Acceleration of \( \dot{V}O_2 \) kinetics in heavy submaximal exercise by hyperoxia and prior high-intensity exercise

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MacDonald, Maureen, Preben K. Pedersen, and Richard L. Hughson. Acceleration of \( \dot{V}O_2 \) kinetics in heavy submaximal exercise by hyperoxia and prior high-intensity exercise. J. Appl. Physiol. 83(4): 1318–1325, 1997.—We examined the hypothesis that \( \dot{O}_2 \) uptake (\( \dot{V}O_2 \)) would change more rapidly at the onset of step work rate transitions in exercise with hyperoxic gas breathing and after prior high-intensity exercise. The kinetics of \( \dot{V}O_2 \) were determined from the mean response time (MRT; time to 63% of total change in \( \dot{V}O_2 \)) and calculations of \( O_2 \) deficit and slow component during normoxic and hyperoxic gas breathing in one group of seven subjects during exercise below and above ventilatory threshold (VT) and in another group of seven subjects during exercise above VT with and without prior high-intensity exercise. In exercise transitions below VT, hyperoxic gas breathing did not affect the kinetic response of \( \dot{V}O_2 \) at the onset of exercise. At work rates above VT, hyperoxic gas breathing accelerated both the on- and off-transient MRT, reduced the \( O_2 \) deficit, and decreased the \( \dot{V}O_2 \) slow component from minute 3 to minute 6 of exercise, compared with normoxia. Prior exercise above VT accelerated the on-transient MRT and reduced the \( \dot{V}O_2 \) slow component from minute 3 to minute 6 of exercise in a second bout of exercise with both normoxic and hyperoxic gas breathing. However, the summatred \( O_2 \) deficit in the second normoxic and hyperoxic steps was not different from that of the first steps in the same gas condition. Faster on-transient responses in exercise above, but not below, VT with hyperoxia and, to a lesser degree, after prior high-intensity exercise above VT support the theory of an \( O_2 \) transport limitation at the onset of exercise for workloads >VT.

ventilatory threshold; oxygen transport; oxygen utilization; oxygen deficit; oxygen debt

A REDUCTION IN THE MAGNITUDE of the \( O_2 \) deficit at the onset of exercise during hyperoxic, compared with normoxic, breathing (19, 23) suggested that if one supplied more \( O_2 \) to working muscle during this transient, it could be used. These data were obtained with Douglas bag collections of mixed expired air during tests requiring 70–80% of maximal \( O_2 \) uptake (\( \dot{V}O_2 \)). To date, the only studies to follow the \( \dot{V}O_2 \) responses at the onset of exercise during hyperoxic gas breathing through breath-by-breath techniques found that there was no difference from control (11, 18). It is possible that hyperoxia failed to accelerate \( \dot{V}O_2 \) kinetics because the fractional concentration of \( O_2 \) was relatively low [inspiratory \( O_2 \) fraction (\( F_{\dot{I}O_2} \) = 0.30) (18)] or that the work rates studied were of a relatively lower intensity, at which increasing arterial \( P_{\dot{O}_2} \) has not been shown to increase \( \dot{V}O_2 \) kinetics (11, 18), than in those studies in which \( \dot{V}O_2 \) kinetics were accelerated (19, 23). In the face of conflicting evidence for accelerated or unaltered \( \dot{V}O_2 \) kinetics with hyperoxic gas breathing, it is appropriate to set out the potential explanations. It is possible that, at least over a range of work rates, adequate \( O_2 \) is delivered at the onset of exercise, and \( O_2 \) utilization establishes the rate at which \( \dot{V}O_2 \) increases (8). Alternatively, hyperoxia might not supply more \( O_2 \) over this same range of work rates because of reduced blood flow as noted by some (26), but not all (16), previous investigators.

For step increases or decreases in work rates above or below VT, there have been numerous examples in which reductions in \( O_2 \) transport could slow the increase in \( \dot{V}O_2 \) at the onset of exercise, including a start from a baseline of existing mild exercise (12), hypoxia (21), \( \beta \)-adrenergic-receptor blockade (9), and supine compared with upright exercise (15). These examples hold open the possibility that \( O_2 \) transport might be rate limiting. It has been shown that, when constant-load exercise has been constrained to be only 60–65% of the work rate at VT, the \( \dot{V}O_2 \) kinetics can be altered by manipulation of arterial perfusion pressure (10). Thus, in subjects in the upright and supine positions during application of lower body negative pressure, the \( \dot{V}O_2 \) kinetics were faster than when the sub-VT exercise was conducted in a supine posture (10). However, in healthy individuals, for upright exercise below VT in normoxia, it has never been demonstrated that increasing \( O_2 \) transport can increase \( \dot{V}O_2 \) kinetics.

For work rates above VT, making more \( O_2 \) available might accelerate \( \dot{V}O_2 \) kinetics. Breathing a 70% inspired \( O_2 \)-gas mixture could increase dissolved \( O_2 \) by up to 10 ml \( O_2/\)l of blood. The examples of smaller \( O_2 \) deficits with hyperoxia were probably for work rates above VT (19, 23). Two reports (6, 7) have suggested that \( \dot{V}O_2 \) increased more rapidly in the second of two step transitions to work rates about halfway between VT and maximum \( \dot{V}O_2 \) and no effect of prior high-intensity exercise for a subsequent subthreshold exercise bout. They attributed this to the existing changes in local muscle environment that promoted both more rapid increases in blood flow and a rightward shift of the \( O_2 \)-hemoglobin dissociation curve that facilitated \( O_2 \) release at the working muscle.

The purposes of this study were threefold. First, we wanted to obtain data from breath-by-breath analysis of \( \dot{V}O_2 \) with hyperoxic gas breathing during the challenge of exercise to work rates both below and above
VT. Second, we wanted to examine the relationships between the magnitude of the O2 deficit and the slow component of the O2 increase in normoxia and hyperoxia. Third, we wanted to determine whether the second of two step increases in work rate to intensities above VT might be further accelerated by a subject completing this exercise while breathing a hyperoxic gas mixture. These experiments allowed the testing of the hypothesis that, at least for work rates above VT, O2 transport to the exercising muscle acts as the rate-limiting step for the increase in VO2 at the onset of exercise.

METHODS

The present study was conducted in two parts. The first examined the effect of hyperoxia on VO2 kinetics in response to step changes in work rate to below and above VT. The second investigated the effect of hyperoxia and prior high-intensity exercise on VO2 kinetics after step changes to above VT.

Subjects

Seven subjects participated in each part of the study, with one subject participating in both parts. In the first part, five men and two women volunteered, and in the second part four men and three women volunteered. Each subject signed a consent form approved by the Office of Human Research of the University of Waterloo after reading a description of the methods and possible risks. Preliminary testing of all subjects consisted of an incremental exercise test to exhaustion in normoxia by using a ramp work rate protocol (15 W/min ramp at a cycling frequency of 60 revolutions/min). The gas-exchange data obtained from the normoxic ramp test were used to estimate the VT and the peak VO2. These values were used in choosing the individual work rates for the step tests. The VT was determined from the point of increased minute ventilation (Ve)-to-VO2 ratio (Ve/VO2) with no change in the Ve-to-CO2 output (VCO2) ratio, as previously described (11). The number of tests performed by each subject varied according to the noise observed in the breath-by-breath signal (17). Normally, four tests were sufficient because of the large amplitude of the steps.

Experimental Design

Part 1 involved testing both below and above VT with step changes in work rate. Subjects cycled at 25 W for 4 min to establish a baseline, before the following work rate changes: a step increase in work rate to below VT (80% VT) for 6 min, a step decrease back to 25 W for 6 min, a step increase in work rate to a level halfway between VT and peak VO2 for 10 min, and a final step decrease to 25 W for 6 min. Subjects exercised in both normoxia (room air, FIO2 = 0.21) and hyperoxia (FIO2 = 0.70). The four possible conditions were normoxic breathing in the first and second step transitions (NN), normoxic breathing in the first followed by hyperoxic breathing in the second step transition (NH), hyperoxic breathing in the first and second step transitions (HH), and hyperoxic breathing in the first followed by normoxic breathing in the second step transition (HN).

Breath-by-Breath Data

Breath-by-breath ventilation and gas exchange were measured on a computerized system (First Breath, St. Agatha, ON), which sampled inspired and expired volumes with a volume turbine (VMM-110, Alpha Technologies, Laguna Beach, CA) and fractional concentrations of O2, CO2, and N2 by mass spectrometry (Marquette MGA-1100A, Milwaukee, WI) at a frequency of 200 Hz. VO2 and VCO2 were calculated as alveolar values with compensation for lung-gas stores and with computation of the effective lung volume (15).

For the hyperoxic testing, a large Tissot tank was filled with inspiratory gases from cylinders containing 70% O2-30% N2. The gas was not humidified. The Tissot tank was connected to a Y valve (model 2730, Hans Rudolph, St. Louis, MO) to permit inspiration from the tank. The Y valve was open to room air during the normoxic transitions. The volume turbine was calibrated with a manually pumped syringe and with the equipment configured as it was during testing, including hyperoxic gas, for these tests. The mass spectrometer was calibrated for normoxia and hyperoxia by using two precision gas mixtures that spanned the anticipated fractional gas concentrations in both normoxia and hyperoxia. A calibration procedure was performed to determine the time required for gas transport and mass spectrometric response (lag time) (14). Separate lag times were determined for normoxia and hyperoxia because of the effect of gas density. The lag time for the hyperoxic mixture was ~30 ms slower than for the normoxic mixture (11). Heart rate was measured with an electrocardiograph (7803A, Hewlett-Packard) by using standard bipolar electrode placement. Mean heart rate over each breath was recorded.

Data Analysis

Breath-by-breath data for VO2 from at least three repetitions of an identical test condition for each subject were linearly interpolated between breaths to give values at 1-s intervals. The identical tests were then time aligned, superimposed, and ensemble averaged to give a single data set per subject. The average individual response was fit to a curve by using an exponential model. The curve-fitting procedure involved the calculation of a modeled exponential output for test values of the various parameters by using the least-squares error approach (13). These modeled outputs were compared with the actual individual averaged data set for that variable. The curve-fitting procedure was iterated until any further changes in the parameters for the model did not result in a reduction in the mean squared error between the curve drawn from the model and the averaged data set.

In part 2 of the study, the focus was on the effect of previous high-intensity exercise on a subsequent identical transition in work rate. After a period of 4 min with subjects pedaling at a baseline work rate of 25 W, the work rate was increased to approximately halfway between the work rates at VT and peak VO2 for 10 min. This was followed by a step decrease in work rate back to the 25 W baseline for 6 min before a second identical step transition was performed. No warning was given to the subjects before any of the step transitions, although they were made aware of the protocol before the test. Experiments were performed with normoxia (room air, FIO2 = 0.21) and hyperoxia (FIO2 = 0.70). The four possible conditions were normoxic breathing in the first and second step transitions (NN), normoxic breathing in the first followed by hyperoxic breathing in the second step transition (NH), hyperoxic breathing in the first and second step transitions (HH), and hyperoxic breathing in the first followed by normoxic breathing in the second step transition (HN).
The two-component model used to fit the responses to the low-step tests had a baseline (G0) and two amplitude terms (G1 and G2), two time constants (τ1 and τ2), and two time delays (TD1 and TD2) as previously described (13)

\[ \dot{V}O_2(t) = G_0 + G_1[1 - e^{-(t-TD1)/\tau_1}] \cdot u_1 + G_2[1 - e^{-(t-TD2)/\tau_2}] \cdot u_2 \]

where

\[ u_1 = 0 \quad \text{for} \quad t < TD1 \quad \text{and} \quad u_1 = 1 \quad \text{for} \quad t \geq TD1 \]

\[ u_2 = 0 \quad \text{for} \quad t < TD2 \quad \text{and} \quad u_2 = 1 \quad \text{for} \quad t \geq TD2 \]

\[ \dot{V}O_2(t) \] is the time-dependent variation in \( \dot{V}O_2 \).

The data from the high-step tests were fitted to a three-component model. The three-component model contained an extra amplitude term (G3) and time constant (τ3) to fit the slower adaptive phase in these tests. In the absence of a rationale for letting the third component begin at some time after the second, we used a model equivalent to that of Linnarsson (18) and had the second and third components start together. This issue is considered further in DISCUSSION

\[ \dot{V}O_2(t) = G_0 + G_1[1 - e^{-(t-TD1)/\tau_1}] \cdot u_1 + G_2[1 - e^{-(t-TD2)/\tau_2}] \cdot u_2 + G_3[1 - e^{-(t-TD3)/\tau_3}] \cdot u_3 \]

where \( u_1 \) and \( u_2 \) were defined above and

\[ TD_2 = TD_3 \]

\[ u_2 = 0 \quad \text{for} \quad t < TD_2 \quad \text{and} \quad u_2 = 1 \quad \text{for} \quad t > TD_2 \]

\[ u_3 = 0 \quad \text{for} \quad t < TD_3 \quad \text{and} \quad u_3 = 1 \quad \text{for} \quad t > TD_3 \]

The overall time course of the response was determined from mean response time (MRT). The MRT is the time it takes to reach ∼63% of the total amplitude of the response from the baseline to the final plateau value. It was calculated as a weighted sum of the time delay and time constant for each component

\[ \text{MRT} = \frac{G_1/G(1+G_2+G_3)}{(TD_1 + \tau_1)} \\
+ \frac{G_2/(G_1 + G_2 + G_3)}{(TD_2 + \tau_2)} \\
+ \frac{G_3/(G_1 + G_2 + G_3)}{(TD_3 + \tau_3)} \]

In addition to the curve-fitting procedure, the \( \dot{V}O_2 \) responses were also analyzed by calculating the \( O_2 \) deficit and by determining the slow component response of the \( \dot{V}O_2 \) response from 3 to 6 min and from 6 to 10 min after the step change in work rate. The \( O_2 \) deficit was taken as the difference between the measured \( \dot{V}O_2 \) at any time after the start of the higher-work-rate exercise and the average \( \dot{V}O_2 \) measured during the last minute of exercise.

Statistics

Statistical analysis was performed by using two-way repeated measures analysis of variance of the main effects. In part 1 the main effects, i.e., inspired gas concentration and work rate, and in part 2 the main effects, i.e., prior exercise and inspired gas concentration, were examined across various parameter estimates for \( \dot{V}O_2 \). The parameters examined were those generated from the curve-fitting procedure when applied to the average individual data set for each subject. Significant differences in MRT because of main effects were interpreted as reflecting differences in kinetics, while differences in other parameters were also noted. In part 2, when no significant difference in MRT was observed within step 2 because of the effect of previous gas condition, tests with the same gas condition for step 2 and with different previous gas conditions in step 1 were treated as identical and averaged before further statistical analysis. When significant main effects were observed, post hoc testing included comparisons by the Student-Newman-Keuls test. A significance level of \( P < 0.05 \) was maintained for all comparisons.

RESULTS

The mean peak \( \dot{V}O_2 \) values of the subjects during testing in normoxia were 45.3 ± 1.6 (SE) ml·kg\(^{-1}\)·min\(^{-1}\) in part 1 and 44.4 ± 2.4 ml·kg\(^{-1}\)·min\(^{-1}\) in part 2. The mean \( \dot{V}O_2 \) values achieved during the below-VT (low-step) and above-VT (high-step) tests in part 1 were 50.4 ± 0.9 and 78.6 ± 1.0% of peak \( \dot{V}O_2 \) at average work rates of 125 and 215 W, respectively. In part 2, the mean \( \dot{V}O_2 \) achieved during the high-step tests was 82.0 ± 0.8% of peak \( \dot{V}O_2 \) at an average work rate of 195 W.

\( \dot{V}O_2 \) Response Fitting

Part 1. The effect of hyperoxic gas breathing on \( \dot{V}O_2 \) kinetics was examined for work rate transitions to and from below and above VT (Fig. 1, Table 1). The on-transient kinetics of \( \dot{V}O_2 \) represented by the MRT were not accelerated for low steps with exercise in hyperoxia compared with exercise in normoxia. In contrast, hyperoxic gas breathing resulted in a faster adjustment to steady-state \( \dot{V}O_2 \) for high steps. No effect of hyperoxic gas breathing on the kinetics of the off-transient responses was observed for either low- or high-step transitions. For both on- and off-transients, the MRT was significantly less for low steps compared with high steps regardless of gas-breathing condition. The high-step off-transient responses were faster than the corresponding on-transient responses, for both normoxic and hyperoxic gas-breathing conditions. The low-step off-transient responses were slower than the on-transient responses for hyperoxic gas breathing, and there was no difference between the on- and off-transients during normoxic gas-breathing tests.

Fig. 1. Oxygen uptake (\( \dot{V}O_2 \)) at baseline and during transitions in exercise to low and high work rates for 1 subject breathing normoxic gas (dotted line) and hyperoxic gas (solid line). Lines represent average response for 4 identical transitions.
Table 1. Parameter estimates from fitting VO$_2$ responses for step transitions below and above VT in normoxia and hyperoxia

<table>
<thead>
<tr>
<th></th>
<th>G$_0$, ml/min</th>
<th>G$_1$, ml/min</th>
<th>TD$_1$, s</th>
<th>$\tau_1$, s</th>
<th>G$_2$, ml/min</th>
<th>TD$_2$, s</th>
<th>$\tau_2$, s</th>
<th>G$_3$, ml/min</th>
<th>$\tau_3$, s</th>
<th>MRT, s</th>
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<td><strong>On-transient</strong></td>
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<tr>
<td>Normoxia</td>
<td>734 ± 22</td>
<td>387 ± 42</td>
<td>3.4 ± 0.6</td>
<td>11.2 ± 1.1</td>
<td>561 ± 64</td>
<td>23.5 ± 1.2</td>
<td>19.8 ± 2.6</td>
<td>31.3 ± 1.3</td>
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<tr>
<td>Hyperoxia</td>
<td>742 ± 21</td>
<td>402 ± 52</td>
<td>3.6 ± 0.6</td>
<td>12.1 ± 1.7</td>
<td>578 ± 66</td>
<td>23.6 ± 1.3</td>
<td>18.0 ± 2.6*</td>
<td>31.4 ± 1.4</td>
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<td>&gt;VT</td>
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<tr>
<td>Normoxia</td>
<td>739 ± 24</td>
<td>614 ± 94†</td>
<td>3.4 ± 0.8</td>
<td>10.8 ± 2.3</td>
<td>779 ± 60†</td>
<td>17.8 ± 0.6†</td>
<td>17.6 ± 1.0†</td>
<td>516 ± 32</td>
<td>104 ± 17</td>
<td>53.9 ± 6.2†</td>
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<td>Hyperoxia</td>
<td>723 ± 20</td>
<td>539 ± 92†</td>
<td>3.6 ± 0.3</td>
<td>8.2 ± 1.6</td>
<td>1,180 ± 129*†</td>
<td>16.6 ± 0.8†</td>
<td>23.6 ± 2.0*</td>
<td>239 ± 112*</td>
<td>101 ± 10</td>
<td>44.1 ± 5.2*†</td>
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<td><strong>Off-transient</strong></td>
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<tr>
<td>Normoxia</td>
<td>1,682 ± 116‡</td>
<td>-324 ± 79‡</td>
<td>1.7 ± 0.4</td>
<td>10.9 ± 3.5</td>
<td>-620 ± 92‡</td>
<td>16.6 ± 1.7†</td>
<td>28.5 ± 0.6‡</td>
<td>34.6 ± 0.7</td>
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<tr>
<td>Hyperoxia</td>
<td>1,715 ± 125‡</td>
<td>-388 ± 113‡</td>
<td>2.4 ± 0.6</td>
<td>12.2 ± 3.4</td>
<td>-599 ± 120*‡</td>
<td>14.9 ± 1.5†‡</td>
<td>33.3 ± 2.4*‡</td>
<td>35.4 ± 1.2‡</td>
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<td>&gt;VT</td>
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<tr>
<td>Normoxia</td>
<td>2,641 ± 173‡</td>
<td>-503 ± 95‡</td>
<td>1.6 ± 0.2</td>
<td>14.7 ± 8.2</td>
<td>-1,084 ± 132‡</td>
<td>18.9 ± 0.4</td>
<td>21.9 ± 1.3†</td>
<td>-265 ± 62‡</td>
<td>82.7 ± 8.8†</td>
<td>43.5 ± 1.1†‡</td>
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<tr>
<td>Hyperoxia</td>
<td>2,676 ± 195†‡</td>
<td>-435 ± 63†‡</td>
<td>2.2 ± 0.4</td>
<td>11.2 ± 7.4</td>
<td>-1,218 ± 131†‡</td>
<td>16.8 ± 0.9*</td>
<td>21.7 ± 0.6</td>
<td>-260 ± 34†</td>
<td>78.1 ± 6.7</td>
<td>40.9 ± 1.4†‡</td>
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</table>

Values are means ± SE for at least 4 repetitions by 7 subjects. VT, ventilatory threshold; G$_0$, 2-component model baseline; G$_1$ and G$_2$, 2-component 2 amplitude terms; G$_3$, 3-component model amplitude term; TD$_1$ and TD$_2$, 2-component model time delays; $\tau_1$ and $\tau_2$, 2-component model time constants; $\tau_3$, 3-component model time constant; MRT, mean response time. *Significantly different from normoxia for same step change in work rate, P < 0.05. †Significantly different from <VT step in same gas-breathing condition, P < 0.05. ‡Significantly different from the on-transient for same work rate and same gas-breathing condition, P < 0.05.

Part 2. In this part of the study, when normoxic and hyperoxic gas breathing were balanced between the step 1 and step 2 transitions, it was found that there was no effect of prior gas breathing on the MRT of the second of two exercise transitions (P > 0.05). Consequently, results were pooled and analyzed according to the gas condition within the exercise transition being examined (Fig. 2, Table 2). As in part 1, during high-step exercise transitions the VO$_2$ on-response was faster in hyperoxia than in normoxia, and this was true for both steps 1 and 2 (Table 2). Similarly, there were no effects of hyperoxia on off-transient VO$_2$ kinetics after the step 1 or step 2 test. The VO$_2$ on-transient kinetics were significantly accelerated as a result of prior exercise in both the normoxic and hyperoxic gas-breathing tests. Prior high-intensity exercise had no effect on any of the off-transient MRT. In step 1, during normoxic gas breathing the off-transient responses were faster than the corresponding on-transient responses, and no difference was observed between the on- and off-transients during hyperoxic gas breathing. During the step 2 transition, slower VO$_2$ kinetics were observed during the off-transient in hyperoxia than during the corresponding on-transient, whereas there were no differences between the on- and off-transient responses in normoxic gas breathing.

O$_2$ Deficit and VO$_2$ Slow Component

Low steps. There was no difference in the O$_2$ deficit calculated for hyperoxic and normoxic tests to below VT. There was not a significant slow component of VO$_2$ in either hyperoxic or normoxic low-step transitions (Table 3). These results were consistent with those obtained by curve fitting (Table 1).

High steps. Also consistent with the curve-fitting results presented above were the observations of a significantly smaller O$_2$ deficit in high-step transitions with hyperoxia compared with normoxia in both parts 1 and 2 (Table 3). However, calculated O$_2$ deficit in the second normoxic and hyperoxic steps was not different from step 1 in the same gas conditions.

The indication of VO$_2$ kinetics, from the VO$_2$ slow component between minutes 3 and 6 of the high-step tests, was consistent with the curve-fitting results (Tables 1 and 2). There was significantly less slow component in hyperoxia compared with normoxia, and the step 1 transition had a greater O$_2$ slow component than that in step 2 (Table 3). Only for step 2 in normoxia was there a significant further slow component in VO$_2$ between minutes 6 and 10 of the step tests. These results indicate that most effects of the experimental
Table 2. Parameter estimates for VO₂ kinetics for step transitions above VT in normoxia and hyperoxia without and with prior exercise

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Step 2</th>
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<tbody>
<tr>
<td>Normoxia</td>
<td>Hyperoxia</td>
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<tr>
<td>Normoxia</td>
<td>Hyperoxia</td>
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</tbody>
</table>

Values are means ± SE; n = 7 subjects. *Significantly different from normoxia for same step change in work rate, P < 0.05. †Significantly different from step 1 in the same gas-breathing condition, P < 0.05. ‡Significantly different from on-transient for same step change in work rate and same gas-breathing condition, P < 0.05.

smaller O₂ deficit, and reduced VO₂ slow component from 3 to 6 min of exercise) for work rates above VT. When the two manipulations were combined, there was further speeding of the VO₂ response, indicating that the two stimuli may work independently to increase O₂ transport at the onset of exercise. For work rates below VT, there was no significant effect of hyperoxia on the time course of V/O₂ at the onset of exercise. The postexercise rate of decrease in VO₂ was faster after the below-VT exercise than after the above-VT exercise, yet there was no difference between normoxia and hyperoxia.

Methodological Considerations

There are two components of the design of this study that merit further consideration before physiological interpretation of the data can be discussed. The first is the selection of the work rates for the study, and the second is the model used to fit the experimental data. We selected work rates that were constant across the normoxia or hyperoxia treatments even though the peak work rate and VO₂ are often found to be increased by up to 10% by hyperoxia (25). It was felt that this would not affect the kinetics responses because in each of the below- and above-VT cases, the work rates were clearly within the domains required. Furthermore, it has been observed that kinetics of VO₂ are altered across a range of work rates, being slower for above-VT work rates, as we found; except for minor differences in percentage of peak work rate, there is little effect on the time course of VO₂ at the onset of exercise (4, 28). In this study, our focus was on the effects of hyperoxia and/ or prior exercise on the VO₂ response to a fixed work rate. Fitting of the VO₂ response at the onset and end of exercise has been done by a variety of methods, primarily on the basis of the observation of an exponential, or near-exponential, change (18). At the below-VT work rate, we used a two-component exponential, in which the first component accounted for the rapid increase in
VO₂ at the onset or decrease in VO₂ at the end of exercise, because the return of venous blood is altered with the change in work rate. The second component represents the major change to the new steady-state value and is described by a single time constant with time delay (15). The major difference between studies has been in the description of the VO₂ response to work rates above VT. We used a three-component exponential model.

The first component of the above-VT model was identical to that in the below-VT exercise. The second and third components represent a relatively rapid and a more slowly developing component, respectively. This interpretation is consistent with other research (28) and with our observations from the VO₂ slow-component analysis (Table 3). In accord with Linnarsson (18), we had both phases 2 and 3 start at the same time point. In contrast, some researchers have allowed the time delay of the third phase to vary, demonstrating that this component of the response started 90–120 s after the onset of the exercise (2, 22). Curve fitting of physiological responses can incorporate physiological correlates, or it can simply attempt to minimize the error of the distribution of the data points about the line of best fit. In this case, it is not possible to identify specifically the physiological mechanism responsible for the slow component of the VO₂ response (28). Therefore, we justify our selection of the model with a common time delay for phases 2 and 3 by the absence of a statistically significant improvement in fit between our model and that with an extra parameter for a third time delay. Whichever model is selected, the physiological interpretation as presented below is not altered.

Effect of Hyperoxia

In the steady-state phases of the present experiments, there were only minor differences in measured VO₂ between normoxia and hyperoxia. In the baseline period before step 1 of part 2 of the study (Table 2), there was a small but significantly greater VO₂ with hyperoxia compared with normoxia. Later within this same protocol, during the baseline period before step 2, VO₂ was also higher with hyperoxia. Some previous research (25) has found an increase in fat utilization with hyperoxic breathing, although this was not suggested in the present study because the respiratory exchange ratio was unaltered. The elevated VO₂ could have also been a consequence of inadequate time for equilibration to hyperoxia. Careful calibration of the equipment in this study was performed. We cannot, however, totally disregard the possibility that small errors in our measurements might have caused this statistical finding.

The faster VO₂ on-transient MRT and the smaller O₂ deficit and VO₂ slow component observed for the above-VT steps in hyperoxia, compared with normoxia, are in agreement with previous studies using Douglas bags and measurements of O₂ deficit to estimate VO₂ kinetics (19, 23). The faster VO₂ responses at the same absolute work rate are consistent with the pattern to be expected when the relative work rate is reduced by hyperoxia. Closer examination of the parameter estimates for the exponential curve fitting (Tables 1 and 2) shows that the increase during phase 3 was less in the hyperoxia tests than in normoxia. Therefore, to attain similar VO₂ values at the end of exercise, a greater slow increase (see G₃ and τ₃ in Tables 1 and 2) occurred in normoxia. This observation is also supported by a greater slow component between minutes 3 and 6 during normoxia compared with hyperoxia (Table 3). This observation supports the findings of Paterson and Whipp (22).

Hyperoxic gas breathing was used in this study as an attempt to increase the transport of O₂ to working muscle and therefore to determine whether O₂ transport is a limiting factor in the transient VO₂ response after a step increase in work rate above and below VT. Others have shown that hyperoxia does not accelerate the kinetics of VO₂ for step transients below VT (11, 18). The mechanism responsible for this could be that adequate O₂ is already being delivered at the onset of this light exercise, and hence O₂ delivery would not be limiting, or that hyperoxia does not, in fact, provide more O₂ at the onset of exercise. During steady-state exercise, blood flow to working muscles is reduced (26) or unaltered (16) with hyperoxic gas breathing. It is not known whether hyperoxic breathing resulted in decreased blood flow to the exercising muscle in this study. A reduction in blood flow, to counter the increase in blood O₂ content, would serve to maintain the O₂ delivery to the working muscle at approximately the same level as in normoxia. Another unknown is the mean capillary PO₂. Knight et al. (16) identified an apparent nonlinear relationship between their estimated value for mean capillary PO₂ and peak leg muscle VO₂ with hyperoxia. Among other mechanisms that might account for this, Knight et al. included heterogeneity of flow distribution to the exercising muscle because of hyperoxia-induced vasoconstriction. The observation that on-transient VO₂ kinetics were accelerated with hyperoxic gas breathing for step transitions to levels above VT indicates that the rate of O₂ transport was probably accelerated by hyperoxia during these step transitions.

Effect of Prior Exercise

Prior high-intensity exercise was also used in this study as a means of attempting to increase the O₂ transport to the working muscle. A prior bout of high-intensity exercise (>VT) accelerated the VO₂ on-transient kinetics in normoxia and in hyperoxia, as evidenced by a smaller MRT. These findings are in agreement with previous research using a similar work rate protocol (6, 7), which found that, for exercise in normoxia at work rates above VT, prior exercise accelerated the VO₂ kinetics of a subsequent exercise bout.

Metabolic acidosis as a result of the prior exercise bout has been suggested as a possible explanation for the faster VO₂ kinetics of the second exercise bout (6, 7). These previous reports postulated that the prior exercise elevated the concentration of blood lactate and decreased the pH in the working muscle, thereby...
promoting changes in osmolality and acidity that result in vasodilation in the working muscles. Other vasoactive substances might also still be elevated after 6 min of recovery. An additional factor that could promote O$_2$ delivery to the working muscle would be a rightward shift of the O$_2$-hemoglobin dissociation curve resulting from the accumulation of H$^+$ and increased CO$_2$ (5). These results support the theory that O$_2$ transport is a limiting factor to high-intensity-exercise V˙O$_2$ on-transient kinetics, although changes in the intracellular metabolic environment that might promote a more rapid increase in oxidative metabolism have not been investigated.

The time course of increase in oxidative phosphorylation at the onset of exercise has been estimated by a range of techniques, yet it is uncertain over what range of work rates the time course of the adaptive process remains constant (14, 20, 28). With cycling exercise, there are definitely slower kinetics for V˙O$_2$ measured at the mouth at high work rates (28). Results from recent studies with nuclear magnetic resonance spectroscopy indicate both slower changes (20) and no differences in the rates of change in phosphocreatine (30) at higher work rates. Measurement of muscle V˙O$_2$ as the product of blood flow and arteriovenous O$_2$ content difference also showed a slower response at higher work rates (14). None of the experimental conditions resulted in high-step kinetics that were as fast as the low-step kinetics (Tables 1 and 2). This indicates either that O$_2$ transport was not the only limiting factor for the high steps or that the experimental conditions did not completely alleviate the O$_2$ transport deficit.

O$_2$ Deficit and O$_2$ Debt

The literature contains reports of the magnitude of O$_2$ debt exceeding, equaling, or being less than the magnitude of the O$_2$ deficit. Part of this discrepancy arises from the differences in exercise work rates studied, and part arises from differences in baseline state after the exercise. In an earlier study (1) in which debt exceeded deficit, the intensity of exercise studied was high, and the baseline after exercise was considered to be basal rest. In many studies in which lighter intensities of exercise (< VT) were studied with either rest or light exercise baselines, O$_2$ deficit and O$_2$ debt were normally about equal (9, 27, 31). The present results for below VT in both normoxia and hyperoxia, in which the time course of recovery (MRT) and the magnitude of change are almost the same as those at the onset of exercise, are in agreement with this. When the O$_2$ deficit is increased, by β-adrenergic-receptor blockade (9) or by higher intensity exercise, as shown in the present study by the slower MRT, the O$_2$ debt can be found to be smaller than O$_2$ deficit when the recovery baseline is mild exercise. The most probable explanation for this is that lactate produced during the on-transient to compensate for the inadequate O$_2$ delivery is metabolized as a substrate during exercise and in the mild exercise recovery (3). That is, it is not necessary to repay this component of the debt (11).

Wilson et al. (29) have shown that the ATP-to-ADP ratio can be altered at a given steady-state V˙O$_2$ as a function of intracellular PO$_2$. This could account for the different concentrations of lactate observed in hypoxia vs. normoxia or hyperoxia (19). Recently, Hughson et al. (14) speculated that altered intracellular PO$_2$ at the onset of exercise might modify the V˙O$_2$ response during the non-steady-state transition. The intracellular PO$_2$ at this time would be a function of O$_2$ delivery (arterial PO$_2$ and blood flow) and O$_2$ utilization. The present results are consistent with this hypothesis for work rates > VT.

The O$_2$ deficit and V˙O$_2$ slow-component values were smaller than the corresponding measurements of Gerbino et al. (7). These differences are likely to be because of the higher work rates used in the high-step transitions of the previous study. Although in both studies subjects were assigned a high work rate that was approximately halfway between VT and peak V˙O$_2$, the measured values in the previous study (92% peak V˙O$_2$) were considerably higher than in the present study (79 and 82% of peak V˙O$_2$). These differences in protocol may also explain the observation that prior high-intensity exercise did not influence the magnitude of the O$_2$ deficit in the present study, in contrast to the findings of Gerbino et al. (7). The major contribution to O$_2$ deficit occurs before 3 min. However, we measured O$_2$ deficit over the full 10 min of exercise. The lack of effect of prior exercise could have resulted from small differences in the early response or in the apparent plateau value with the longer exercise duration in this study.

Conclusions

The faster V˙O$_2$ kinetics observed for the on-transient during step changes above VT with hyperoxia, and to a lesser degree with prior exercise, provide evidence that the supply of O$_2$ contributes to the control of tissue V˙O$_2$ for this relatively high, exercise intensity. The observation of no change in V˙O$_2$ kinetics for steps below VT may indicate that O$_2$ transport is not a limiting factor in this light-exercise-intensity condition. However, in the absence of definitive data concerning O$_2$ transport in the critical adaptive phase, it is not possible to rule out the alternative hypothesis. Off-transient kinetics above VT did not change significantly because of prior exercise or hypoxic gas breathing, indicating that regulatory mechanisms for O$_2$ supply and utilization may be different in on- and off-transients above VT.

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