO2 kinetics at ~20 s, the mechanistic basis for the changes seen in VO2 kinetics by the prior heavy exercise must await further studies.

DeLorey et al. (16) found a larger increase (i.e., amplitude) in local muscle deoxy-[Hb + Mb] during phase II of the VO2 response during the second bout compared with the first bout, which they suggested was reflective of an increase in local muscle VO2 (extrusion) following prior heavy-intensity knee extension exercise. These authors considered that the metabolic acidosis that accompanies exercise in the heavy-intensity domain results in a rightward shift of the oxyhemoglobin dissociation curve, thereby enabling a greater offloading of O2 from Hb at a given PO2. Unfortunately, we do not know to what extent the absolute amplitudes of deoxy-[Hb + Mb] of the different regions influence the temporal profile of the mean muscle PO2 and VO2 (38). The effects of the optical path length, the scattering and absorption coefficients on the NIRS profiles during exercise, are controversial (21), and thus the spatial heterogeneity of the amplitudes may be related to these factors. The definitive impact of different profiles of deoxygenation on the mVO2 kinetics must await development of more powerful and comprehensive technologies.

VO2 slow component. The SC of pVO2 kinetics was decreased by prior heavy exercise (see e.g., Refs. 7, 8, 22, 42, 52). It has been suggested that pVO2 SC is linked either directly or indirectly to the recruitment of type II muscle fibers at higher work rates and/or to metabolic changes occurring within the initially recruited fibers and that the availability of O2 plays an important role in regulating the recruitment of these high-threshold type II motor units (2, 31, 40, 41, 49). Thus it is possible that the shorter TD, slower pVO2 kinetics, and/or the decreased spatial heterogeneity of muscle deoxygenation kinetics in the second bout reflected an improved distribution of local Q and matching of mVO2 to mVO2 in those fibers recruited early into exercise, which may have delayed their fatigue, thereby reducing the recruitment of more type II fibers. Alternatively, the changes in muscle deoxygenation kinetics might have decreased the degree of metabolic perturbation, causative of the VO2 SC, within already recruited fibers. However, in the present study, the shorter TD, slower pVO2 kinetics, and the decrease in the spatial heterogeneity of the muscle deoxygenation kinetics (as the primary component τ and the RMSE) did not correlate with the decrease of pVO2 SC between the two bouts. Whether this result arose from inadequate signal-to-noise ratio caused, in part, by the limited intersubject range of responses remains to be determined.

The shorter TD, slower pVO2 kinetics, and decreased spatial heterogeneity of the muscle deoxygenation kinetics during the primary component suggest a better matching of mQO2 to mVO2 such that microvascular Po2, and therefore intracellular Po2, are maintained higher through the transition during the subsequent heavy exercise. Thus the overall higher mQO2/mVO2 (i.e., lower mVO2/mQO2) and any increased intracellular Po2 may be of crucial importance for reducing the degree of intracellular perturbation and/or other events that set the stage for the development of the slow component. Therefore, the greater intracellular Po2 (as reflected in the higher mQO2/mVO2) during the primary component might be related to the reduction in the SC in the second bout.

In conclusion, prior heavy exercise reduced the spatial heterogeneity of muscle oxygenation kinetics (τ and the point-by-point RMSE of the primary component) during subsequent heavy exercise. The significantly shorter TD and slower τ of ∆deoxy-[Hb + Mb] kinetics suggest that the performance of prior heavy exercise improved the matching of muscle O2 delivery and O2 utilization at multiple sites within the muscles during the subsequent bout of exercise. However, the reduction of the spatial heterogeneity of muscle oxygenation kinetics did not translate into faster primary pVO2 kinetics during subsequent heavy exercise, suggesting that the heterogeneity of microvascular O2 delivery (in relation to O2 uptake) was not associated with discernable O2 delivery limitation of the primary phase of mVO2 kinetics. Furthermore, the decrease in the spatial heterogeneity of the muscle deoxygenation kinetics was not correlated with to the reduction in the SC of the pVO2 response.

GRANTS

This work was supported by a grant for scientific research from the Ministry of Education, Science, and Culture of Japan (Grant-in-Aid 18207019) to S. Koga.

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