Effects of hypoxic hypoxia on O_2 uptake and heart rate kinetics during heavy exercise

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Engelen, Marielle, Janos Porszasz, Marshall Riley, Karlman Wasserman, Kazuhira Maehara, and Thomas J. Barstow. Effects of hypoxic hypoxia on O_2 uptake and heart rate kinetics during heavy exercise. *J. Appl. Physiol.* 81(6): 2500–2508, 1996.—It is unclear whether hypoxia alters the kinetics of O_2 uptake ($\dot{V}O_2$) during heavy exercise [above the lactic acidosis threshold (LAT)] and how these alterations might be linked to the rise in blood lactate. Eight healthy volunteers performed transitions from unloaded cycling to the same absolute heavy work rate for 8 min while breathing one of three inspired O_2 concentrations: 21% (room air), 15% (mild hypoxia), and 12% (moderate hypoxia). Breathing 12% O_2 slowed the time constant but did not affect the amplitude of the primary rise in $\dot{V}O_2$ (period of first 2–3 min of exercise) and had no significant effect on either the time constant or the amplitude of the slow $\dot{V}O_2$ component (beginning 2–3 min into exercise). Baseline heart rate was elevated in proportion to the severity of the hypoxia, but the amplitude and kinetics of increase during exercise and in recovery were unaffected by level of inspired O_2. We conclude that the predominant effect of hypoxia during heavy exercise is on the early energetics as a slowed time constant for $\dot{V}O_2$ and an additional anaerobic contribution. However, the sum total of the processes representing the slow component of $\dot{V}O_2$ is unaffected.

oxygen uptake kinetics; curve fitting

HYPOXIA, which reduces the P_{O_2} in the arterial blood, reduces both peak O_2 uptake ($\dot{V}O_{2peak}$) and the lactic acidosis threshold (LAT; i.e., the threshold for accumulation of blood lactate, as estimated by gas-exchange responses) (31). In addition, during moderate exercise, hypoxia also results in slower O_2 uptake ($\dot{V}O_2$) kinetics (longer time constant), but ultimately the same steady-state $\dot{V}O_2$ can be achieved (22, 31). In concert with the slower kinetics seen with hypoxia, the O_2 deficit is greater than under normoxia (19), implying greater reliance on anaerobic sources of high-energy phosphates [e.g., phosphocreatine (PCr) and anaerobic glycolysis with lactate production], at least transiently during the adjustment to a new steady state. Indeed, the slowed $\dot{V}O_2$ kinetics with hypoxia are associated with a greater reduction in muscle PCr and a greater rise in blood and muscle lactate concentration, the latter being inversely related to the inspiratory O_2 fraction ($F_{I_{O_2}}$) (19).

It is presently unclear how hypoxia might affect $\dot{V}O_2$ kinetics during heavy exercise (i.e., above the LAT, with sustained lactic acidosis). During heavy exercise under normoxic conditions, there is an additional slow rise in $\dot{V}O_2$ that begins, on average, 2–3 min into exercise. This additional slow $\dot{V}O_2$ component has two consequences: *1*) delay in attaining a steady state, if achieved at all, before fatigue occurs; and *2*) increase in the overall O_2 cost of the exercise above that predicted from extrapolation of the $\dot{V}O_2$-work rate relationship for moderate (<LAT) exercise (5). The amplitude and rate of increase of this slow component are significantly correlated with the magnitude and rate of change of blood lactate (30), but the mechanism(s) that result in increased O_2 utilization remains obscure (25). If heavy (>LAT) exercise during hypoxia is associated with greater rise in blood lactate compared with room air breathing and the slow $\dot{V}O_2$ component were coupled to the blood lactate level, this would predict a greater amplitude for the slow $\dot{V}O_2$ component with hypoxia. On the basis of the above findings, we hypothesized that hypoxic heavy exercise would be associated with a longer time constant for the predominant component of $\dot{V}O_2$ and a larger slow component associated with greater blood lactate accumulation. One purpose of the present study was to test these hypotheses by characterizing the effects of acute hypoxia on the fast and slow components of $\dot{V}O_2$ during the adjustment to heavy-intensity exercise (>LAT) and in recovery.

A second purpose of this study was test how hypoxia affected the heart rate response during heavy exercise and in recovery. Hypoxia results in a higher heart rate than during normoxia both before and during transitions to moderate (22, 31) and heavy exercise (18). Whether heart rate kinetics are affected is equivocal. Some (18, 22) have reported no difference in the rate of increase in heart rate after a step change in work rate during hypoxia, whereas others (31, 35) found a significant slowing of the heart rate response during low and moderate exercise. These discrepancies may be due to different mathematical models being used to describe the responses. During recovery, however, a consistent slowing of heart rate and $\dot{V}O_2$ kinetics is observed with hypoxia (18). A second purpose of this study was to characterize the heart rate responses during heavy exercise under varying concentrations of inspired O_2.

METHODS

Subjects

Eight healthy nonsmoking volunteers (7 men, 1 woman), aged 29.5 ± 6.0 yr, with body mass 78.1 ± 9.1 kg, agreed to participate in this study after giving informed consent. The protocol was approved by the Human Subjects Committee of the Research and Education Institute at Harbor-University of California at Los Angeles Medical Center. All subjects were free of cardiac and pulmonary disease.

Protocol

All tests were performed with the subjects in the upright position on an electronically braked cycle ergometer (Quinton Corival). Seat and handlebar heights were held constant for each subject for all the tests, as was the pedaling frequency, which was selected by the subject at a rate between 60 and 85 revolutions/min. The tests were performed while subjects were breathing room air (21% O_2) or breathing hypoxic gas mixtures of 12 or 15% O_2 provided from a meteorological balloon in which the O_2 concentrations were achieved by diluting room air with N_2.

All tests started with 2 min at rest with subjects breathing room air. In the hypoxic conditions, 15 additional minutes at rest were allowed while subjects were breathing the hypoxic gas to equilibrate body gas stores of O_2 and CO_2, as judged by a return of the respiratory exchange ratio (RER) to its prehypoxia value.

Incremental-exercise tests. Preliminary incremental- exercise tests were performed by each subject at each inspired O_2 (21, 15, and 12%). After a period of rest, the subjects started exercising at unloaded cycling for 4 min, followed by a progressively increasing (ramp-pattern) work rate test to determine $\dot{V}O_{2peak}$ and the LAT. The work rate increase was selected so as to reach the maximum-tolerated work rate in ~8–12 min, as signaled by the subject. The $\dot{V}O_2$ at the LAT was determined as the breakpoint in the plot of CO_2 uptake ($\dot{V}CO_2$) as a function of $\dot{V}O_2$, where the slope becomes >1 (V-slope method) (7).

Constant work rate tests. For each of the three different $F_{I_{O_2}}$ conditions, each subject performed heavy-intensity, constant work rate exercise for 8 min. The exercise was preceded by 4 min, and followed by 10 min, of unloaded cycling. The high-intensity exercise levels were selected for each subject from the 12% O_2 incremental exercise test at a work rate that corresponded to the $\dot{V}O_2$ at the LAT plus 50% of the difference between the LAT and $\dot{V}O_{2peak}$ [$50\%\Delta$ = LAT + $0.5*(\dot{V}O_{2peak} - LAT)$]. This work rate averaged 154.5 ± 29.3 W. Two repetitions of this same absolute work rate were then performed at each $F_{I_{O_2}}$ on subsequent days or on the same day but separated by at least 2 h. A maximum of two heavy-intensity exercise bouts were performed on any single day.

In addition, five of the subjects performed moderate-intensity constant work rate exercise in subsequent weeks under the two extreme $F_{I_{O_2}}$ conditions (21 and 12% O_2). The work rate used for both breathing conditions corresponded to a $\dot{V}O_2$ of 95% of the LAT determined during the 12% O_2 incremental test. The work rate lasted 6 min and was repeated four times in a single session, separated by 6 min of unloaded cycling.

Measurements

Breath-by-breath gas exchange was measured throughout each protocol, as previously described (6). Heart rate was recorded beat by beat and averaged over each breath. Static calibration and dynamic validation of the breath-by-breath system by using a metabolic simulator (15) were performed on a daily basis.

During the constant work rate exercise tests, blood samples (1.5 ml) were drawn from an antecubital vein into heparinized syringes for determination of lactate content. The samples were taken in the last minute of unloaded cycling and at 2 min of recovery after the first exercise bout under each level of inspired O_2 and immediately analyzed by using an automated lactate analyzer (YSI 2300).

Data Analysis

The breath-by-breath data were interpolated to give values second by second. For each work rate and $F_{I_{O_2}}$ condition within each subject, the repetitions were time aligned to the start of exercise and averaged to reduce the breath-to-breath noise and enhance the underlying physiological response pattern. These averaged responses for each subject were then used to evaluate the effect of $F_{I_{O_2}}$ level and exercise intensity on $\dot{V}O_2$ and heart rate kinetics.

To facilitate comparisons, the time courses of $\dot{V}O_2$ and heart rate were described in terms of exponential functions that were fit to the data by using non-linear-regression techniques. The computation of best fit parameters was chosen by the program so as to minimize the sum of the squared differences between the fitted function and the observed response.

$\dot{V}O_2$. The mathematical model for the $\dot{V}O_2$ response consisted of three exponential terms, each representing one of the phases described earlier (Fig. 1*A*). The first exponential term started with the onset of exercise (*time 0*), whereas the other terms began after independent time delays

$$\begin{aligned}\dot{V}O_2(t) = \dot{V}O_2(b) + A_0*(1 - e^{-t/\tau_0}) \quad & \textit{phase 1}\\ + A_1*[1 - e^{-(t-TD_1)/\tau_1}] \quad & \textit{phase 2}\\ + A_2*[1 - e^{-(t-TD_2)/\tau_2}] \quad & \text{slow component} \qquad (1)\end{aligned}$$

where $\dot{V}O_2(b)$ is the unloaded cycling baseline value; A_0, A_1, and A_2 are the asymptotic values for the exponential terms; τ_0, τ_1, and τ_2 are the time constants; and TD_1 and TD_2 are the time delays. The *phase 1* term was terminated at the start of *phase 2* (i.e., at TD_1) and assigned the value for that time (A_0')

$$A_0' = A_0*(1 - e^{-TD_1/\tau_0})$$

The physiologically relevant amplitude of the primary exponential component during *phase 2* (A_1') was then set equal to the sum $A_0' + A_1$ (Fig. 1*A*). Because the $\dot{V}O_2$ response during moderate-intensity exercise (<LAT) reaches a new steady state within 3 min after the onset of exercise in normal subjects, the slow exponential term invariably dropped out during the iterative-fitting procedure.

We also tested the hypothesis that, although hypoxia would slow $\dot{V}O_2$ kinetics during exercise, there would still be a symmetry between on and off responses. The three-exponential model used during exercise was modified slightly for use during recovery, with the second and third exponentials starting together after a common time delay (Fig. 1*B*)

$$\begin{aligned}\dot{V}O_2(t) = EE\dot{V}O_2 - A_0*(1 - e^{-t/\tau_0})\\ - A_1*[1 - e^{-(t-TD)/\tau_1}] - A_2*[1 - e^{-(t-TD/\tau_2}] \qquad (2)\end{aligned}$$

where the parameters have the same correlation to those in *Eq. 1*, except that TD is a common time delay for both A_1 and A_2 exponential terms, and $EE\dot{V}O_2$ is the end-exercise level of $\dot{V}O_2$. As with the exercise responses, the A_0 term was terminated at TD, with A_1' in recovery equal to the sum $A_0' + A_1$ for the recovery fit. The justification for this model was as follows. The two main exponential processes observed during heavy exercise (A_1' and A_2) begin at different times into exercise (TD_1 and TD_2), but both are present at the end of exercise. Thus both theoretically would be present and decaying simultaneously during early recovery but presumably at different rates. The initial exponential term, as for the exercise responses, described an equivalent off-transient *phase 1* response that was always present. Preliminary *F*-tests confirmed the better fit of this three-exponential model over a

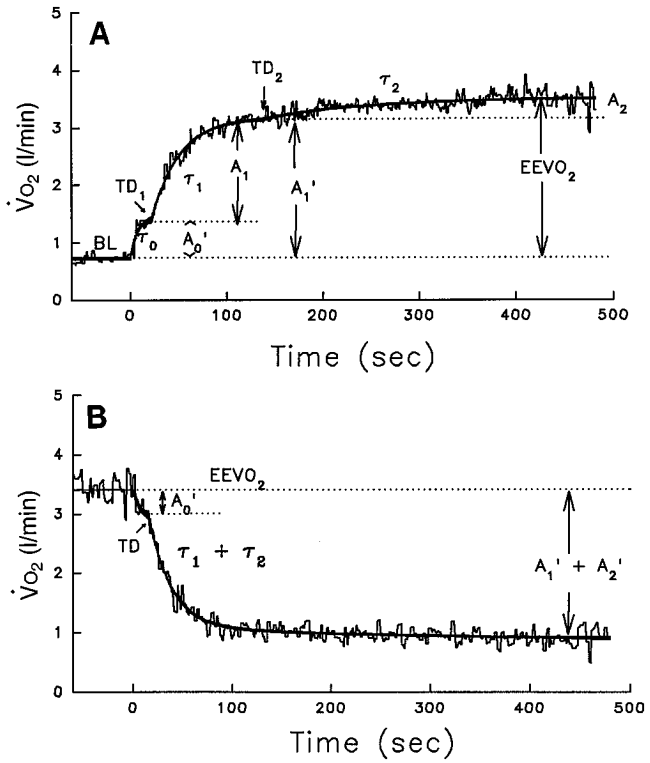

Fig. 1. Features of three exponential models used to describe O_2 uptake ($\dot{V}O_2$) response during exercise (*A*) and recovery (*B*). Parameters correspond to those in *Eqs. 1* (exercise) and *2* (recovery). TD, time delay; EE$\dot{V}O_2$, end-exercise $\dot{V}O_2$, A_1 and A_1, asymptomatic values for exponential delays; τ, time constant.

two-exponential model (without *phase 1*) for describing the responses after the heavy exercise. As with the exercise responses, if the responses were fundamentally monoexponential with a *phase 1* component (as with recovery from moderate exercise), the third exponential term would drop out during the iterative-fitting procedure.

Heart rate. The heart rate response during the heavy exercise had a similar but not identical appearance to $\dot{V}O_2$, with three phases to the response. The first phase consisted of an initial rapid rise that was linear in nature and was usually followed by a short notch or plateau for a few seconds before a second, exponential rise began. Some previous studies used an exponential term to describe the first phase (35), whereas others did not distinguish it from the primary exponential component (18). We consistently found *phase 1* for heart rate to be well described by a linear, but not an exponential, slope, for heavy exercise. This portion of the response for heart rate was, therefore, described by a linear slope and an overall amplitude A_0. The remainder of the heart rate response during exercise was described by two exponential terms

$$HR(t) = HR(b) + A_0 + A_1*[1 - e^{-(t-TD_1)/\tau_1}] + A_2*[1 - e^{-(t-TD_2/\tau_2}] \quad (3)$$

Unlike $\dot{V}O_2$, heart rate in recovery did not exhibit a rapidly decreasing early (*phase 1*) response. We therefore described heart rate during recovery by a model with two exponential terms, both starting after a common time delay

$$HR(t) = HR_{End-Ex} - A_1*[1 - e^{-(t-TD)/\tau_1}] - A_2*[1 - e^{-(t-TD)/\tau_2}] \quad (4)$$

Statistical Methods

Preliminary *F*-tests were performed to confirm the appropriateness of the two- or three-exponential models compared with simpler descriptions of the responses. Differences in the parameters of interest among the three FI_{O_2} conditions were evaluated by analysis of variance with repeated measures. When significant differences were found, these were further evaluated by post hoc Duncan's multiple-range test. Differences were declared to be significant for $P < 0.05$.

RESULTS

Incremental Exercise

As anticipated, hypoxia led to a reduced exercise capacity, $\dot{V}O_{2peak}$, and LAT for both 15 and 12% inspired O_2 compared with room air (Table 1). Interestingly, the LAT was reduced in direct proportion to the $\dot{V}O_{2peak}$ so that the LAT/$\dot{V}O_{2peak}$ remained constant at ~49% for all three inspired O_2 concentrations (Table 1).

Heavy Constant Work Rate Exercise

Associated with the decrease in exercise capacity, 12% O_2 resulted in a significant increase in the relative intensity of the designated heavy work rate, as denoted by %Δ, and end-exercise lactate compared with that seen at 21% O_2 ($P < 0.05$) (Table 2). Although there was a trend, mild hypoxia of 15% did not lead to a signifi-

Table 1. *Effects of hypoxia on $\dot{V}O_{2peak}$ and LAT*

Subject No.	12% O_2			15% O_2			21% O_2		
	$\dot{V}O_{2peak}$, l/min		LAT, %max	$\dot{V}O_{2peak}$, l/min		LAT, %max	$\dot{V}O_{2peak}$, l/min		LAT, %max
1	2.83	1.30	45.9	3.38	2.05	60.7	3.35	1.86	55.5
2	2.35	1.17	49.8	2.84	1.42	50.0	3.15	1.77	56.2
3	3.03	1.60	52.8	4.50	2.00	44.4	4.62	2.20	47.6
4	2.55	1.55	60.8	3.19	2.03	63.6	3.53	2.15	60.9
5	2.35	1.20	51.1	2.80	1.20	42.9	3.18	1.52	47.8
6	1.72	0.85	49.4	2.02	1.00	49.5	2.08	1.06	51.0
7	2.52	1.05	41.7	3.42	1.40	40.9	3.42	1.65	48.2
8	2.65	1.00	37.7	2.85	1.06	37.2	3.25	1.15	35.4
Mean ± SD	2.50 ± 0.39*	1.22 ± 0.26*	48.7 ± 7.1	3.13 ± 0.71†	1.52 ± 0.44†	48.7 ± 9.4	3.32 ± 0.69	1.67 ± 0.42	50.3 ± 7.7

$\dot{V}O_{2peak}$, peak O_2 uptake; LAT, lactic acidosis threshold. *Significantly different from both 15 and 21% O_2 values, $P < 0.01$; †significantly different from 21% O_2, $P < 0.05$.

Table 2. *Work rate, %Δ, and end-exercise lactate values*

	$F_{I_{O_2}}$		
	12%	15%	21%
Work rate, W	154.5 ± 29.3	154.5 ± 29.3	154.5 ± 29.3
%Δ	88.7 ± 19.8*	51.9 ± 19.9	44.7 ± 15.7
Net lactate, mmol/l	6.1 ± 2.1*	3.1 ± 1.4	2.6 ± 1.3

Values are means ± SD; $n = 8$. $F_{I_{O_2}}$, inspiratory O_2 fraction. Increase in relative intensity of designated work rate (%Δ), calculated as (end-exercise $\dot{V}O_2$ − LAT)∗100/($\dot{V}O_{2peak}$ − LAT). *Significantly different compared with 15 and 21% O_2 values, $P < 0.05$.

cant increase in blood lactate or the calculated %Δ (Table 2).

The group mean on and off kinetic responses for $\dot{V}O_2$ during heavy exercise and recovery are shown in Fig. 2. Although the $\dot{V}O_2$ responses were not appreciably different visually, the kinetics of $\dot{V}O_2$ were significantly slower with moderate (12% O_2) compared with mild hypoxia (15% O_2) or normoxia (21% O_2). This slowing was due solely to a significantly longer time constant for the primary component τ_1 ($P < 0.01$). Both the amplitude of the primary response (A_1') and the end-exercise $\dot{V}O_2$ were unaltered by hypoxia. Furthermore, hypoxia did not consistently affect the time constants or amplitudes of either *phase 1* or the slow component for the $\dot{V}O_2$ response (Table 3). Recovery of $\dot{V}O_2$ was slower with 12% O_2 breathing, primarily because of an increase in τ_1.

The O_2 deficit and debt were calculated for the three $F_{I_{O_2}}$ conditions, on the assumption that the end-exercise $\dot{V}O_2$ (at 8 min) represented the O_2 requirement for the exercise. Although the $\dot{V}O_2$ kinetics were statistically slower during 12% O_2 breathing compared with 15 and 21% O_2, the increase in O_2 deficit (1.87 ± 0.56 vs. 1.62 ± 0.69 liters) and O_2 debt (2.38 ± 0.15 vs. 1.62 ± 0.81 liters) for 12% O_2 breathing compared with 21% O_2, respectively, did not reach statistical significance due to intersubject variability.

To determine whether blood lactate concentration per se was related to the slow component for $\dot{V}O_2$ at end-exercise, the amplitude of the slow component at the end of exercise (A_2') was plotted against the corresponding blood lactate levels for the three $F_{I_{O_2}}$ conditions (Fig. 3*A*). As can be seen, there was no association between the observed lactate levels and the amplitude of the slow component of $\dot{V}O_2$. However, blood lactate level was positively correlated with τ_1 across inspired O_2 levels (Fig. 3*B*).

Heart rate was noticeably affected by hypoxia (Fig. 4). However, the primary effect on 12% O_2 was a significant increase in the baseline value ($P < 0.01$), which was sustained throughout the exercise and recovery with little effect on the response kinetics or amplitudes (Table 3). During recovery, 12% O_2 breathing resulted in a significant slowing of the primary time constant ($P < 0.01$) compared with normoxia, with no change in the amplitudes (Table 3).

The baseline and end-exercise values for $\dot{V}CO_2$ and minute ventilation ($\dot{V}E$) are given in Table 4. Hypoxia had no effect on baseline $\dot{V}CO_2$ levels, but the end-exercise level during 12% inspired O_2 was significantly greater than during 21% O_2. Hypoxia did not affect $\dot{V}E$ during baseline exercise but led to progressively greater $\dot{V}E$ during exercise for both 15 and 12% inspired O_2 experiments compared with 21% O_2.

Moderate Constant Work Rate Exercise

For the five subjects who also completed moderate-exercise studies, hypoxia (12% O_2) also resulted in slowed $\dot{V}O_2$ kinetics (as τ_1) compared with those observed with 21% O_2 (Table 5). However, the steady-state increase in $\dot{V}O_2$ (as A_1') was unchanged during hypoxia. Furthermore, when the responses to moderate exercise with 21% O_2 were compared with the corresponding above LAT exercise for the five subjects, τ_1 also became longer, but the amplitude, expressed as a

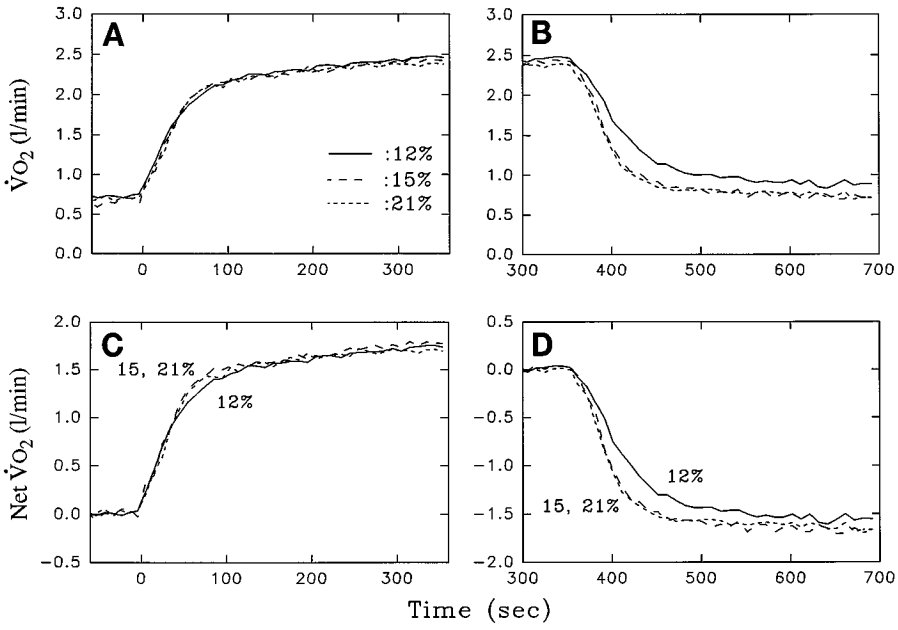

Fig. 2. Group mean responses ($n = 8$) for $\dot{V}O_2$ during heavy exercise averaged over 10-s periods for 3 inspired O_2 conditions. *A*, *C*: onset of exercise; *B*, *D*: recovery responses. *A*, *B*: total $\dot{V}O_2$; *C*, *D*: normalized to unloaded cycling (*C*) or end-exercise (*D*) levels of $\dot{V}O_2$. Note slowing of early $\dot{V}O_2$ kinetics both during exercise and in recovery for 12% O_2 but unaltered slow increase in $\dot{V}O_2$ after 100 s during exercise.

Table 3. $\dot{V}O_2$ and HR response parameters for heavy (>LAT) exercise

	FI_{O_2}, %	BL, l/min	A_0', l/min	τ_0, s	A_1', l/min	τ_1, s	TD_1, s	A_2', l/min	τ_2, s	TD_2, s
					$\dot{V}O_2$					
On	21	0.68 ± 0.15	0.53 ± 0.17	30.5 ± 48.4	1.52 ± 0.38	23.0 ± 9.0	25.5 ± 3.9	0.22 ± 0.13	253.6 ± 208.8	150.0 ± 75.3
	15	0.65 ± 0.10	0.40 ± 0.13	4.1 ± 3.2	1.44 ± 0.41	25.2 ± 5.4	21.4 ± 6.4	0.26 ± 0.10	120.2 ± 80.9	166.8 ± 46.1
	12	0.76 ± 0.17	0.44 ± 0.22	25.8 ± 47.5	1.42 ± 0.42	38.5 ± 13.3*	18.3 ± 11.6	0.23 ± 0.10	114.9 ± 112.7	166.6 ± 67.1
Off	21	2.44 ± 0.57	0.27 ± 0.16	2.8 ± 2.0	1.59 ± 0.38	26.0 ± 6.2	18.4 ± 3.1	0.15 ± 0.12	6,304 ± 5,099	
	15	2.34 ± 0.49	0.35 ± 0.23	11.5 ± 8.4	1.37 ± 0.48	23.0 ± 9.9	25.6 ± 7.2	0.32 ± 0.18	4,455 ± 5,190	
	12	2.35 ± 0.50	0.23 ± 0.07	2,298.5 ± 4,020.1	1.38 ± 0.37	40.6 ± 9.9*	21.9 ± 10.6	0.21 ± 0.12	4,592 ± 5,099	
	FI_{O_2}, %	BL, beats/min	A_0', beats/min	SL, beats·min^{-1}·s^{-1}	A_1, beats/min	τ_1, s	TD_1, s	A_2', beats/min	τ_2, s	TD_2, s
					HR					
On	21	79.5 ± 10.2	31.7 ± 5.0	2.49 ± 0.51	57.9 ± 11.1	38.4 ± 17.7	32.5 ± 8.5	13.3 ± 9.7	463 ± 370	21.5 ± 54.6
	15	86.6 ± 8.3	28.7 ± 5.5	2.23 ± 0.71	59.9 ± 7.4	59.1 ± 33.5	32.5 ± 8.3	10.0 ± 5.2	398 ± 302	191.5 ± 60.1
	12	98.4 ± 9.1*	27.2 ± 5.7	1.73 ± 0.61	56.3 ± 9.9	41.8 ± 20.4	29.7 ± 8.4	14.9 ± 10.1	455 ± 366	152.8 ± 53.5
Off	21	149.8 ± 7.4			42.0 ± 15.7	37.2 ± 20.1	9.2 ± 3.8	18.3 ± 13.9	565 ± 475	
	15	155.8 ± 7.3			43.9 ± 12.1	47.7 ± 27.1	12.7 ± 4.5	16.5 ± 7.9	548 ± 496	
	12	166.3 ± 8.9*			55.0 ± 13.2	67.8 ± 15.4*	12.4 ± 6.2	20.4 ± 25.8	541 ± 647	

Values are means ± SD; $n = 8$ subjects. BL, baseline; A_0, A_1, A_1', A_2': amplitudes of response; TD_1, TD_2: time delays; τ_0, τ_1, τ_2: time constants; SL, linear slope; On, during exercise; Off, recovery; HR, heart rate. * Significantly different compared with 21% O_2 responses, $P < 0.01$.

gain G_1 (A_1'/W), was similar for all four conditions (below and above LAT; 21 and 12% O_2).

As with heavy exercise, the effect of hypoxia on heart rate for the moderate-exercise studies was a greater level during the baseline cycling, with similar increases during exercise for both 12 and 21% inspired O_2 concentrations. However, in contrast to heavy exercise, τ_1 was slowed with hypoxia (Table 5).

Unlike with heavy exercise, hypoxia did not affect $\dot{V}CO_2$ during either baseline or at the end of moderate exercise (Table 4). Whereas $\dot{V}E$ was unchanged during baseline, there was a tendency ($P = 0.066$) for $\dot{V}E$ to be elevated at the end of moderate exercise during 12% O_2 compared with 21% O_2 breathing.

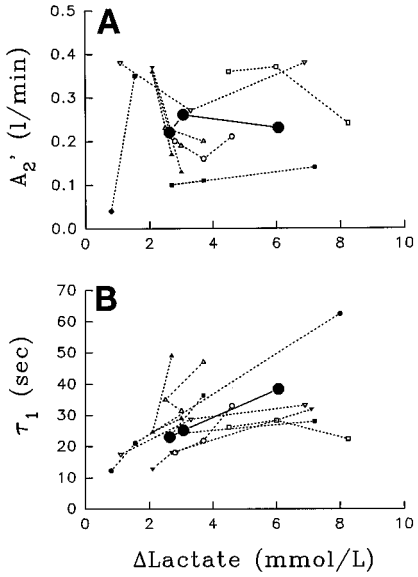

Fig. 3. Relationship between net end-exercise lactate (Δlactate) and amplitude of slow component at end of exercise (A_2'; *A*) and time constant for primary $\dot{V}O_2$ component (τ_1; *B*). There was no significant relationship between A_2' and net lactate ($r = 0.1$), but τ_1 was significantly correlated ($r = 0.44$, $P < 0.05$). Dotted lines connect values of individual subjects; ●, mean values.

DISCUSSION

In the present study, hypoxia during moderate exercise resulted in a significant slowing of τ_1, despite a greater heart rate, but exercise steady state (as A_1') was unaltered, consistent with previous reports by Springer et al. (31) and others (22). During heavy exercise performed under hypoxic conditions, a similar pattern of response was found for the primary component (Table 3, Fig. 2). The longer time constant τ_1 probably reflects both a greater breakdown of PCr (13, 19) and production of lactate by the contracting muscles (19). Indeed, there was a significant positive correlation between τ_1 and the net end-exercise lactate across the inspired O_2 levels (Fig. 3). However, despite slowed $\dot{V}O_2$ kinetics, the initial "steady state" anticipated and approached by the primary exponential component of $\dot{V}O_2$ (as A_1') during heavy exercise was not significantly affected by hypoxia. To the extent that A_1' may reflect the muscle mass initially recruited, this would suggest that muscle mass recruitment at the onset of heavy exercise was unaltered by hypoxia. These data also suggest that the conclusion reached by Ibanez et al. (16) that hypoxia leads to reduced $\dot{V}O_2$ during incremental exercise is a reflection, not of an altered steady state $\dot{V}O_2$-work rate relationship but of a slowed dynamic adjustment of $\dot{V}O_2$ as work rate increased. Consistent with this explanation, Murphy et al. (22) found a reduced $\dot{V}O_2$/work rate slope during incremental exercise in hypoxia compared with room air, but the steady-state $\dot{V}O_2$/work rate response for constant work rate exercise was unaltered by hypoxia.

The slowing of $\dot{V}O_2$ kinetics during hypoxic exercise suggests that the elevated heart rate does not completely compensate for the reduced arterial O_2 content (Ca_{O_2}) to maintain normal O_2 delivery to the contract-

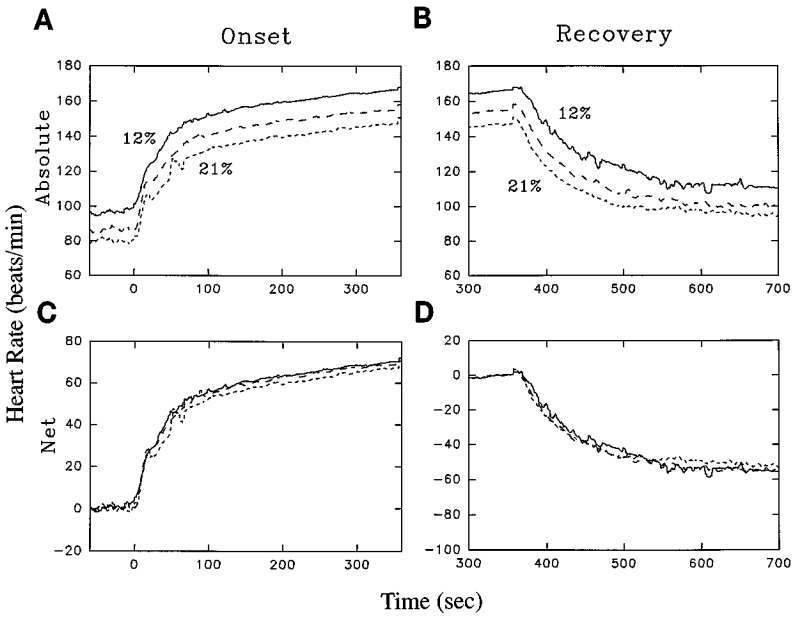

Fig. 4. Group mean responses for heart rate during heavy exercise averaged over 10-s periods for 3 inspired O_2 conditions. Solid line, 12% O_2; dashed line, 15% O_2; dotted line, 21% O_2. *A*, *C*: onset of exercise; *B*, *D*: recovery responses. *A*, *B*: total heart rate; *C*, *D*: normalized to unloaded cycling (*C*) or end-exercise (*D*) levels. Primary effect of heart rate was elevation of baseline (unloaded cycling) level with no effect on either amplitude or kinetics of change in heart rate during exercise. During recovery, kinetics of fast component to heart rate decay were significantly slower.

ing muscles during the exercise transition. Relevant to this, Wolfel et al. (34) found during acute exposure to altitude that heart rate and cardiac output were significantly increased during exercise, but leg blood flow was unchanged. Thus the resulting calculated O_2 delivery was significantly less and leg $\dot{V}O_2$ was significantly reduced with acute exposure to hypoxia. Hogan et al. (14) showed in an isolated dog gastrocnemius preparation that even under equivalent O_2 delivery conditions, elevated muscle perfusion with low Ca_{O_2} did not support the same $\dot{V}O_{2peak}$ as did lower perfusion with higher Ca_{O_2}. These data collectively demonstrate *1*) the importance of arterial P_{O_2} (and Ca_{O_2}) in establishing the driving force for O_2 diffusion from the capillaries to the mitochondria; and *2*) the circulatory responses to acute hypoxia appear to be insufficient to fully compensate for the reduced Ca_{O_2}.

Unlike previous analyses (4, 5), under room-air conditions in the present study there was a significant slowing of τ_1 for heavy exercise compared with moderate exercise (Table 5). This slowing of τ_1 with increasing work rates has also been reported by Paterson and Whipp (23). The reason(s) for the observed differences in response of τ_1 as a function of work intensity among the various studies is presently not clear. There was a tendency in a previous study for τ_1 to become longer for work rates above the LAT (5), but in that study the increase did not reach statistical significance. This may have represented a type II error because the number of subjects was small (4). Breakdown of PCr is greater (2) and slower (21) for heavy exercise, suggestive of a slowing of muscle $\dot{V}O_2$ kinetics during heavy exercise. Although the recent work of Grassi et al. (12) suggests that, during moderate upright exercise, adjustments in O_2 delivery are faster than muscle $\dot{V}O_2$ kinetics, a slowing of τ_1 for $\dot{V}O_2$ during moderate exercise can result when O_2 delivery to the muscle mitochondria is compromised, such as when O_2 content of the blood (17, 31) or dynamic adjustments of the circulation (24) are reduced. Interestingly, the lengthening of τ_1 during heavy exercise under room-air conditions in the present study was similar to that seen during moderate exercise with hypoxia, but the effects were not consistently additive. These data imply that with heavy exercise, O_2 delivery during the transition may be compromised in some subjects to a similar extent as during moderate exercise with hypoxia, both causing a slowing of $\dot{V}O_2$ kinetics and an increase in blood lactate. Taken collectively, our data from this study and those from previous studies (4, 5) suggest that τ_1 may become longer in some subjects as work rate transitions exceed the LAT.

In contrast to our hypothesis, the contribution of the slow component to the $\dot{V}O_2$ response was unaltered in hypoxia. The mechanism(s) for the slow component remains poorly defined (25). Measurement of tissue oxygenation by near-infrared spectrometry (8), direct femoral vein oxyhemoglobin (HbO_2) saturation (32), and leg $\dot{V}O_2$ (27) all point to the contracting muscles as the predominant site for the additional slow component

Table 4. *$\dot{V}CO_2$ and $\dot{V}E$ exercise responses under varying FI_{O_2} conditions*

		>LAT		<LAT	
	FI_{O_2}, %	BL, l/min	End-ex, l/min	BL, l/min	End-ex, l/min
$\dot{V}CO_2$	21	0.61 ± 0.16	2.44 ± 0.55	0.62 ± 0.17	1.13 ± 0.47
	15	0.58 ± 0.10	2.52 ± 0.50		
	12	0.69 ± 0.17	2.70 ± 0.64*	0.59 ± 0.15	1.16 ± 0.42
$\dot{V}E$	21	22.5 ± 7.6	78.7 ± 22.0	21.8 ± 4.2	33.8 ± 10.1
	15	22.5 ± 4.8	92.5 ± 24.3†		
	12	27.3 ± 10.7	112.5 ± 33.6*‡	23.6 ± 5.0	43.3 ± 16.5§

Values are means ± SD; $n = 8$ subjects for >LAT; $n = 5$ subjects for <LAT. $\dot{V}E$, minute ventilation; $\dot{V}CO_2$, CO_2 uptake; End-ex, end-exercise. Significantly different: *$P < 0.01$ compared $\dot{V}$, CO_2 compared with 21% O_2; †$P < 0.05$ compared with 21% O_2; ‡$P < 0.05$ compared with 15% O_2; §$P = 0.066$.

Table 5. *Fitting parameters for $\dot{V}O_2$ and HR for moderate (<LAT) exercise*

		<LAT							>LAT	
	FI_{O_2}, %	BL, l/min	A_0', l/min	τ_0, s	A_1', l/min	TD, s	τ_1, s	G_1, ml·min^{-1}·W^{-1}	τ_1, s	G_1, ml·min^{-1}·W^{-1}
					$\dot{V}O_2$					
On	21	0.69 ± 0.20	0.18 ± 0.13	429.8 ± 478.4	0.56 ± 0.32	26.1 ± 8.1	19.1 ± 1.6	9.6 ± 1.1	28.1 ± 6.3‡	9.6 ± 1.1
	12	0.66 ± 0.16	0.15 ± 0.10	389.1 ± 477.3	0.56 ± 0.22	26.6 ± 9.3	31.7 ± 9.0*	10.2 ± 0.5	36.0 ± 10.5	9.0 ± 1.5
Off	21	1.27 ± 0.62	0.21 ± 0.21	85.6 ± 89.0	0.52 ± 0.29	22.7 ± 4.0	18.4 ± 8.2	8.8 ± 0.8	26.0 ± 3.9	10.2 ± 1.0
	12	1.26 ± 0.49	0.11 ± 0.09	45.3 ± 53.8	0.52 ± 0.34	16.8 ± 12.8	31.8 ± 15.1*	8.4 ± 1.9	39.1 ± 5.5	8.6 ± 1.4

	FI_{O_2}, %	BL, beats/min	A_1, beats/min	TD, s	τ_1, s	ΔEnd-ex, beats/min
			HR			
On	21	82.1 ± 4.7	14.9 ± 6.4	7.3 ± 2.7	10.4 ± 7.2	18.2 ± 8.7
	12	95.0 ± 9.1†	21.6 ± 8.2	6.0 ± 4.8	30.4 ± 12.3†	25.8 ± 5.8
Off	21	100.0 ± 9.7	15.2 ± 5.7	6.6 ± 3.0	17.4 ± 5.6	17.4 ± 6.8
	12	122.8 ± 12.7*	23.4 ± 6.0*	12.3 ± 3.2	35.7 ± 12.9	24.2 ± 6.2†

Values are means ± SD; $n = 5$. G_1, gain of response [$(A_1' + A_1')$/work rate]. Significantly different from FI_{O_2} = 21% O_2: *$P < 0.01$; †$P < 0.05$; ‡$P < 0.05$ compared with <LAT exercise during 21% inspired O_2.

to $\dot{V}O_2$ during heavy exercise. However, during acute altitude exposure with similar inspired O_2 concentration to that in our study (inspiratory P_{O_2} of 87–91 Torr), Wolfel et al. (34) found slightly reduced leg $\dot{V}O_2$, but unchanged pulmonary $\dot{V}O_2$, during moderate-intensity exercise (50–65% $\dot{V}O_{2peak}$). If the $\dot{V}O_2$ from the contracting muscles (or other tissues such as renal or splanchnic) was reduced in our study under hypoxic conditions, then other metabolic processes must have increased to compensate because whole body $\dot{V}O_2$ was unchanged. One possible mechanism is an increased cost of breathing because end-exercise $\dot{V}E$ was increased on average by 40 l/min for 12% compared with 21% inspired O_2. By using the slope for the regression equation for $\Delta\dot{V}O_2/\Delta\dot{V}E$ from Aaron et al. (1) of 3.54 ml/l, an increase in $\dot{V}E$ of 40 l/min would represent ~140 additional milliliters per minute of $\dot{V}O_2$. Thus slight decreases in $\dot{V}O_2$ from contracting muscles could have been compensated for by an increased cost of breathing.

We have previously reported significant correlation between changes in blood lactate and the slow component during heavy exercise (30). It had been hypothesized that this lactic acidosis of heavy exercise results in a shift of the HbO_2 dissociation curve to the right (Bohr effect) (33), allowing further unloading of O_2 from hemoglobin for uptake by the muscle cells at a constant (minimum) capillary P_{O_2} (32). Recent evidence suggests that raising blood lactate concentration without increasing H^+ concentration does not result in additional $\dot{V}O_2$ in contracting muscle (26). The present study suggests that the increase in blood lactate and the slow $\dot{V}O_2$ component are both coupled to the early responses to heavy exercise in the following way. After the start of heavy exercise, the rate of adjustment of O_2 delivery to the capillaries and ultimately to the mitochondria is insufficient to fully support the rising oxidative metabolism. In response, there is greater PCr breakdown than predicted from moderate exercise (2, 20), as implied by the longer τ_1. Associated with the greater PCr breakdown and accumulation of P_i is greater lactate production (19). The resulting acidosis results in a rightward shift in the HbO_2 dissociation curve (Bohr effect), which facilitates the additional unloading of O_2 from hemoglobin and uptake by the muscles later into the heavy exercise. Under hypoxic conditions, the insufficiency of O_2 delivery after the onset of exercise is more pronounced. There is even greater PCr breakdown (longer τ_1) (13) and lactate production (Table 2), both of which create conditions that allow $\dot{V}O_2$ to ultimately rise to similar levels despite the hypoxia. In this scheme, lactate production and the resulting acidosis during heavy exercise can be seen as part of a feedback loop in the capillary microenvironment, in which lactate production continues until conditions are fulfilled for adequate O_2 delivery from the capillaries to the mitochondria to sustain the desired rate of oxidative metabolism.

Symmetry was noted between the exercise and recovery kinetics for $\dot{V}O_2$ at both moderate- and heavy-exercise intensities under all inspired O_2 concentrations. This is in contrast to the observations of Paterson and Whipp (23), who found a greater contribution of the primary exponential component, with reduced or absent slow component, in recovery from exercise of similar heavy intensity under room air conditions. Similarly, Ren et al. (28) found that, at 80% of $\dot{V}O_{2peak}$, the O_2 debt was significantly less than the O_2 deficit. These latter studies imply that the metabolic process(es) associated with the slow component is of delayed onset and slow in developing but has recovery kinetics similar to those of the primary component, which is associated with the contracting muscles (3, 5). Our data, on the other hand, suggest that the mechanism(s) for the slow component is both slow in developing and slow to recover. Further study of the relationship between on- and off-transitions for $\dot{V}O_2$ kinetics is warranted.

The primary effect of hypoxia on heart rate seen in this study is an increase in the baseline level during unloaded cycling (Fig. 4). This is possibly due to an increase in circulating catecholamines (10), resulting

from spillover of the greater sympathetic nerve activation that has been reported to take place under hypoxic conditions. It might also result from peripheral reflexes that stimulate cardiac output when the arteriovenous O_2 content difference decreases. Interestingly, there was no significant effect of hypoxia on the amplitude of rise in heart rate above this baseline level during exercise. This constancy of the net increase in heart rate, independent of inspired O_2, appears to be generally true whether the exercise is moderate (22, 31, 35) or heavy (18) or constant or progressively increasing (22) work rate exercise. Heart rate and norepinephrine levels are linearly correlated across work rates, and both are normalized for inspired O_2 concentrations when expressed as a function of the relative intensity of the exercise (as $\%\dot{V}O_{2peak}$) (10).

However, slowing of the kinetics of heart rate with hypoxia appears to be a phenomenon observed only during moderate exercise (Table 4) (22, 31, 35). Both our data (Table 2) and the analysis by Linnarsson (18) suggest no effect of hypoxia on heart rate kinetics during heavy exercise. These observations for heavy exercise are somewhat surprising given that, under normoxic conditions, increasing cardiac frequency at higher heart rates is primarily achieved by sympathetic activation (29), a slower process than parasympathetic removal, which is the likely mechanism for initial cardiac acceleration at lower heart rates (11). The data on heart rate kinetics shown in Fig. 4*C* suggest that direct neural cardiac control (sympathetic and parasympathetic) during exercise may be unaltered under hypoxic compared with air-breathing conditions and that the primary change in exercise heart rate with hypoxia is one of a shift in baseline, presumably due to increased circulating catecholamines and not to changing kinetic control.

A comment should be made regarding the apparently large values for τ_0 and τ_2 in Tables 3 and 5. For both the responses during *phase 1* and for the slow component, some data sets were best fit by what appeared to be unphysiologically large values for the amplitude and/or time constant. When this occurs, this suggests that the region being described by the exponential term is, in fact, best described by a linear function, the slope of which is the derivative of the exponential, A/τ (9). For this reason, we believe the relevant features of *phase 1* are the amplitude at the end of *phase 1* (A_0'; *Eq. 2*) and the duration of *phase 1* (TD_1) and not necessarily either the projected asymptote (A_0) or time constant (τ_0). Similarly, the relevant aspects of the slow component are the time of onset (TD_2) and the amplitude at the end of exercise (A_2') and not either its asymptotic amplitude (A_2) or time constant (τ_2). Thus, for both *phase 1* and the slow component, neither the individual time constants nor the asymptotic amplitudes by themselves may hold specific physiological relevance.

In conclusion, $\dot{V}O_2$ kinetics during heavy exercise are slowed relative to those seen with room air, but the slowing is confined to the initial predominant rise after *phase 1*. This slowing is correlated with changes in end-exercise blood lactate. The amplitude of the slow component of $\dot{V}O_2$ is unchanged with hypoxia. The baseline heart rate during unloaded cycling is elevated, presumably due to elevated circulating catecholamines, but the kinetics are remarkably similar across the inspired O_2 tested. This latter observation suggests that the neural control of heart rate during the exercise was unaffected by hypoxia. The elevated heart rate and lactate levels reflect at least some of the adjustments to heavy exercise in hypoxia that allow $\dot{V}O_2$ to ultimately reach a similar level as during exercise on normoxia.

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