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Journal
Medicine & Science in Sports & Exercise, 23(1)

ISSN
0195-9131

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Publication Date
1991

DOI
10.1249/00005768-199101000-00012

0195-9131/91/2301-0071$3.00/0
MEDICINE AND SCIENCE IN SPORTS AND EXERCISE

Vol. 23, No. 1
Printed in U.S.A.

Oxygen uptake and heart rate responses during hypoxic exercise in children and adults

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ABSTRACT

SPRINGER, C., T. J. BARSTOW, K. WASSERMAN, and D. M. COOPER. Oxygen uptake and heart rate responses during hypoxic exercise in children and adults. *Med. Sci. Sports Exerc.*, Vol. 23, No. 1, pp. 71–79, 1991. Control of ventilation and heart rate during exercise appears to undergo maturation, while aerobic metabolism (VO_2) may not. Since we had previously found that hypoxia during exercise produced different ventilatory responses in children (C) compared to adults (A), we hypothesized that $\dot{V}O_2$ and heart rate kinetics during exercise would show similar maturational responses to hypoxia. To test this hypothesis, we examined the responses during progressive (ramp) and constant work rate tests in children and adults breathing either room air or hypoxic gas (FiO_2 = 0.15). When corrected for body weight, children and adults had similar values for lactic acidosis threshold (LAT) (C: 29.1 ± 5.0 ml·min^{-1}·kg^{-1}; A: 27.9 ± 4.3) and $\dot{V}O_{2max}$ (C: 40.7 ± 8.6 ml·min^{-1}·kg^{-1}; A: 45.2 ± 6.7) during normoxia. Hypoxia significantly lowered LAT (C: 27.5 ± 5.4 ml·min^{-1}·kg^{-1}; A: 23.2 ± 3.8; both $P < 0.05$) and VO_{2max} (C: 37.7 ± 8.3 ml·min^{-1}·kg^{-1}; A: 40.1 ± 5.3; both $P < 0.05$) in both children and adults. Metabolic efficiency ($\Delta\dot{V}O_2/\Delta$work rate) and the $\dot{V}O_2$-heart rate relationship ($\Delta\dot{V}O_2/\Delta$HR/kg) were similar in the two groups and unaffected by hypoxia. During the constant work rate exercise, $\dot{V}O_2$ kinetics (time constant during phase 2 of the response (τ_1) and the O_2 deficit) were similar between children and adults and were significantly slowed by hypoxia, consistent with current understanding of the control of oxidative metabolism. Finally, heart rate was increased at rest and during exercise with hypoxia, while the time to reach 75% of the end-exercise response was delayed significantly, in both groups. The dynamic adjustments of metabolism and heart rate during exercise are slowed with hypoxia to a similar degree in children and adults.

MATURATION, METABOLISM, $\dot{V}O_2$, CARDIOVASCULAR, KINETICS

Regeneration of adenosine triphosphate (ATP) during exercise requires the stimulation and support of aerobic metabolism in the contracting muscles. This support includes facilitation of the delivery of oxygen from the atmosphere to the mitochondria and concomitant removal of carbon dioxide, by both convective (e.g., ventilation and blood flow) and diffusive processes. One index of the overall effectiveness of O_2 delivery during exercise is the kinetics of oxygen utilization, which can be expressed as an exponential time constant or equivalently as the size of the oxygen deficit (3,24). The oxygen deficit consists of the volume of oxygen removed from the venous O_2 stores and oxygen equivalents for the fall in phosphocreatine (PCr) and any transient lactate production in the contracting muscles (3,24).

In previous investigations focusing on maturation of the control of cardiorespiratory adjustments during exercise in room air, it was observed that, following the start of moderate exercise (below the lactic acidosis, or anaerobic, threshold (LAT)), children exhibited faster responses than adults of both minute ventilation ($\dot{V}_E$) and excretion of CO_2 ($\dot{V}CO_2$) (10). The latter was hypothesized to be due to a relatively smaller storage capacity for CO_2 (28). However, the kinetics of adjustment of $\dot{V}O_2$ (and thus the size of the O_2 deficit for a given $\Delta\dot{V}O_2$) were the same in children and adults, despite slower kinetics for heart rate in the children (9). Thus, in spite of differences in the control of $\dot{V}_E$, $\dot{V}CO_2$, and heart rate between children and adults during moderate exercise, the regulation of oxidative metabolism was independent of age—that is, it did not demonstrate any maturational changes.

Hypoxia, which reduces arterial oxygen partial pressure, represents an additional stress to the ventilatory, circulatory, and metabolic processes during exercise. In spite of a catecholamine-induced tachycardia (11,15), hypoxia reduces both the $\dot{V}O_{2max}$ and the LAT in adults (1,11). Further, the sensitivity of these processes to hypoxia may be greater in children than in adults. In

Submitted for publication June, 1989.
Accepted for publication March, 1990.

children (ages 6–10), the relative contribution of the peripheral chemoreceptors to total ventilatory drive during exercise was greater than in adults (29). Since infants also show much greater ventilatory responsiveness to hypoxia (25), it would appear that control mechanisms governing ventilatory responses to hypoxia become attenuated with maturation of the individual.

At present, however, little is known in either children or adults about the effects of hypoxia on the dynamic adjustments of aerobic metabolism and cardiovascular responses when tissue demand for oxygen suddenly increases following the start of exercise. The present study was thus undertaken to evaluate two questions: 1) are the time courses for adjustment of the cardiovascular system (heart rate) and aerobic metabolism ($\dot{V}O_2$) after the beginning of exercise altered by hypoxia; and 2) are there age-related differences (suggesting maturation) in these responses? To study this, we measured $\dot{V}O_2$ and heart rate responses in healthy children and adults breathing 15% O_2, using two different exercise inputs: 1) a progressive, continually increasing ramp protocol and 2) a constant work rate protocol.

METHODS

Population

All subjects were volunteers, had no chronic diseases, and did not smoke or use medications. The study was approved by the Human Subjects Committee of Harbor-UCLA Medical Center and was in accordance with the policy of the American College of Sports Medicine for human experiments. Informed consent was obtained from each subject or guardian. Ten children (six boys and four girls, aged 6–10 yr, mean age (± SD) 8.1 ± 1.4 yr) and ten adult males (aged 18–33 yr, mean age 26 ± 5 yr) performed progressive exercise tests to volitional fatigue as described below. Constant work rate exercise tests were performed by nine of the same children (five boys and four girls, mean age 8.2 ± 1.4 yr) and by a different group of nine adults (five males and four females, mean age 28 ± 7 yr). Age, gender, height, and weight are given for each subject in Table 1.

Protocol

Progressive exercise tests. Each subject performed a ramp-type progressive exercise test on a cycle ergometer (33) while breathing air and then repeated the test at least 60 min later or on a different day while breathing 15% O_2. These tests were used to evaluate the effect of hypoxia on the lactic acidosis, or anaerobic, threshold (LAT) as determined by gas exchange, maximal O_2 uptake ($\dot{V}O_{2max}$), and the oxygen cost for work (as $\Delta\dot{V}O_2/\Delta$work rate).

Constant work rate exercise tests. Each subject performed five rest-to-constant work rate exercise tests during air breathing and during 15% O_2 breathing, in random order. The subjects were signaled to begin exercise by a green light which was activated at end-expiration. The ergometer flywheel was motorized and maintained at a rate of 60 rpm until the start of exercise to minimize the energy expenditure needed to overcome its inertia.

The work rate used for the constant exercise tests was chosen so as to require a steady state $\dot{V}O_2$ below (80% of) the hypoxic LAT in all the subjects. These work rates were determined for each subject, from the progressive exercise test performed during 15% O_2 breathing, as follows. The work rate which would result in a $\dot{V}O_2$ equal to the LAT was defined as the work rate which occurred 45 s before the LAT was actually exceeded during the ramp test. The 45 s offset accounts for the delay in the response of $\dot{V}O_2$ to the ramp forcing function (33). The work rate chosen for each subject for the constant work rate test corresponded to 80% of this LAT work rate. The actual $\dot{V}O_2$ responses at these work rates were 89% of the LAT in the children and 85% in the adults. This work rate was chosen to ensure that the tests performed during both air breathing and hypoxic gas breathing would be below the subject's LAT, thus ensuring attainment of a true steady state for calculation of the O_2 deficit (27). Steady state exercise continued for 6 min, followed by a period of rest which was long enough (approximately 10 min) to allow $\dot{V}_E$, $\dot{V}O_2$, $\dot{V}CO_2$, and heart rate (HR) to return to the preexercise levels.

Measurement of Gas Exchange and Heart Rate

Ventilation and gas exchange were measured breath-by-breath as previously described (4) in order to measure precisely their kinetic responses. The subjects breathed through a mouthpiece connected to a turbine flow meter for continuous measurement of inspired and expired volumes, in series with a low resistance two-way valve. The apparatus dead space was 140 ml for the children and 170 ml for the adults. Fractions of CO_2 (FCO_2) and O_2 (FO_2) were measured by a mass spectrometer (Perkin-Elmer MGA 1100) which sampled continuously from the mouthpiece at 1 $ml \cdot s^{-1}$. $\dot{V}_E$ (BTPS), $\dot{V}O_2$ (STPD), $\dot{V}CO_2$ (STPD), and end-tidal pressures of O_2 ($PETO_2$) and CO_2 ($PETCO_2$) were computed on-line, breath-by-breath, as previously described (4). Heart rate was measured beat-by-beat by a standard lead I electrocardiogram using three electrodes placed on the chest. The data from each test were stored on digital tape for further analysis.

TABLE 1. Anthropometric data and aerobic capacity.

Subject	Gender	Age (yr)	Height (cm)	Weight (kg)	$\dot{V}O_{2max}$ Air	$\dot{V}O_{2max}$ Hypoxia	LAT Air	LAT Hypoxia
					($ml \cdot min^{-1} \cdot kg^{-1}$)			
Children								
1	F	9.1	126	26.4	38.6	33.3	29.5	26.5
2	M	6.0	113	20.0	51.0	47.5	39.0	37.5
3	M	7.0	140	32.7	34.2	32.7	23.2	20.8
4	M	7.5	127	27.0	50.3	48.9	29.6	29.6
5	M	6.9	124	28.1	39.1	39.1	29.2	29.2
6	F	8.1	145	28.1	31.3	29.2	27.0	22.8
7	F	10.0	150	38.6	31.9	28.0	22.0	21.8
8	F	9.2	132	23.2	55.2	48.3	34.5	33.6
9	M	10.0	151	49.0	34.7	29.6	26.5	23.5
10	M	7.2	127	22.7	40.8	40.8	30.6	29.4
$\bar{X}(N = 10)$[a]		8.1	134	30.3	40.7	37.7[c]	29.1	27.5[c]
SD		1.4	13	8.8	8.6	8.3	5.0	5.4
$\bar{X}(N = 9)$[b]		8.2	134	29.6	40.7	37.4	28.9	27.3
SD		1.4	13	8.6	9.1	8.7	5.3	5.7
Adults								
Ramp								
1	M	33	173	66.0	45.4	39.4	27.3	24.2
2	M	25	174	86.8	31.7	31.7	20.2	18.4
3	M	32	173	63.0	55.6	40.5	36.5	27.0
4	M	28	178	65.2	45.2	36.8	30.7	25.3
5	M	29	188	86.0	50.0	46.5	26.1	21.2
6	M	18	182	71.4	41.3	33.6	29.4	23.8
7	M	25	169	71.5	46.2	39.2	29.4	26.6
8	M	18	165	56.4	40.8	40.8	23.9	18.6
9	M	24	190	75.0	44.0	44.0	26.7	18.7
10	M	30	186	72.0	52.1	48.5	28.4	28.4
$\bar{X}$		26	178	71.3	45.2	40.1[c]	27.9	23.2[c]
SD		5	8	9.6	6.7	5.3	4.3	3.8
Square wave transitions								
1	F	18	166	63.0		28.6		15.1
2	M	26	180	70.0		35.0		22.9
3	F	25	161	58.6		32.4		17.1
4	F	26	168	64.0		48.4		24.2
5	M	40	170	65.0		30.8		18.5
6	M	34	173	66.0		46.1		27.9
7	M	34	160	50.0		38.0		21.0
8	M	21	168	62.0		38.7		19.4
9	M	28	175	75.0		26.7		16.0
$\bar{X}$		28	169	63.7		36.1		20.2
SD		7	6	7.0		7.4		4.2

[a] Mean of all ten children who completed ramp test.
[b] Mean of first nine children who also performed square wave transitions.
[c] $P < 0.01$, compared with room air value.

Data Analysis

Incremental tests. The LAT and $\dot{V}O_{2max}$ were measured noninvasively from the gas exchange data obtained during the progressive exercise. LAT was defined as the $\dot{V}O_2$ at which the ventilatory equivalent for O_2 ($\dot{V}_E/\dot{V}O_2$) and the $PETO_2$ increased without an increase in the ventilatory equivalent for CO_2 ($\dot{V}_E/\dot{V}CO_2$) and the $PETCO_2$ (31). $\dot{V}O_{2max}$ was defined as the highest $\dot{V}O_2$ achieved by the subject. The relationships between the change in $\dot{V}O_2$ and change in work rate ($\Delta\dot{V}O_2/\Delta WR$) and between the change in weight-adjusted $\dot{V}O_2$ and change in heart rate ($\Delta\dot{V}O_2/\Delta HR/kg$) were calculated from the linear portion of the appropriate curves (i.e., after the transient period up to the LAT (12)).

Constant work rate tests. The results of each rest-to-constant work rate exercise transition for each subject were time-aligned from the start of exercise, and the second-by-second responses of each replicate study were averaged together to reduce random noise and thus enhance the underlying characteristics of the physiological responses (19). $\dot{V}O_2$ responses to constant work-rate exercise, as previously described (30), can be divided into three phases. Phase 1 is the abrupt increase in $\dot{V}O_2$ at the start of exercise which lasts for 15–20 s before $\dot{V}O_2$ starts an exponential rise (phase 2). Phase 1 is thought to be caused by the sudden increase in blood flow at the start of exercise, while phase 2 likely represents the return of blood from the exercising muscles (2,3). Phase 3 is the steady-state exercise $\dot{V}O_2$ (i.e.,

the period after the first 3–4 min of light or moderate exercise).

To distinguish age-related differences between children and adults from those associated with body mass *per se*, responses were normalized to body weight (8). The effects of hypoxia and age (corrected for differences in body size) on $\dot{V}O_2$ kinetics were thus expressed in the following ways: 1) the increase in $\dot{V}O_2$ during phase 1, normalized to body weight and expressed as the increase in $\dot{V}O_2$ above the resting level, and 2) the time constant (τ_1) of $\dot{V}O_2$ fitted during phase 2 to a first-order exponential model with a time delay (5),

$$\dot{V}O_2(t) = \dot{V}O_2b + \Delta\dot{V}O_2 \cdot (1 - e^{-(t-TD)/\tau_1}), \quad [1]$$

where $\dot{V}O_2(t)$ is the increase in $\dot{V}O_2$ above the prior rest baseline value ($\dot{V}O_2b$) at any given time (t); $\Delta\dot{V}O_2$ is the difference between rest ($\dot{V}O_2$) and steady state exercise $\dot{V}O_2$; τ_1 is the phase 2 time constant; and TD is the displacement from time 0 for the extrapolation of the best fit exponential back to $\dot{V}O_2b$. In both children and adults, phase 1 for moderate exercise lasts approximately 15 s. To describe the rise during phase 2, therefore, only the data after 15 s were included in the regression analysis.

The O_2 deficit was estimated from the gas exchange data by fitting all of the data (phases 1 and 2) to a monoexponential equation starting at time 0:

$$\dot{V}O_2(t) = \dot{V}O_2b + \Delta\dot{V}O_2 \cdot (1 - e^{-t/\tau_0}). \quad [2]$$

The oxygen deficit could then be calculated as the product of $\Delta\dot{V}O_2$ and the time constant τ_0 (32):

$$O_2 \text{ deficit} = \Delta\dot{V}O_2 \cdot \tau_0. \quad [3]$$

In order to compare $\dot{V}O_2$ deficits between children and adults, we normalized the increase in $\dot{V}O_2$ during exercise in the two groups to body weight:

$$O_2 \text{ deficit} \cdot kg^{-1} = \Delta\dot{V}O_2 \cdot kg^{-1} \cdot \tau_0. \quad [4]$$

Thus, for a given increase in $\dot{V}O_2 \cdot kg^{-1}$ in children and adults, the O_2 deficit will be determined by τ_0.

The heart rate response, unlike that for $\dot{V}O_2$, is poorly characterized by a single exponential equation (20). Heart rate responses to constant work rate can be described by up to three components: 1) a very fast change during the first 10–15 s, 2) a slower rise during the following 60–90 s, and 3) depending on the work intensity and environmental conditions, a slow upward drift throughout the work period (20). We chose to quantify HR responses by the time required to reach 75% of the end-exercise response ($T_{0.75}$). The reason for choosing the time to reach 75% rather than 50% was that, in the adults, the fast component comprised more than 50% of the total response. However, the effect of hypoxia became apparent mainly during the second component (Fig. 3). The oxygen pulse was calculated for the constant-work-rate tests as the ratio of $\dot{V}O_2$/HR and was compared within groups to test the effects of hypoxia and across children and adults to evaluate the influence of age on the response.

Statistical Analysis

Two-way analysis of variance with one repeat measure was used to evaluate differences between children and adults and between room air and hypoxia responses. *Post hoc* testing for significance was performed using Duncan's Multiple Range test. When appropriate, single comparisons were made with paired or unpaired *t*-tests. Significance was declared when $P < 0.05$. Values are expressed as mean ± 1 SD.

RESULTS

Progressive Exercise Studies

During air breathing, children and adults had similar LAT per kg and $\dot{V}O_{2max}$ per kg (Table 1). In addition, hypoxia resulted in a small but significant decrease in the group mean LAT and $\dot{V}O_{2max}$ for both groups (Table 1). The decrease in LAT induced by hypoxia was significantly smaller in children compared with adults (5.1 ± 4.5% reduction in children and 16.3 ± 9.0% in adults, $P < 0.05$). However, the decrease in $\dot{V}O_{2\,max}$ induced by hypoxia was not significantly different between the two groups (8.3 ± 5.0% in the children and 10.7 ± 9.4% in the adults).

Metabolic efficiency as $\Delta\dot{V}O_2/\Delta WR$ was not statistically different between children and adults during air breathing (11.6 ± 1.3 ml $O_2 \cdot min^{-1} \cdot W^{-1}$ in children and 10.9 ± 1.5 ml $O_2 \cdot min^{-1} \cdot W^{-1}$ in adults). Hypoxia resulted in a small and insignificant decrease of the slope in both groups (10.8 ± 1.6 ml $O_2 \cdot min^{-1} \cdot W^{-1}$ in children and 10.0 ± 1.5 ml $O_2 \cdot min^{-1} \cdot W^{-1}$ in adults).

The weight-adjusted slope of the $\dot{V}O_2$-HR relationship (as $\Delta\dot{V}O_2/\Delta HR/kg$) was similar in children and adults during air breathing (0.37 ± 0.08 ml $O_2 \cdot beat^{-1} \cdot kg^{-1}$ in children and 0.38 ± 0.07 ml $O_2 \cdot beat^{-1} \cdot kg^{-1}$ in adults). These results are consistent with previous observations from this laboratory (12). Hypoxia caused a small but insignificant drop in $\Delta\dot{V}O_2/\Delta HR/kg$ to 0.33 ± 0.07 ml $O_2 \cdot beat^{-1} \cdot kg^{-1}$ in children; no change was observed in adults.

Constant Work Rate Studies

Steady state mean $\dot{V}O_2$ responses. The group mean $\dot{V}O_2$ responses to exercise in children and adults, and the best fit for the responses, are shown in Figure 1. Mean resting $\dot{V}O_2$ per kg was significantly higher in children compared with adults (Table 2) (10.4 ± 2.0 ml $O_2 \cdot min^{-1} \cdot kg^{-1}$ and 6.4 ± 0.6 ml $O_2 \cdot min^{-1} \cdot kg^{-1}$, respectively, $P < 0.005$). Mean steady state exercise $\dot{V}O_2$ per kg was also significantly higher in children than in adults (25.5 ± 4.8 ml $O_2 \cdot min^{-1} \cdot kg^{-1}$ and 17.1 ± 2.5

ml $O_2 \cdot min^{-1} \cdot kg^{-1}$, respectively, $P < 0.005$), as was the rest-to-exercise increase in $\dot{V}O_2$ per kg (15.1 ± 3.3 ml $O_2 \cdot min^{-1} \cdot kg^{-1}$ for children and 10.7 ± 2.0 ml $O_2 \cdot min^{-1} \cdot kg^{-1}$ for adults, respectively, $P < 0.05$). Hypoxia had no effect on resting or steady state exercise $\dot{V}O_2$ or in the increase in $\dot{V}O_2$ with exercise, for either children or adults (Table 2).

Phase 1 responses. Mean responses of $\dot{V}O_2$ at the end of phase 1 were similar in the children and the adults during air breathing, and hypoxia resulted in a similar and significant decrease in the response in both groups (Fig. 2A). In children, phase 1 $\dot{V}O_2$ was 5.7 ± 1.7 ml $\cdot min^{-1} \cdot kg^{-1}$ during air breathing and 4.3 ± 1.4 ml $\cdot min^{-1} \cdot kg^{-1}$ during hypoxia, $P < 0.05$. In the adults, phase 1 $\dot{V}O_2$ was 5.4 ± 1.6 ml $\cdot min^{-1} \cdot kg^{-1}$ during air breathing and 4.3 ± 1.1 ml $\cdot min^{-1} \cdot kg^{-1}$ during hypoxia, $P < 0.005$. In children, these responses represented 39 ± 6% of the rest to steady state exercise increase in $\dot{V}O_2$ during air breathing; hypoxia significantly ($P < 0.05$) reduced the response to 30 ± 8%. The corresponding room air value in adults was 51 ± 11%, and hypoxia produced a similar, significant decrease to 40 ± 8% ($P < 0.05$).

Phase 2 responses. The group mean τ_1 for $\dot{V}O_2$ (equation 1) was similar in the two groups during air breathing (23.9 ± 4.6 s in children and 26.8 ± 4.3 s in adults (NS); Fig. 2B). During hypoxia, τ_1 was increased significantly and similarly in the two groups (30.1 ± 4.2 s in the children, $P < 0.05$, and 37.3 ± 9.9 s in the adults, $P < 0.005$).

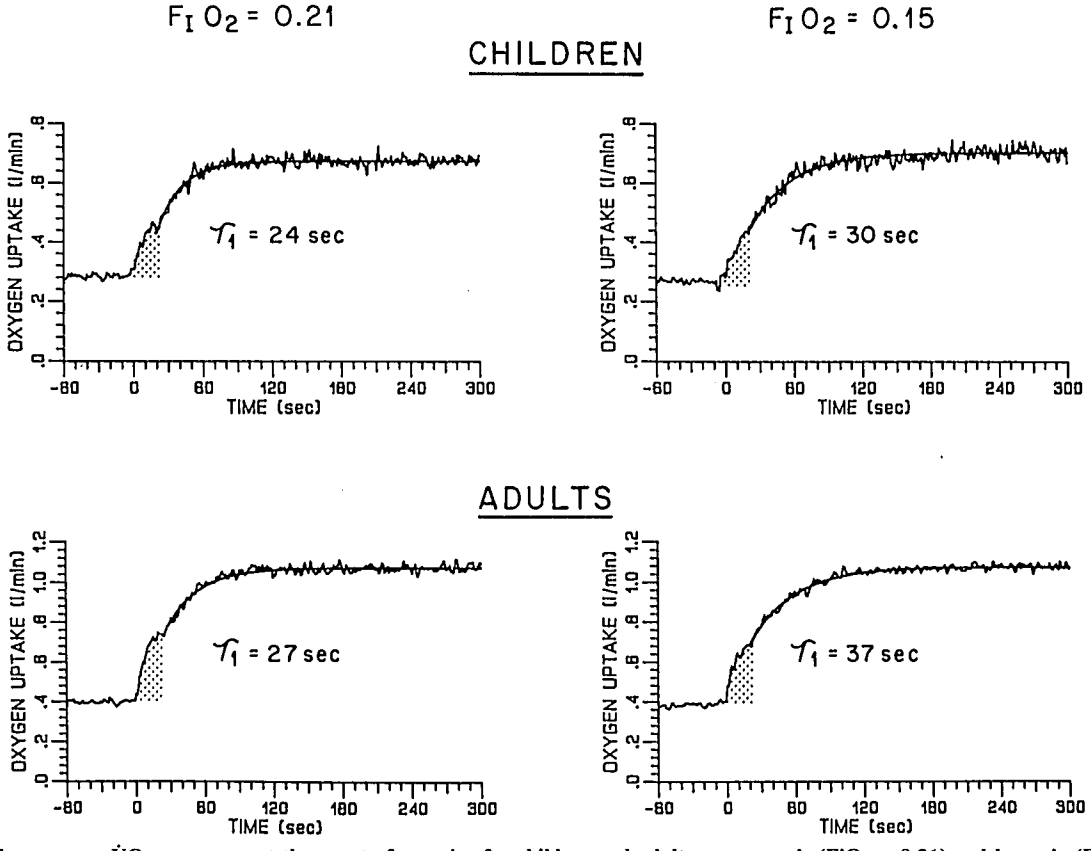

Figure 1—Group mean $\dot{V}O_2$ responses at the onset of exercise for children and adults on room air (FiO_2 = 0.21) and hypoxia (FiO_2 = 0.15). Exercise intensity represented 85–90% of the lactate threshold on hypoxia for each subject. τ_1 is the time constant for the rise of $\dot{V}O_2$ during phase 2 (from equation 1). *Shaded area* represents increase in $\dot{V}O_2$ over baseline during phase 1.

TABLE 2. Effect of hypoxia during constant-work-rate exercise on steady state $\dot{V}O_2$ and heart rate.

	Children		Adults	
	Room Air	Hypoxia	Room Air	Hypoxia
Rest				
$\dot{V}O_2$ (ml $\cdot min^{-1} \cdot kg^{-1}$)	10.4 ± 2.0	10.0 ± 2.1	6.4 ± 0.6	6.2 ± 0.5
Heart rate (beats $\cdot min^{-1}$)	105 ± 5	110 ± 5†	85 ± 13	89 ± 11*
Exercise				
$\dot{V}O_2$ (ml $\cdot min^{-1} \cdot kg^{-1}$)	25.5 ± 4.8	25.7 ± 5.0	17.1 ± 2.5	17.1 ± 2.4
Heart rate (beats $\cdot min^{-1}$)	137 ± 10	148 ± 10*	109 ± 11	116 ± 10*

* $P < 0.005$, compared with room air value.
† $P < 0.01$, compared with room air value.

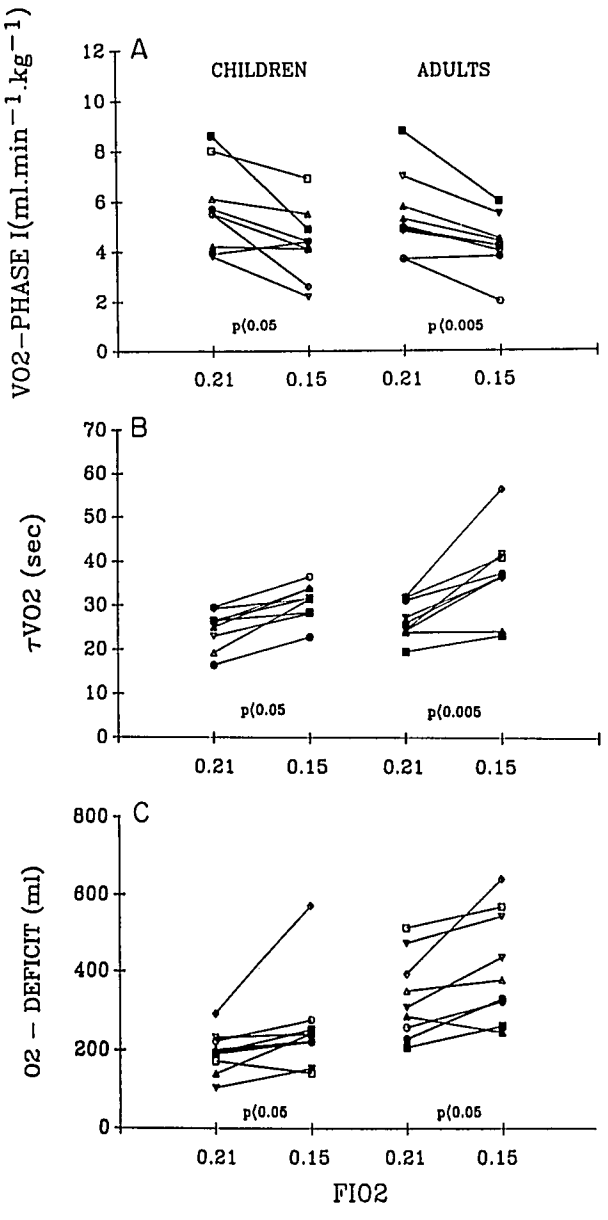

Figure 2—Effect of hypoxia on dynamic characteristics of $\dot{V}O_2$ during constant exercise in children and adults. Panel A: increase in $\dot{V}O_2$ during phase 1 (first 15–20 s). Panel B: time constant for $\dot{V}O_2$ response during phase 2 (τ_1). Panel C: O_2 deficit from equation 3. Note how hypoxia slows both the overall response (larger O_2 deficit) and the kinetics of $\dot{V}O_2$ during phase 2 (longer τ_1) in both children and adults.

Oxygen deficit. Hypoxia resulted in a significant increase in the O_2 deficit in both children and adults (Fig. 2C). In children, the O_2 deficit increased from 193 ± 48 ml O_2 during air breathing to 264 ± 116 ml O_2 during hypoxia ($P < 0.05$). In adults, the O_2 deficit increased from 335 ± 106 ml O_2 to 415 ± 142 ml O_2, respectively ($P < 0.05$). However, when these results were normalized for each subject to a unit $\Delta\dot{V}O_2$ (by dividing the deficit by the corresponding $\Delta\dot{V}O_2$), differences between the two groups for each condition were eliminated (air: 27.5 ± 3.9 ml $O_2 \cdot kg^{-1}$ in children and 29.9 ± 8.7 ml $O_2 \cdot kg^{-1}$ in adults (NS); hypoxic gas breathing: 35.2 ± 8.4 ml $O_2 \cdot kg^{-1}$ in children and 35.5 ± 4.0 ml $O_2 \cdot kg^{-1}$ in adults (NS)).

Heart rate responses. The averaged, time-aligned heart rate responses to exercise in children and adults are shown in Figure 3, as well as the normalized responses presented as the fractional change from rest to steady state exercise. In children, heart rate rose from 105 ± 5 beats·min^{-1} at rest to 137 ± 10 with exercise; hypoxia significantly increased both resting (110 ± 5 beats·min^{-1}, $P < 0.05$) and exercise heart rates (148 ± 10 beats·min^{-1}, $P < 0.05$). A similar effect of hypoxia was observed in adults, with resting heart rate increasing from 85 ± 13 to 89 ± 11 beats·min^{-1} ($P < 0.05$) and heart rate during exercise increasing from 109 ± 11 to 116 ± 10 beats·min^{-1} ($P < 0.01$).

Mean $T_{0.75}$ HR responses during air breathing were not significantly different in the two groups (46.6 ± 5.9 s in children and 54.1 ± 20 s in adults). Hypoxia resulted in a significant increase in $T_{0.75}$ in children to 60.0 ± 8.7 s ($P < 0.05$) and in adults to 70.9 ± 24.3 s ($P < 0.05$) (Fig. 4). This represented a similar increase in $T_{0.75}$ in the two groups (31.3 ± 34.4% in children and 33.9 ± 20.9% in adults (NS)).

DISCUSSION

The ability of the organism to increase O_2 delivery rapidly at the onset of exercise is of critical importance to cellular homeostasis. The amount of O_2 available for substrate utilization from intracellular stores of oxymyoglobin is small (23), while the O_2 requirement can increase by as much as 10- or 20-fold at the level of the muscle cell. The present investigation confirmed our previous finding for low-intensity (below LAT) exercise that τ_1 during air breathing was the same in children and adults despite the large differences in body size, LAT, and $\dot{V}O_{2max}$ (9). Because τ_1 is likely a good approximation of muscle $\dot{V}O_2$ kinetics (2,3), this implies that the control of muscle oxidative metabolism during exercise is similar in children and adults. Moreover, in the present study we found $\dot{V}O_2$ kinetics during exercise below the LAT to be slowed during hypoxia and that the slowing of the response was the same for both children and adults. Thus, it also appears that the mechanisms responsible for the adjustment of muscle oxidative metabolism to hypoxia are mature early in childhood.

The observation here and in the study by Linnarsson et al. (21) of a greater O_2 deficit but unchanged steady state exercise $\dot{V}O_2$ with hypoxia yields important information regarding the control of oxidative metabolism in children and adults. The cellular oxidation rate in skeletal muscle is primarily determined by the concentrations at the mitochondria of four compounds: ADP, inorganic phosphate [Pi], NADH, and oxygen (7). As-

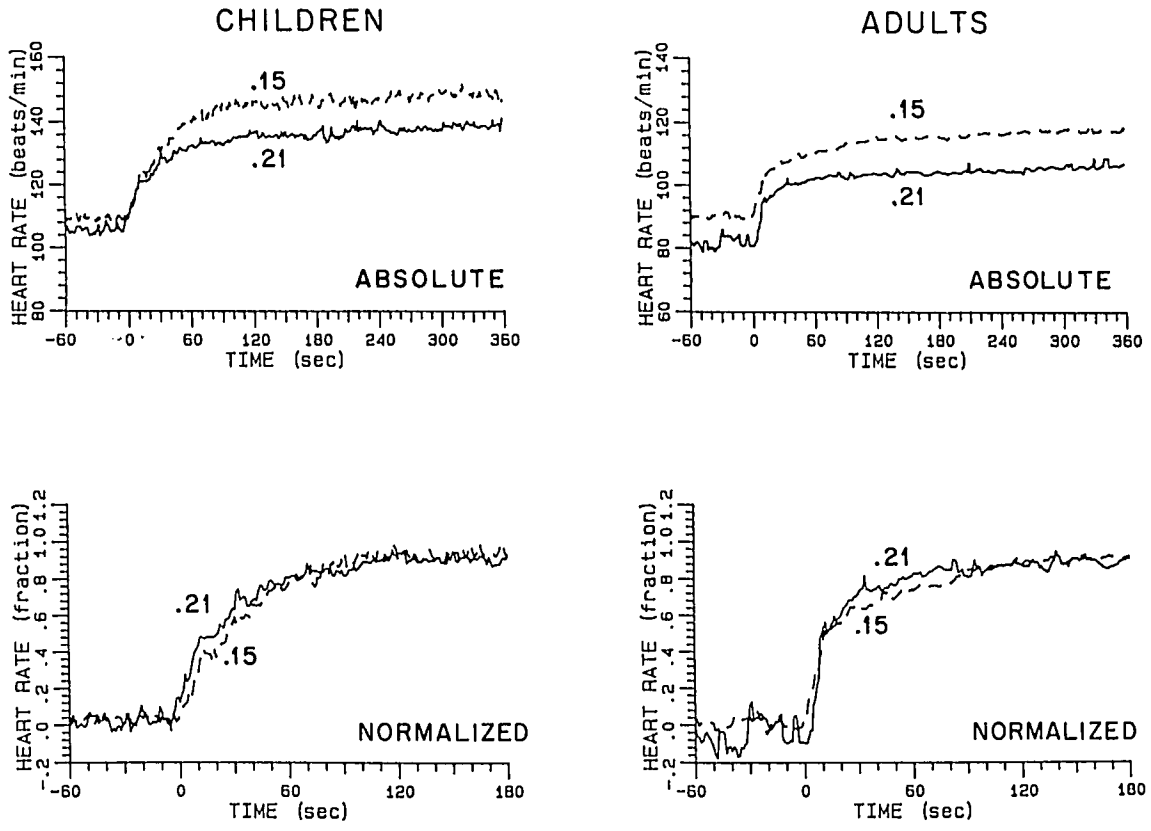

Figure 3—Group mean responses of heart rate for children and adults. *Upper panels* show absolute responses during room air ($FiO_2 = 0.21$) and hypoxia ($FiO_2 = 0.15$), while *lower panels* represent responses normalized to the net change over the first 180 s, to illustrate better the different time courses under the two inspired oxygen concentrations. Hypoxia resulted in higher heart rates (for both rest and exercise) and slowed kinetics.

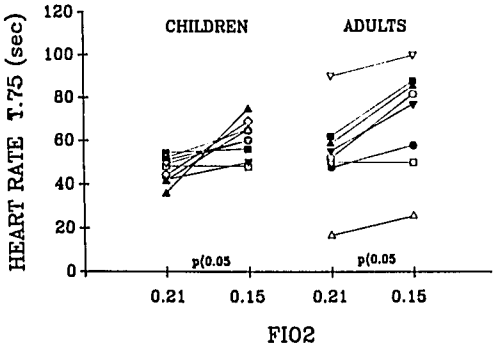

Figure 4—Time for heart rate to reach 75% of the response ($T_{0.75}$). Hypoxia significantly lengthened the time for heart rate to approach a steady state level during exercise in both children and adults.

suming near-equilibrium of the creatine kinase reaction, changes in ADP and Pi can be estimated from changes in phosphocreatine (6,7). Under conditions where oxygen is presumed to be in excess, phosphocreatine falls linearly with increasing oxygen utilization (24) and/or rates of contraction (22) by isolated muscles, and the time course for both is similar and relatively constant across tension development, suggesting a linear system (22,24). Thus, in the absence of any anaerobic glycolysis, the muscle metabolic rate is a linear function of the muscle oxygen deficit (as decreased muscle phosphocreatine). The increased O_2 deficit under hypoxic conditions found in the present study implies that the additional energy was derived from greater changes in phosphocreatine, tissue and venous oxygen stores, or anaerobic metabolism resulting in lactate production.

Hypoxia would lead to a reduction in the O_2 diffusion gradient between the capillaries and the muscle mitochondria and, thus, in the tissue oxygen concentration. The similarity in normalized O_2 deficit between children and adults in the present study and the similar increase with hypoxia suggest that the determinants of the tissue oxygen concentration (such as oxygen delivery and diffusion gradients, diffusion distances, etc.) are also similar between children and adults. Since the exercise $\dot{V}O_2$ was maintained constant under these conditions, one or more of the other determinants of the cellular oxidation rate mentioned above presumably increased to compensate for the reduced tissue oxygen level (6,7). These changes, in fact, can be inferred from the data of Linnarsson et al. (21) for work at 0.68 atmospheres, which represented a reduction in inspired oxygen tension (PiO_2 = 99 mm Hg) similar to that produced here (PiO_2 = 114 mm Hg). From their data, higher tissue concentrations of ADP and Pi with hypoxia are predicted by the greater fall in phosphocrea-

tine, while the greater muscle and blood lactate concentrations suggest an elevation in cytosolic NADH (18). Thus, for the relative intensities of exercise and hypoxia utilized in both the current study and that of Linnarsson et al. (21), steady state $\dot{V}O_2$ was able to be maintained during hypoxia, but with the cost of a greater fall in phosphocreatine and, thus, a larger O_2 deficit.

Hypoxia produces widespread hemodynamic changes, including increased heart rate (11,15; present study), systemic shunt flow (13), and a redistribution of cardiac output away from the splanchnic region (16). In the present study, children demonstrated the same sensitivity to hypoxia as did the adults, as evidenced by similar increases in rest and exercise heart rates. In addition, the kinetics of adjustment of heart rate during exercise were slowed by hypoxia to a similar degree in both children and adults. During exercise, an increase in heart rate is accomplished predominantly by withdrawal of parasympathetic inhibition at lower heart rates and by a combination of further parasympathetic withdrawal and sympathetic activation at higher heart rates (26). In turn, sympathetic activation occurs more slowly than parasympathetic withdrawal (14). The slower kinetics of heart rate adjustment during hypoxic exercise for both groups in the present study may thus have been the result of the shift to higher heart rates at rest and exercise, causing an increased dependence on sympathetic activation and reduced dependence on removal of parasympathetic inhibition. Consistent with this interpretation is the observation that heart rate kinetics are slowed in adult subjects breathing room air when the baseline and exercise heart rates are increased by previous exercise (17). However, both the steady state rest and exercise heart rates were higher for children compared with adults during both conditions. The observation that the kinetics of heart rate adjustment were similar, and slowed to a comparable degree between children and adults, in spite of different baseline and exercise values, suggests that there are aspects of the control of heart rate which mature with age.

Hypoxia during the progressive exercise tests resulted in a significant decrease in LAT and $\dot{V}O_{2max}$ in both the children and the adults (Table 1). As with the slowed $\dot{V}O_2$ kinetics following the onset of constant-work-rate exercise, the lowered LAT with hypoxia could be caused by decreased O_2 availability to the exercising muscles due to the decreased diffusion gradient between the blood and mitochondria. Despite this, hypoxia had no effect on $\Delta\dot{V}O_2/\Delta WR$ for below-LAT exercise in either children or adults. This implies that the efficiency by which potential energy as chemical bonds was converted to mechanical work for exercise below the LAT was not affected by the reduction in tissue PO_2 induced by breathing 15% O_2.

Finally, the use of body weight to normalize the metabolic responses (as $\dot{V}O_2$) eliminated the differences observed between children and adults. Therefore, the differences in metabolic responses between children and adults in this study were due solely to extrinsic (i.e., size- or mass-related) rather than age or other intrinsic differences.

In summary, we have shown that hypoxia (FiO_2 = 0.15) resulted in slowed $\dot{V}O_2$ and heart rate responses to exercise in both children and adults. This was associated with an increase in the O_2 deficit, which is consistent with current understanding of the control of oxidative metabolism in skeletal muscle. In addition, part of the increased O_2 deficit with hypoxia was due to a smaller phase I component of the kinetic phase. This may have been a consequence of the slower heart rate responses found with hypoxia.

As healthy children increase in body size, growth of the cardiorespiratory system appears to be homeostatic. A controlled variable of this homeostatic system is the time required to adjust pulmonary gas exchange to cellular metabolism during a sudden increase in O_2 demand. The robustness of this control is indicated by our finding that the imposition of hypoxia affected the $\dot{V}O_2$ response in adults and children to the same degree.

Dr. Springer was supported by a fellowship from the Joseph Drown Foundation. This work was supported by NIH Grant HL11907.

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