

**ARTERIAL HYPOXEMIA
AND
PERFORMANCE DURING INTENSE EXERCISE**

by

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ABSTRACT

A substantial decrease in percent arterial hemoglobin saturation (%SaO₂) has been observed in some highly aerobically trained athletes during intense exercise [$\geq 90\%$ of maximal oxygen uptake ($\dot{V}O_{2\max}$) or oxygen uptake ($\dot{V}O_2$) ≥ 3.5 l·min⁻¹] at sea level, and a reduction in %SaO₂ has been associated with impaired performance. In order to explore the level of hypoxemia which is sufficient to impair maximal performance, 7 well-trained male cyclists ($\dot{V}O_{2\max} \geq 60$ ml·kg⁻¹·min⁻¹ or $\dot{V}O_{2\max} \geq 5$ l·min⁻¹) who did not develop exercise-induced hypoxemia performed a 5-min performance cycle test to exhaustion at maximal intensity as controlled by the subject, under three experimental conditions: normoxemia (%SaO₂ > 94%), and artificially induced mild (%SaO₂ = 87±1%) and moderate (%SaO₂ = 90±1%) hypoxemia. %SaO₂ was continuously measured using an ear oximeter. In the two hypoxemic conditions, pure N₂ was added to the inspired air throughout the performance test according to the oximeter readings so as to achieve the desired hypoxemic level averaged over the 5-min period. Performance was evaluated as the total work output (Work_{tot}) performed in the 5-min cycle test. Heart rate and ventilatory parameters were measured continuously during the test. ANOVA for repeated measures was used to compare differences in the results among the three experimental conditions. Performance progressively decreased with decreasing %SaO₂ (mean Work_{tot} = 107.40 kJ, 104.07 kJ, and 102.52 kJ, under normoxemia, mild, and moderate hypoxemia, respectively), but only performance in the moderate hypoxemia condition was significantly different than normoxemia ($p = 0.0216$). Mean heart rate (HR) was similar in the three experimental conditions ($p = 0.9536$). Similarly, mean $\dot{V}O_2$ was not significantly different among conditions ($p = 0.1751$). However, end-tidal partial pressure of CO₂ (P_{ET}CO₂) was significantly lower ($p = 0.0053$) during moderate hypoxemia compared with normoxemia, and $\dot{V}E/\dot{V}CO_2$ was significantly higher ($p = 0.0052$) in both hypoxemic conditions when compared with normoxemia, indicating hyperventilation possibly compensating for

increasing metabolic acidosis during hypoxemia. It is concluded that maximal performance capacity is significantly impaired in highly trained cyclists working under an arterial oxyhemoglobin saturation level of 87% but not under a milder desaturation level of 90%. Since $\dot{V}O_2$ was not different among the experimental conditions, the reduction in maximal performance capacity is possibly related to a worsening of the metabolic acidosis elicited by hypoxemia.

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LIST OF SYMBOLS

$(a-v) O_2$:	arteriovenous oxygen difference
CaO_2	:	arterial oxygen content
CO_2	:	carbon dioxide
2,3-DPG	:	2,3-diphosphoglycerate
ECG	:	electrocardiogram
f	:	respiratory rate
F_{IO_2}	:	fractional concentration of inspired oxygen
H^+	:	hydrogen ion
Hb	:	hemoglobin
HbO_2	:	oxyhemoglobin
$He:O_2$:	helium:oxygen
HR	:	heart rate
kJ	:	kilojoules
N_2	:	nitrogen
O_2	:	oxygen
P_{50}	:	PO_2 at 50% of O_2 saturation of Hb
P_{di}	:	diaphragmatic pressure
P_{ETCO_2}	:	end-tidal partial pressure of carbon dioxide
P_{ETO_2}	:	end-tidal partial pressure of oxygen
pH	:	negative algorithm of H^+ concentration
PO	:	power output
PO_2	:	partial pressure of oxygen
Q_{max}	:	maximal cardiac output
RER	:	respiratory exchange ratio
SaO_2	:	arterial oxygen saturation

SE	:	standard error
\dot{V}_E	:	minute ventilation
V_t	:	tidal volume
\dot{V}_{CO_2}	:	expired carbon dioxide
\dot{V}_{O_2}	:	oxygen uptake
$\dot{V}_{O_{2max}}$:	maximal oxygen consumption
$\dot{V}_{O_2 \text{ resp}}$:	oxygen uptake of the respiratory system
\dot{V}_E/\dot{V}_{O_2}	:	ventilatory equivalent for oxygen
\dot{V}_E/\dot{V}_{CO_2}	:	ventilatory equivalent for carbon dioxide
Work _{tot}	:	total work performed

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DEDICATION

TO MY PARENTS,
WHO, DESPITE THEIR LIMITED EDUCATIONAL BACKGROUND,
PROVIDED ME WITH LIMITLESS SUPPORT AND UNDERSTANDING
THROUGHOUT MY ENDEAVOR IN PURSUING GRADUATE STUDIES.

INTRODUCTION

There is growing evidence that oxygen delivery to muscle is the most important factor determining the maximal oxygen uptake ($\dot{V}O_{2\max}$) of an individual (Ekblom, 1986; Buick et al., 1980; Williams et al., 1981; Ekblom, 1986; Di Prampero and Ferretti, 1990). It has been calculated that the oxygen delivery system accounts for 72-75% of the overall limits to $\dot{V}O_{2\max}$ (Di Prampero, 1985; Lawler et al., 1988). Arterial oxyhemoglobin saturation (SaO_2), which depends mainly on gas exchange, is a determinant of the oxygen delivery system. Oxygen delivery to contracting skeletal muscle is the product of arterial oxygen content (CaO_2) and local blood flow. By inducing low SaO_2 (hypoxemia) due to pulmonary insufficiency, arterial oxygen content is also reduced, which in turn may lead to decreased oxygen delivery, decreased capillary-to-mitochondrial diffusion gradient, decreased arteriovenous oxygen difference and, consequently, to a reduction in $\dot{V}O_{2\max}$.

However, traditionally, the pulmonary system has been dismissed as a potential limiting factor to $\dot{V}O_{2\max}$ and exercise performance in healthy individuals at sea level, since its capacity to facilitate oxygen transport is more than adequate to meet the increased metabolic demands (Dempsey et al., 1980; Wasserman et al., 1981). Evidence supporting this notion was the finding that the partial pressure of oxygen in arterial blood (PaO_2) and percent arterial oxyhemoglobin saturation ($\%SaO_2$) remain close to the resting values during light, moderate, and short term heavy exercise at sea level (Asmussen and Nielsen, 1960; Barr et al., 1964; Hesser and Matell, 1965; Wasserman et al., 1967). Recent evidence, though, suggests that this generalization may not apply to the highly trained athlete competing at high intensity exercise. Several recent studies (Dempsey et al., 1982, 1984; Powers et al., 1984, 1988a, 1989; Williams et al., 1986; Lawler et al., 1988; Hopkins and McKenzie, 1989) have demonstrated that a substantial reduction in PaO_2 and percent arterial oxyhemoglobin saturation can occur during intense exercise ($\geq 90\% \dot{V}O_{2\max}$ or $\dot{V}O_2 > 3.5 \text{ l}\cdot\text{min}^{-1}$) at sea level, in highly aerobically trained athletes who are capable of achieving extremely high

metabolic rates. These findings confirmed some similar scattered observations reported earlier in the literature (Harrop, 1919; Holmgren and Linderholm, 1958; Rowell et al., 1964). In these studies %SaO₂ values as low as 84% have been reported (Powers et al., 1984; Williams et al., 1986), however most of the values fall in the range between 87% and 93%. Apparently, the adaptations in muscle tissue and changes in cardiovascular function developed by these athletes cannot be matched by those of the less-adaptive pulmonary system (Dempsey, 1986; Lindstedt et al., 1988; Rasmussen and Ryan, 1989).

The mechanisms underlying the marked arterial desaturation observed in highly trained endurance athletes during heavy exercise are still unclear. However, several potential causes of exercise-induced hypoxemia including venoarterial shunt, ventilation-perfusion inequality (VA/Q), hypoventilation, diffusion limitation, and increased extra-vascular lung water have been proposed (for review see Powers and Williams, 1987; Rasmussen and Ryan, 1990).

Interesting is the observation that not all highly trained athletes develop substantial hypoxemia during heavy exercise; 40% (Dempsey et al., 1990) or 52% (Powers et al., 1988a) of highly trained young athletes tested achieved significant exercise-induced hypoxemia (SaO₂ 84-92%). Development of hypoxemia has been observed to be more common and severe among athletes with $\dot{V}O_{2\max} > 65 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ (Dempsey et al., 1990, 1984; Williams et al., 1986; Powers et al., 1988a, 1988b, 1989). Generally, the level of arterial desaturation during heavy exercise has been found to be inversely related to the subject's $\dot{V}O_{2\max}$ (Rowell et al., 1964; Williams et al., 1986; Powers et al., 1988b, 1989; Cymerman et al., 1989). Concurrently, a reduced %SaO₂ should affect individual $\dot{V}O_{2\max}$. Indeed, a strong positive correlation ($r=0.96$) was found between $\dot{V}O_{2\max}$ at various simulated altitudes and %SaO₂ measured at the time of $\dot{V}O_{2\max}$ (Cymerman et al., 1989). In addition, it has been shown that SaO₂ reduced from 95% or even 92% to 85% can cause a 7-10% reduction in $\dot{V}O_{2\max}$ (Pugh, 1967; Dempsey, 1988). In a recent study, prevention of hypoxemia (i.e. increase in oxygen saturation from a mean of 92% to a mean of 96%) led to a significant 6-8% increase in $\dot{V}O_{2\max}$ (Powers et al., 1989).

Powers et al. (1989) studied the effect of prevention of desaturation below 94-96% on $\dot{V}O_{2\max}$ in a group of highly trained endurance athletes, who demonstrated exercise-induced reductions in $\%SaO_2 \leq 92\%$. The authors suggested that an exercise-induced reduction in SaO_2 to $\sim 92-93\%$ is sufficient to cause a measurable effect on $\dot{V}O_{2\max}$ and that, on the average, this effect approximates about a 1% decrement in $\dot{V}O_{2\max}$ for each 1% decrement in $\%SaO_2$. The above suggestion, however, was based on a simple observation of this study's data in which $\%SaO_2$ was treated as a dependent variable. Horvath et al. (1975), on the other hand, found a significant reduction in $\dot{V}O_{2\max}$ when SaO_2 was lowered four or more percentage points by carbon monoxide replacement of oxygen from the hemoglobin binding sites; Squires and Buskirk (1982) confirmed this finding by inducing similar arterial desaturation of the same magnitude ($\geq 3.6\%$ reduction from the control values) in an altitude chamber and observing the detrimental effect in the $\dot{V}O_{2\max}$ of their highly aerobically trained subjects. However, in this study as well, $\%SaO_2$ was estimated and not controlled.

Despite the aforementioned hypoxemia studies, the level of arterial desaturation sufficient to exert a significant detrimental effect on $\dot{V}O_{2\max}$, and maximal performance, remains equivocal. Therefore, the present study was conducted to explore the critical level of arterial desaturation at which maximal performance capacity is significantly impaired in highly trained athletes exercising at sea level. Different levels of arterial hypoxemia were induced and their effects on maximal performance were quantified.

METHODS

SUBJECTS

Experiments were conducted on 7 healthy, non-smoking, competitive male cyclists, selected from volunteers ranging in age from 19 to 32 yrs (Table 1). Two criteria were set for participation in the study: 1) a $\dot{V}O_{2\max} \geq 60 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ or $\dot{V}O_{2\max} \geq 5 \text{ l}\cdot\text{min}^{-1}$; and 2) no arterial desaturation during heavy exercise ($\%SaO_2 \geq 94\%$). All subjects were highly trained, experienced and motivated athletes, able to carefully adjust the exercise intensity during the test and to sustain high intensity exercise until the development of physiological signs of exhaustion. All the procedures had been previously explained to them and their written consent for participating in the experiments was required. The subjects continued with their regular training programs throughout the study.

PROTOCOL

Each subject was asked to complete two to three practice trials and three experimental trials on a 5-min performance cycle test to exhaustion. Subjects were required to abstain from exhaustive physical exercise for 24 hrs before each experiment and from food and caffeine intake at least 3 hrs prior to reporting to the laboratory.

Preliminary Testing

Descriptive physical characteristics, $\dot{V}O_{2\max}$, and $\%SaO_2$ during heavy exercise were measured for each subject one to three weeks prior to testing.

$\dot{V}O_{2\max}$ was determined using an incremental cycling test to exhaustion on an electronically braked cycle ergometer. The starting work load was 0 Watts and it was increased in ramp fashion by 30 Watts per minute until volitional fatigue. Pulmonary ventilation and mixed expired gas composition were continuously recorded in order to calculate oxygen uptake. Heart rate was also continuously monitored using direct chest lead

electrocardiography (ECG). Attainment of $\dot{V}O_{2\max}$ was considered when at least three of the four following criteria were met: 1) identification of a plateau in oxygen uptake with increasing workrate; 2) a respiratory exchange ratio > 1.15 ; 3) a plateau in heart rate; and 4) volitional fatigue.

Arterial oxyhemoglobin saturation was also monitored during the $\dot{V}O_{2\max}$ test in order to detect possible development of substantial hypoxemia, defined as $\%SaO_2 < 94\%$, during heavy exercise. Once a subject reached the 300 Watts workload, $\%SaO_2$ values were recorded each second thereafter and then averaged for the remainder of the test to obtain a baseline measure of arterial saturation upon which subjects were judged as developing hypoxemia or not.

Experimental Protocol

Experimental sessions required performance of a five minute cycle ergometer test to exhaustion.

After the subject was seated on the cycle ergometer with the legs in a comfortable slightly flexed position, he was instrumented with the oximeter earpiece, the ECG leads and the mouthpiece. The skin of the helix of the ear was rubbed with a vasodilator nicotine cream (Finalgon[®], Boehringer Ingelheim), in order to achieve adequate perfusion before the oximeter earpiece was secured in position with a headband. A 2-min resting period followed the instrumentation procedure. The exercise test started with a 5-min warmup at a power output (PO) equivalent to 50% of subject's maximal oxygen uptake, as previously determined from a linear relationship obtained between $\dot{V}O_2$ and PO in the $\dot{V}O_{2\max}$ test. Another 2-min resting period followed. Thereafter the subject was asked to increase the PO to a value equivalent to 90% of his maximal oxygen uptake and as soon as this desired PO was reached, the 5-min performance cycle began. The subject then controlled the power output manually via a variable output supply, according to the degree of his perceived exhaustion, while remaining ignorant of the numerical magnitude of each adjustment. This protocol allowed the

subject to adjust his power output, and thereby the work performed, such that he was able to finish the test in a state of complete exhaustion, having performed the highest possible amount of work within the 5-min period. The subject was informed about the elapsed time every 30 s, and no verbal encouragement was provided. The goal of this performance test was to simulate a real 5-min maximal cycling pursuit. The reliability of this performance test had been previously confirmed in this laboratory with a high test-retest intraclass correlation coefficient ($R = 0.958$). For the particular sample used in this study the corresponding test-retest intraclass correlation coefficient was also high ($R = 0.997$).

In order to ensure appropriate execution of the cycling protocol, each subject was given two or three practice trials on different days prior to the experimental conditions. In these practice trials arterial oxygen saturation was also monitored in order to confirm that exercise-induced hypoxemia did not develop during the experimental conditions. Subjects were free to follow different strategies among the practice trials as well as in the experimental trials.

Each subject performed the aforementioned exercise test under three different experimental conditions:

- 1) *normoxemia*: the subjects were breathing normoxic air (21% O₂, 79% N₂);
- 2) *mild hypoxemia*: F_IO₂ was adjusted using N₂ to induce a hypoxemic level of 90 ± 1 % SaO₂; and
- 3) *moderate hypoxemia*: F_IO₂ was adjusted with N₂ to induce a hypoxemic level of 87 ± 1 % SaO₂.

The subject was inspiring room air from a 13.5 l mixing chamber through a two-way valve (Hans Rudolph). In the two hypoxemic conditions, during the 5 min of the performance cycle test, pure N₂ was added into the mixing chamber according to the oximeter readings in order to achieve the desired hypoxemic level averaged over the 5-min period. In all three experimental conditions the inspired air was passing through the same mixing chamber in order to ensure the same external respiratory resistance. Heart rate (HR) and ventilatory

parameters [minute ventilation (\dot{V}_E), tidal volume (V_t), oxygen uptake ($\dot{V}O_2$), expired carbon dioxide ($\dot{V}CO_2$), end-tidal pressures of O_2 (P_{ETO_2}) and CO_2 (P_{ETCO_2}), respiratory exchange ratio (RER), and respiratory rate (f)] were measured continuously and averaged at 15 second intervals. Oxygen saturation was continuously monitored via the ear oximeter and recorded every second during the 5-min performance cycle test. Instantaneous power output (Watts) and total work (kJ) were also recorded every second during the 5-min performance cycle test.

The three experimental trials were separated by at least a two day interval for each subject and took place at approximately the same time of day (± 1 hr) for each subject in order to avoid diurnal variation. Furthermore, each subject was asked to maintain a consistent diet in the 24 hours preceding each trial. The three experimental conditions were administered in a counterbalanced order, so that any sequencing effect would be prevented. Subjects were randomly assigned to a condition sequence and they remained naive to this order.

Instrumentation

A Mijnhardt (Type KEM-3, Holland) electronically-braked cycle ergometer was used for all the exercise tests. Additionally, a variable output power supply was connected to the ergometer to allow fine manual adjustment of the work load over a work range of 0-500 Watts. The ergometer was interfaced with an IBM microcomputer (Model 30 286, International Business Machines Corporation, Armonk, New York, U.S.A.) such that the analog power output signal was sampled, digitally converted, and integrated in real time to provide a record of instantaneous power output and total work. The computed results were simultaneously displayed on the computer screen for instant visual inspection.

An HP 47201A ear oximeter (Hewlett Packard, U.S.A.) was used for measuring arterial oxygen saturation since arterialized capillary blood of the ear accurately reflects arterial oxygenation during exercise (Godfrey et al., 1971; Saunders et al. 1976). This apparatus differs from conventional oximeters by measuring light absorption on eight instead of only two wavelengths; this allows automatic calibration and automatic compensation for variations

in ear characteristics as well as changes in the position of the earpiece. In order to eliminate noisy readings, measurements were made with the oximeter in the slow operational mode. The ear oximeter was calibrated against internal standards before each experiment. For optimum signal to noise ratio in the slow mode and maximum accuracy it was initially standardized twice and restandardized after the first 15 minutes of operation. The ear oximeter was also interfaced with the IBM microcomputer so the computed %SaO₂ from the analog signal was recorded every second and simultaneously displayed on the computer screen.

A Medical Graphics Exercise System 2001 (MGC) (Medical Graphics Corporation, St. Paul, Minnesota, U.S.A.) was used for the measurement of ventilatory parameters and oxygen uptake. The pneumotachograph of the system was calibrated with a 3 l capacity syringe and the gas analyzers were calibrated with air and gases of known concentration prior to each experiment.

A Cardioscope/Recorder Module (Lifepak 6, Physio-Control, Washington, U.S.A.) was used for monitoring heart rate; its 3 digit heart rate meter provides a continuous display of the R-wave rate from 20 to 300 beats per minute.

STATISTICAL ANALYSIS

The differences in total work output ($Work_{tot}$), as well as in %SaO₂, among the three experimental conditions were compared for statistical significance using a one way analysis of variance (ANOVA) for repeated measures. Two way (condition X time) ANOVA for repeated measures was used for the comparison of the differences in PO , $\dot{V}O_2$, $\dot{V}E/\dot{V}CO_2$, $P_{ET}CO_2$ and HR among the conditions. Post hoc comparisons were conducted with the Tukey's test. Test-retest reliability of the 5-min performance cycle test was determined using intraclass correlation. The level of significance was set at $p < 0.05$.

RESULTS

Baseline Measures

Individual and mean values of the physical characteristics of the 7 subjects, $\dot{V}O_{2\max}$, baseline SaO_2 measured during the $\dot{V}O_{2\max}$ test, and peak power output (PO_{peak}) achieved during the $\dot{V}O_{2\max}$ test are shown for all subjects in Table 1. The power outputs equivalent to 50% and 90% of the subjects' $\dot{V}O_{2\max}$ are given in Table A1.

TABLE 1. Subjects' physical characteristics, maximal oxygen uptake ($\dot{V}O_{2\max}$), baseline arterial oxyhemoglobin saturation (SaO_2), and peak power output (PO_{peak}) achieved during the $\dot{V}O_{2\max}$ test.

Subject No.	Age (years)	Weight (kg)	Height (cm)	$\dot{V}O_{2\max}$ (l·min ⁻¹)	$\dot{V}O_{2\max}$ (ml·kg ⁻¹ ·min ⁻¹)	SaO_2 (%)	PO_{peak} (Watts)
1	29	74	176	4.91	66.2	95	414
2	31	77	178	4.83	62.8	96	397
3	22	87	192	5.04	58.1	96	444
4	32	67	175	4.80	71.6	95	395
5	25	86	188	5.32	61.5	95	482
6	29	71	175	4.38	62.1	97	330
7	19	70	182	4.71	67.3	96	433
Mean	26.7	76.0	180.9	4.86	64.2	95.7	413.6
± SD	4.86	7.83	6.79	0.29	4.46	0.76	47.59

Performance cycle test

Induction of hypoxemia. The method used in this study for inducing artificial arterial hypoxemia and maintaining it during the performance cycle test within the predetermined ranges was quite successful (Table 2, Figs. 1, 2). Individuals and mean values for average % SaO_2 over the 5-min period of the performance cycle test in the three experimental conditions are shown in Table 2. During mild and moderate hypoxemia, % SaO_2 attained mean±SE values equal to 90.02±0.23 and 87.35±0.12 respectively. These values were significantly different from each other as well as from the % SaO_2 attained in the normoxemia

condition (95.93 ± 0.29) (Fig.1). Figure 2 depicts the time course of the mean %SaO₂ as subjects were exposed to normoxemia, mild, and moderate hypoxemia; as soon as the desired hypoxemic level was achieved, only minor adjustments were needed as a result of the increasing ventilatory response (Table 3). It is worthnoting that the pattern of the induced decline in %SaO₂ achieved in the two hypoxemic conditions simulated that of athletes who naturally desaturate during a high intensity exercise task. The selection of subjects of similar trained state who did not develop hypoxemia during heavy exercise facilitated the implementation of the method, since no exercise-induced hypoxemia was present to interfere with the artificial induction of desaturation, and, also, similar physiological responses to heavy exercise and hypoxemia were attained. The amount of N₂ that needed to be added to the inspired air to lower the saturation levels was very small (Fig. A1) and the response remarkably fast as a result of the high ventilatory response of our elite athletes to the high intensity exercise. The manipulation of SaO₂ was well tolerated by the subjects; some of them complained of mild nausea during the hypoxemia treatments but none felt that these symptoms affected performance. This discomfort was associated with a marked hyperventilatory response resulting in excessive elimination of CO₂.

Total work. Table 2 also presents the individual and mean values for total work output (Work_{tot}). A progressive decrease in Work_{tot} was observed with decreasing %SaO₂, and ANOVA for repeated measures showed a significant condition effect on Work_{tot} ($F=5.37$, $p=0.0216$). Post-hoc analysis conducted with the Tukey's test indicated that mean Work_{tot} in the moderate hypoxemia condition (102.52 ± 4.73 kJ) was significantly lower when compared to the normoxemia (107.40 ± 4.54 kJ), whereas even though Work_{tot} during mild hypoxemia (104.07 ± 5.56 kJ) was less than during normoxemia, the difference was not statistically significant; similarly, the Work_{tot} performed in moderate hypoxemia was less than in mild hypoxemia but not statistically different (Fig. 3). The linear trend observed between the mean

values of the induced levels of %SaO₂ and the mean total work performed within the 5 min of cycling to exhaustion under the three experimental conditions is depicted in Fig. 3.

TABLE 2. Average percent arterial oxyhemoglobin saturation (%SaO₂) and total work performed (Work_{tot}) during the 5-min maximal performance test under the three experimental conditions (normoxemia, mild, and moderate hypoxemia).

Subject No.	%SaO ₂			Work _{tot} , kJ		
	Normo- xemia	Mild Hypoxemia	Moderate Hypoxemia	Normo- xemia	Mild Hypoxemia	Moderate Hypoxemia
1	95.35	89.88	87.50	113.82	107.42	105.76
2	96.48	91.20	87.65	86.91	78.77	81.07
3	96.39	89.82	87.59	120.13	119.61	114.95
4	94.81	89.24	87.07	109.64	101.74	106.09
5	95.89	90.37	87.62	112.12	116.52	114.00
6	97.05	89.64	86.89	94.63	91.25	89.91
7	95.53	90.00	87.15	114.51	113.15	105.87
Mean	95.93 *	90.02 *	87.35 *	107.40	104.07	102.52 **
± SE	0.29	0.23	0.12	4.54	5.56	4.73

* Significantly different from each other ($p < 0.01$).

** Significantly different from "normoxemia" Work_{tot} ($p < 0.05$).

Power output. A similar large decline in mean PO response for all experimental conditions occurred during the first 3 minutes of the cycle performance test (Fig. 4). The mean PO response increased during the last 2 minutes of the cycle performance test in normoxemia and moderate hypoxemia conditions, whereas a similar increase in mean PO occurred during only the last minute of the performance test while subjects were mildly hypoxemic. Averaged over the 5-min period PO was statistically different only between normoxemia and moderate hypoxemia ($F=5.30$, $p=0.0224$).

Heart rate. Mean heart rate was similar among the three experimental conditions ($F=0.05$, $p=0.9536$) and the time course of its changes over the 5 min period of the performance cycle test followed the same pattern during the three tests (Fig. 5). The high

mean HR values reached at the last minute of the performance test (186.4, 183.7, and 185.0 beats/min under normoxemia, mild, and moderate hypoxemia, respectively) indicate that the subjects worked to exhaustion.

Ventilatory response. Means \pm SE for 1-min interval measures of \dot{V}_E , V_t , f , $\dot{V}O_2$, $P_{ET}CO_2$, $\dot{V}_E/\dot{V}O_2$, and $\dot{V}_E/\dot{V}CO_2$ are reported in Table 3. \dot{V}_E reached high levels at the end of the performance test, and the highest values were attained during the moderately hypoxemic test. V_t was similar among the three experimental conditions, whereas f reached the highest values during moderate hypoxemia and the pattern of its changes over time was similar to that of \dot{V}_E . $\dot{V}O_2$ was not significantly different among conditions ($F=2.02$, $p=0.1751$) and showed similar changes over time in all three tests (Fig. 6). $P_{ET}CO_2$ was progressively decreased with decreasing levels of %SaO₂ (Fig. 7); statistical analysis revealed a significant condition effect on $P_{ET}CO_2$ ($F=8.39$, $p=0.0053$) which was accounted for by the significantly different $P_{ET}CO_2$ values between normoxemia and moderate hypoxemia. The $\dot{V}_E/\dot{V}CO_2$ values were significantly higher ($F=8.40$, $p=0.0052$) in both hypoxemic conditions compared with normoxemia (Fig. 8), indicating hyperventilation during hypoxemia. The marked hyperventilatory response during moderate hypoxemia was further shown by the markedly increased $\dot{V}_E/\dot{V}O_2$ in this condition.

TABLE 3. 1-min Interval measures of ventilatory variables during a 5-min cycle ergometer test to exhaustion under the three experimental conditions (normoxemia, mild, and moderate hypoxemia). Values are means \pm SE; n=7 subjects.

	TIME min	VE, l·min ⁻¹	V _t , l	f, min ⁻¹	VO ₂ , l·min ⁻¹	P _{ET} CO ₂ , mmHg	VE/VO ₂	VE/VCO ₂
Normo- xemia	1	95.0 ± 4.3	2.97 ± 0.21	33.0 ± 2.9	3.54 ± 0.15	44.2 ± 0.9	26.9 ± 0.6	26.6 ± 0.5
	2	130.8 ± 6.9	3.53 ± 0.28	38.6 ± 4.0	4.22 ± 0.19	44.7 ± 1.2	31.1 ± 1.4	26.2 ± 0.6
	3	142.9 ± 9.8	3.57 ± 0.27	41.4 ± 4.4	4.41 ± 0.21	43.1 ± 1.3	32.4 ± 1.6	27.3 ± 0.8
	4	156.0 ± 10.0	3.56 ± 0.27	45.3 ± 4.3	4.56 ± 0.22	40.4 ± 1.4	34.2 ± 1.6	29.3 ± 1.0
	5	176.0 ± 5.6	3.48 ± 0.30	52.3 ± 3.0	4.69 ± 0.24	37.9 ± 1.1	37.9 ± 1.4	31.7 ± 1.1
	1	107.5 ± 6.1	3.17 ± 0.19	34.4 ± 2.3	3.73 ± 0.21	43.1 ± 1.1	28.9 ± 0.9	27.2 ± 0.7
	2	144.3 ± 9.1	3.61 ± 0.25	40.7 ± 2.7	4.24 ± 0.24	43.3 ± 1.0	34.1 ± 1.5	26.7 ± 0.7
	3	155.0 ± 13.0	3.56 ± 0.23	44.0 ± 3.6	4.47 ± 0.27	41.1 ± 1.0	34.4 ± 1.6	28.1 ± 0.8
	4	162.4 ± 13.8	3.53 ± 0.23	46.4 ± 4.3	4.66 ± 0.26	39.3 ± 1.5	34.5 ± 1.8	30.0 ± 1.4
	5	174.6 ± 12.3	3.40 ± 0.23	50.3 ± 3.8	4.75 ± 0.27	36.9 ± 1.2	36.7 ± 1.2	31.8 ± 1.5
Mild Hypoxemia	1	102.8 ± 4.2	3.13 ± 0.19	33.7 ± 2.6	3.44 ± 0.21	42.6 ± 0.6	30.3 ± 1.4	27.4 ± 0.5
	2	141.6 ± 6.1	3.59 ± 0.24	40.9 ± 3.6	4.10 ± 0.17	42.6 ± 0.9	34.8 ± 1.9	27.4 ± 0.7
	3	161.5 ± 9.9	3.53 ± 0.26	47.3 ± 4.5	4.34 ± 0.20	39.3 ± 1.1	37.3 ± 1.8	29.8 ± 1.1
	4	168.7 ± 8.5	3.45 ± 0.27	50.3 ± 4.1	4.51 ± 0.16	37.1 ± 1.1	37.5 ± 1.8	31.6 ± 1.2
	5	187.1 ± 4.4	3.45 ± 0.25	55.9 ± 3.2	4.60 ± 0.20	34.9 ± 0.9	41.1 ± 1.7	34.4 ± 1.1
Moderate Hypoxemia	1	102.8 ± 4.2	3.13 ± 0.19	33.7 ± 2.6	3.44 ± 0.21	42.6 ± 0.6	30.3 ± 1.4	27.4 ± 0.5
	2	141.6 ± 6.1	3.59 ± 0.24	40.9 ± 3.6	4.10 ± 0.17	42.6 ± 0.9	34.8 ± 1.9	27.4 ± 0.7
	3	161.5 ± 9.9	3.53 ± 0.26	47.3 ± 4.5	4.34 ± 0.20	39.3 ± 1.1	37.3 ± 1.8	29.8 ± 1.1
	4	168.7 ± 8.5	3.45 ± 0.27	50.3 ± 4.1	4.51 ± 0.16	37.1 ± 1.1	37.5 ± 1.8	31.6 ± 1.2
	5	187.1 ± 4.4	3.45 ± 0.25	55.9 ± 3.2	4.60 ± 0.20	34.9 ± 0.9	41.1 ± 1.7	34.4 ± 1.1

VE, ventilation; V_t, tidal volume; f, respiratory rate; $\dot{V}O_2$, O₂ uptake; P_{ET}CO₂, end-tidal partial pressure of CO₂; $\dot{V}E/\dot{V}O_2$, ventilatory equivalent of O₂; $\dot{V}E/\dot{V}CO_2$, ventilatory equivalent of CO₂.

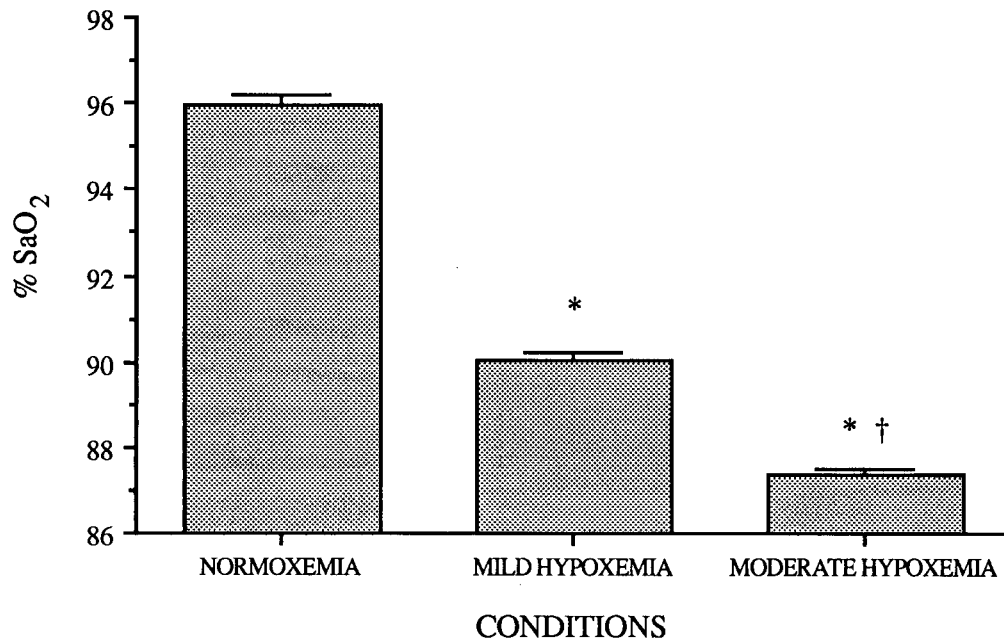


Fig. 1. Mean (\pm SE) of %SaO₂ attained over the 5-min of the performance test in the three experimental conditions (normoxemia, mild, and moderate hypoxemia) (n=7).

* Significantly different from "normoxemia" (p<0.01).

† Significantly different from "mild hypoxemia" (p<0.01).

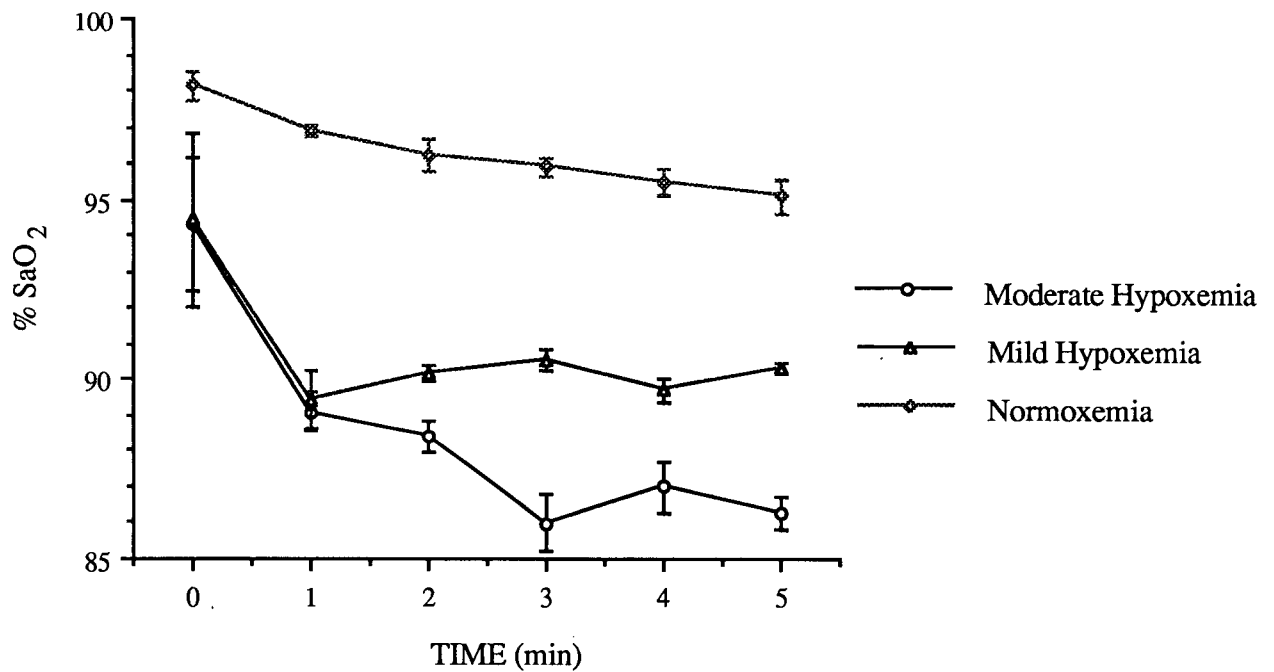


Fig. 2. Time course of mean changes (\pm SE) in %SaO₂ in a group of young elite cyclists (n=7) during a 5-min cycle ergometer test to exhaustion under normoxemia and induced mild and moderate hypoxemia.

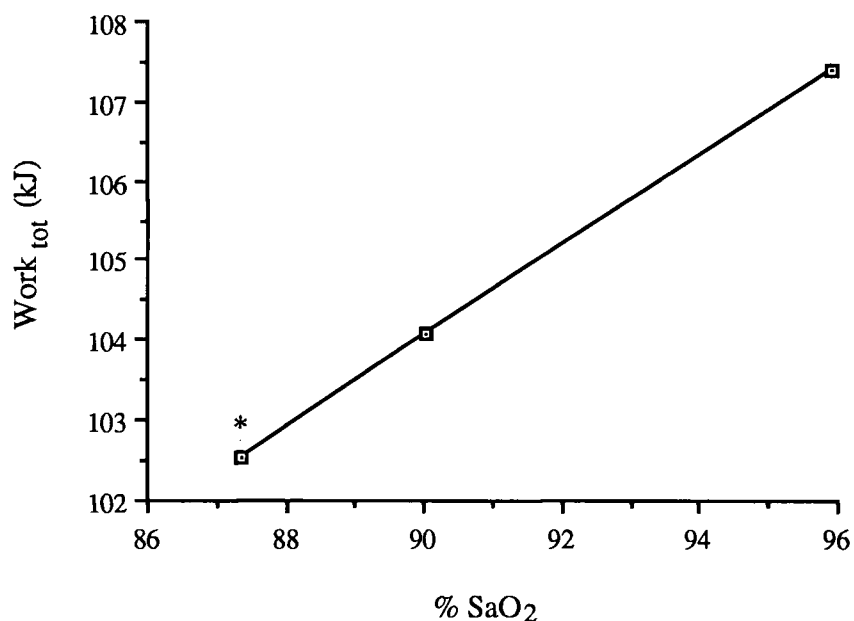


Fig. 3. Effect of three different levels of %SaO₂ (under normoxemia, and induced mild and moderate hypoxemia) on total work (Work_{tot}) performed by 7 elite cyclists during a 5-min cycle ergometer test to exhaustion. Symbols represent means.

* Significantly different from "normoxemia" Work_{tot} ($p < 0.05$).

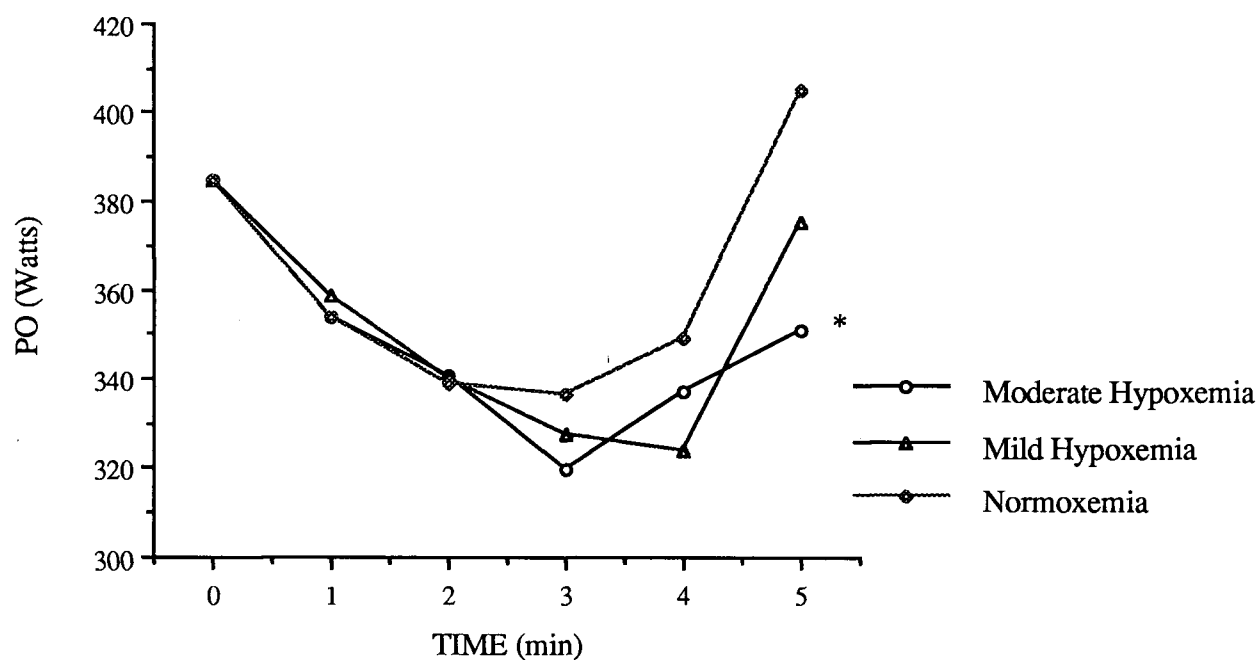


Fig. 4. Time course of mean changes in power output (PO) response in a group of young elite cyclists ($n=7$) during a 5-min cycle ergometer test to exhaustion under normoxemia and induced mild and moderate hypoxemia.

* Significantly different from "normoxemia" PO ($p < 0.05$).

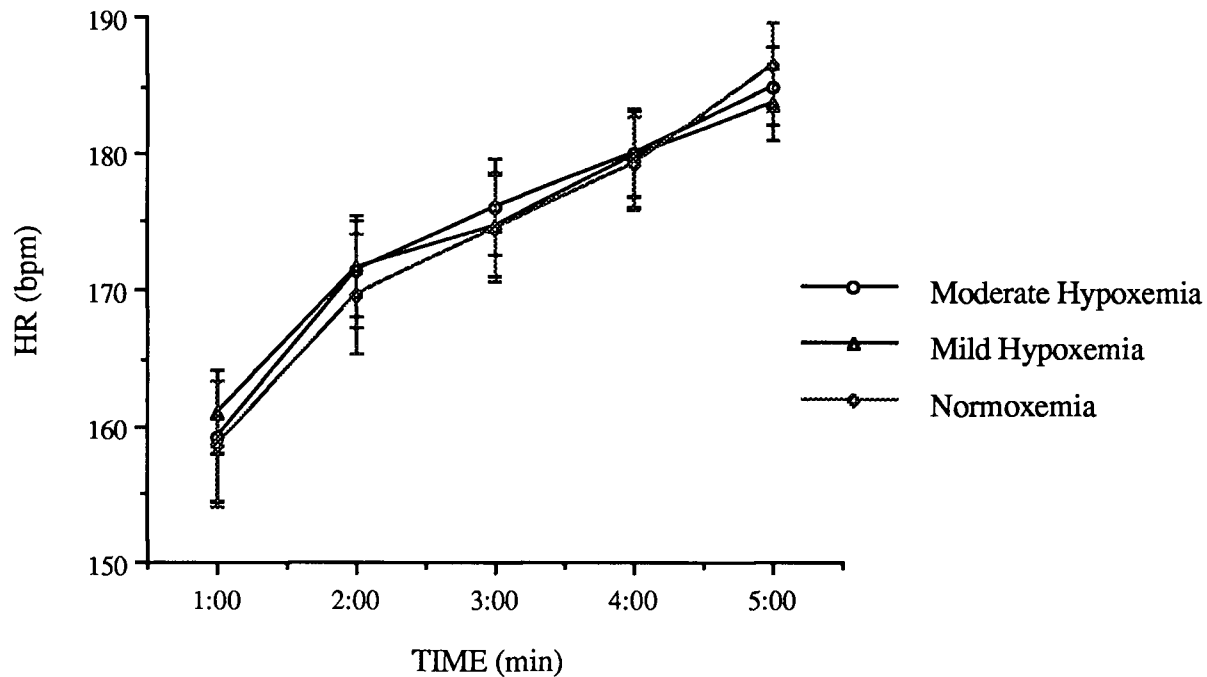


Fig. 5. Time course of mean (\pm SE) heart rate (HR) response in a group of young elite cyclists ($n=7$) during a 5-min cycle ergometer test to exhaustion under normoxemia and induced mild and moderate hypoxemia.

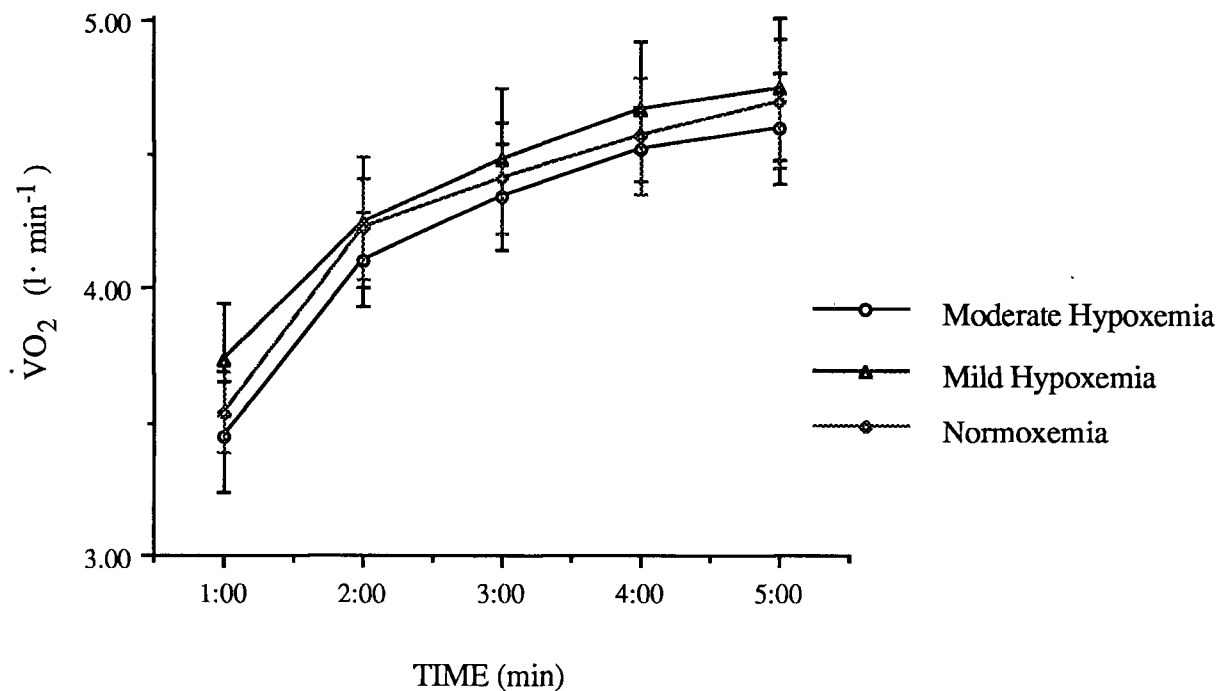


Fig. 6. Time course of mean (\pm SE) oxygen uptake ($\dot{V}O_2$) response in a group of young elite cyclists ($n=7$) during a 5-min cycle ergometer test to exhaustion under normoxemia and induced mild and moderate hypoxemia.

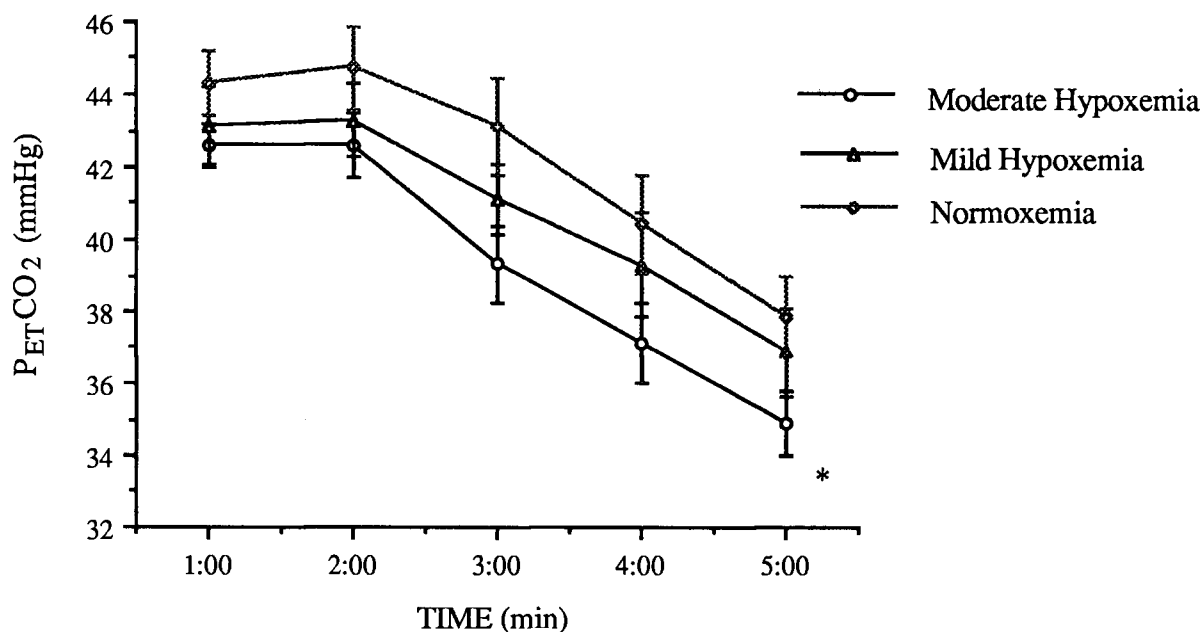


Fig. 7. Time course of mean (\pm SE) end-tidal partial pressure of CO_2 ($P_{ET}CO_2$) response in a group of young elite cyclists ($n=7$) during a 5-min cycle ergometer test to exhaustion under normoxemia and induced mild and moderate hypoxemia.

* Significantly different from "normoxemia" $P_{ET}CO_2$ ($p<0.05$).

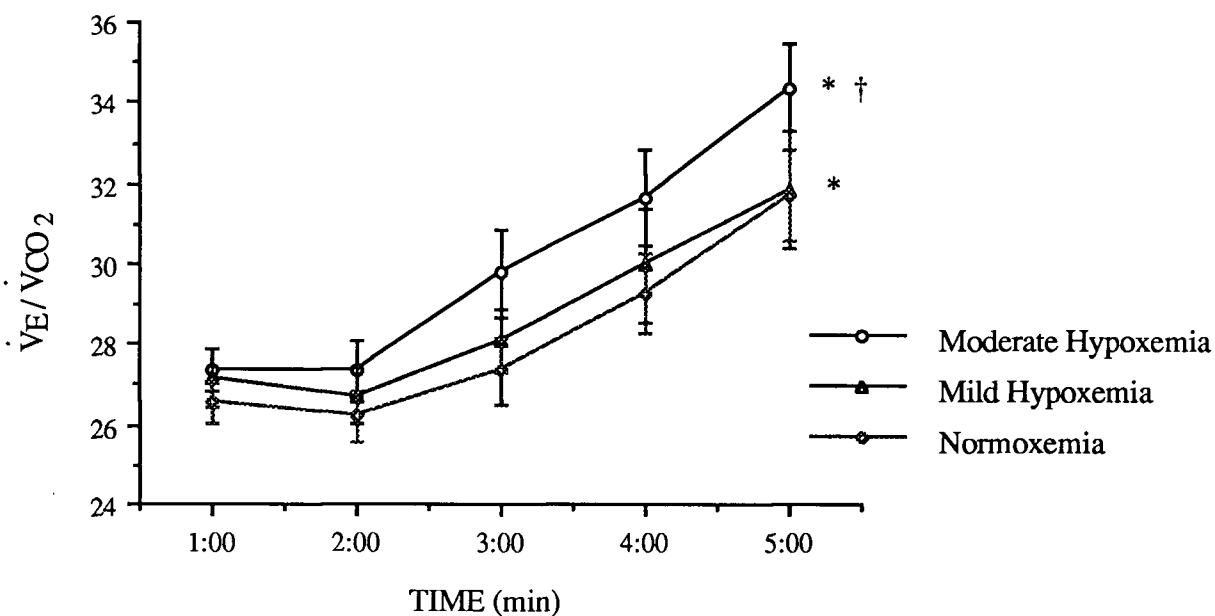


Fig. 8. Time course of mean (\pm SE) ventilatory equivalent of CO_2 ($\dot{V}E/\dot{V}CO_2$) in a group of young elite cyclists ($n=7$) during a 5-min cycle ergometer test to exhaustion under normoxemia and induced mild and moderate hypoxemia.

* Significantly different from "normoxemia" $\dot{V}E/\dot{V}CO_2$ ($p<0.05$).

† Significantly different from "mild hypoxemia" $\dot{V}E/\dot{V}CO_2$ ($p<0.05$).

DISCUSSION

It is well established that the capacity for physical work requiring large muscle groups for longer than 2 to 3 min depends mainly on aerobic metabolism. Thus, aerobic performance capacity, as indicated by work time during maximal exercise, should be expected to follow $\dot{V}O_{2\max}$. However, numerous studies (for review see Snell and Mitchell, 1984) have shown that $\dot{V}O_{2\max}$ is not a good predictor of exercise performance, since aerobic capacity, defined as the maximal amount of oxygen that can be utilized for the duration of an event, is related to both $\dot{V}O_{2\max}$ and factors related to fatigue. Nevertheless, it has been shown that $\dot{V}O_{2\max}$ and aerobic performance capacity change in parallel during acute hypoxia, as well as after carbon monoxide inhalation (Ekblom and Huot, 1972; Ekblom et al., 1975). The effect of arterial hypoxemia on work capacity has so far been investigated by measuring the reduction in $\dot{V}O_{2\max}$ resulting from lowered levels of arterial saturation. The present study investigated the effect of arterial hypoxemia on maximal performance capacity so that the results could be readily applied to a athletic population; therefore, performance in the current study is evaluated as the total work output performed in a 5-min cycle test to exhaustion at maximal intensity controlled by the subject, in an attempt to simulate a real 5-min cycling pursuit.

The results of this study suggest that a reduction in arterial oxyhemoglobin saturation to a level of 87% is associated with a significant adverse effect on performance of highly trained athletes, whereas desaturation to a level of 90% is not sufficient to elicit such an effect. Mild hypoxemia elicited a detrimental effect on performance, but this effect was not sufficient to reach statistical significance. There was, however, a clear linear trend between decreasing levels of arterial saturation and reduced performance.

Determination of hypoxemia. The decision to study the levels of $90 \pm 1\%$ and $87 \pm 1\%$ SaO_2 as possible critical arterial desaturation levels for impaired performance was based on the following considerations: 1) Healthy, untrained or moderately trained individuals generally have SaO_2 values of 94-95% during maximal exercise (Williams et al., 1986; Powers et al., 1988a, 1989); 2) According to previous studies' suggestions (Horvath et al., 1975; Squires and Buskirk, 1982), an $\sim 4\%$ reduction in $\%\text{SaO}_2$ from control values is required before $\dot{\text{V}}\text{O}_{2\text{max}}$ is significantly decreased; 3) Most of the exercise-induced hypoxemia values reported in the literature fall in the range between 87 and 93% SaO_2 . Thus, the first level, $90 \pm 1\%$, is 4% lower than the normal-control values, and the second level, $87 \pm 1\%$, represents the most severe incidence of hypoxemia, commonly observed among highly trained subjects. The $\pm 1\%$ margin accommodated the variability in the readings from the ear oximeter.

Performance. The differences in performance among the three experimental conditions seem to have occurred as a result of changes at the end of the performance test. Although the subjects were free to follow different strategies among the trials, the pattern of the changes in the mean power output response (Fig. 4) is similar during the first three minutes of the performance cycle test, showing a decline from the starting level. The final PO gain (Fig. 4) exceeded the initial value during normoxemia, whereas it was less profound during mild hypoxemia and even less during moderate hypoxemia.

Total work - Mild hypoxemia: Despite the reduced $\%\text{SaO}_2$ in the mild hypoxemia condition, $\dot{\text{V}}\text{O}_2$ remained unchanged in comparison with the normoxemia condition. The crucial factors implicated in maximal oxygen delivery and utilization are maximal cardiac output (Q_{max}) and maximal arteriovenous oxygen difference. Oxygen delivery to contracting skeletal muscle, though, is the product of arterial oxygen content and local blood flow. Cardiac output was not measured in the present study, but it appears that Q_{max} is not different in acute hypoxia and normoxia (Hartley et al., 1973; Stenberg et al., 1966). Because, however, the effective solubility of oxygen in blood is increased in acute hypoxia (Shephard,

1971), more O_2 is transported per unit of cardiac output. In addition, when hypoxia is added to exercise, an increase in circulating epinephrine is elicited (Escourrou et al., 1984) which can stimulate muscle glycogenolysis (Richter et al., 1982) and may lead both to metabolic acidosis and increased levels of 2,3 DPG (Klocke, 1972). Both factors, in conjunction with the exercise-induced increase in body temperature, enhance the extraction of O_2 by the muscle via a rightward shift of the oxyhemoglobin dissociation curve (Klocke, 1972). Åstrand and Rodhal (1977) allege that if the pH fell from 7.4 to 7.2, 26 ml of oxygen are liberated from each liter of blood improving the effective oxygen transport by $\sim 12\%$. It has also been shown that during maximal exercise under hypoxic conditions, a more complete tissue extraction of oxygen from the arterial blood, as indicated by decreased mixed venous oxygen content, can fully compensate for a 3% decrease in CaO_2 and partly for an $\sim 10\%$ decrease in CaO_2 (Kaijser, 1970). Although the importance of the aforementioned factors cannot be quantified in the present study, the higher $\dot{V}E/\dot{V}CO_2$ and lower $P_{ET}CO_2$ values observed during mild hypoxemia compared with normoxemia suggest occurrence of metabolic acidosis. Further, since a progressive reduction in $\dot{V}O_{2max}$ with increased hypoxia has been reported (Kollias and Buskirk, 1974), the similar $\dot{V}O_2$ values attained in all conditions suggest that the relative exercise intensity (i.e. $\% \dot{V}O_{2max}$) was slightly higher during mild hypoxemia and even higher during moderate hypoxemia when compared with normoxemia, which further supports the occurrence of increasing metabolic acidosis. Additionally, the lower final $P_{ET}CO_2$ in mild hypoxemia compared with normoxemia indicates the prevalence of hypocapnia in the former condition. Hypocapnia reduces cutaneous (Durand and Martineud, 1971) and visceral (Tucker and Horvath, 1974) blood flow, whereas a local decrease of O_2 tension and pH, which might have occurred in the present study, enhances muscular blood flow (Stanbrook, 1978; Haddy and Scott, 1975). Indeed, Hogan and Welch (1986) found in isolated animal tissue that blood flow to active muscles increases in mild hypoxia, so that oxygen delivery remains relatively constant. Lastly, exercise-induced hemoconcentration could result in an increase in oxygen delivery opposing the detrimental effect of the reduced CaO_2 caused by hypoxemia.

Total work - Moderate hypoxemia: Surprisingly but not uniquely (Hogan et al, 1983; Adams and Welch, 1980), the further reduced level of %SaO₂ in the moderate hypoxemia condition did not change $\dot{V}O_2$ significantly compared with normoxemia, probably due to the previously described mechanisms. Total work, however, was significantly lower. Moderate hypoxemia in the present study drove ventilation to excessive levels, as indicated by a significantly higher $\dot{V}E/\dot{V}CO_2$ comparing with normoxemia and mild hypoxemia, suggesting enhanced effort for compensation of an increased metabolic acidosis in this condition (Wasserman et al., 1987; Adams and Welch, 1980). Indeed, Dempsey et al. (1984) found that the mean pH of a group of highly trained subjects dropped to 7.27 during a 4-min exercise task at 85-90% $\dot{V}O_{2max}$ while breathing hypoxic gas ($F_{IO_2} = 17.5\%$). Moreover, the accumulation of lactate or hydrogen ions (H⁺) has been postulated as a significant factor affecting performance, evaluated as time to exhaustion in an exercise task at 90% $\dot{V}O_{2max}$ (Hogan and Welch, 1984; Adams and Welch, 1980), or at a work intensity assumedly sustainable for ~ 6 minutes (Kaijser, 1970) under hypoxia ($F_{IO_2} = 15-17\%$). In addition, the higher $\dot{V}E/\dot{V}CO_2$ during moderate hypoxemia resulted in a lower level of bicarbonate and buffering capacity, as indicated by the low $P_{ET}CO_2$. Further, the quite low values of $P_{ET}CO_2$ seen during this condition imply hypocapnia which is known to reduce cerebral blood flow (Dempsey et al., 1975); the resulting neurobehavioral impairment (Hornbein et al., 1989) may have contributed to a diminished voluntary effort for maximum performance.

The nonsignificant difference in performance between normoxemia (mean %SaO₂ = 95.93%) and mild (mean %SaO₂ = 90.02%) hypoxemia found in this study suggests that a greater than 6% decrement in %SaO₂ is needed before maximal performance capacity is significantly impaired. Kaijser (1970) found that a higher than 3% decrease in SaO₂ should occur before performance time to exhaustion and maximal oxygen uptake are influenced. Squires and Buskirk (1982) and Horvath et al. (1975) agree that no significant decreases in $\dot{V}O_{2max}$ are noted until SaO₂ is lowered approximately 4% from control values, and Powers et al. (1989) have suggested that a level of ~ 92-93%SaO₂ is sufficient to affect $\dot{V}O_{2max}$.

measurably. Differences in protocols may explain the small discrepancy in the aforementioned results.

Heart rate. In the present study, hypoxemia affected neither the mean HR values nor changes in HR over time (Fig. 6). This result is consistent with the HR responses seen by Squires and Buskirk (1982) in different simulated altitudes for both submaximal and maximal exercise. Although there is conflicting evidence in the literature, many studies agree that maximal HR is not affected by mild levels of hypoxia (Dill et al., 1966; Hughes et al., 1968). The results of the present study are in fair agreement with the above notions, since similar mean values and changes in HR were observed among the experimental conditions, also indicating that equivalent maximal exercise intensities were attained in all three tests.

Ventilatory response. An increased ventilatory response was observed in the two hypoxemic conditions compared with normoxemia. \dot{V}_E was slightly higher during hypoxemia than during normoxemia, with the highest values reached during moderate hypoxemia. The observed differences in \dot{V}_E seem to be accounted for by concurrent changes in respiratory rate, and not by changes in tidal volume. The observed hyperventilatory response during hypoxemia, as indicated by the increased \dot{V}_E/\dot{V}_{O_2} , can be viewed as an attempt to ensure that high alveolar PO_2 levels maintain an adequate driving force for oxygen diffusion across the blood gas interface offsetting the decrease in inspired PO_2 (Dempsey, 1988; Lawler et al., 1988). The $P_{ET}O_2$ values in the present study (Fig. A2) are not very indicative of the concurrent hyperventilation, since they have been affected by the altered F_{IO_2} (Fig. A1) in the hypoxemic conditions. The $P_{ET}CO_2$ excessive decrease in moderate hypoxemia is caused by a disproportional increase in ventilatory drive in this experimental condition, indicated by the high \dot{V}_E/\dot{V}_{CO_2} .

Exercise protocol. In the present study arterial saturation was treated as an independent variable. %SaO₂ was continuously controlled and the impact of its different levels on performance was measured. This approach simulates the real conditions in a competition where the athletes who develop hypoxemia have to sustain this defect for a certain period of time. The 5-min cycle test at maximal intensity used in this study appropriately reflects an exercise task where arterial hypoxemia could occur, since it has been shown that arterial saturation begins to fall at work rates above 70% $\dot{V}O_{2max}$, with the greatest decline occurring at intensities greater than 90% $\dot{V}O_{2max}$ (Powers et al., 1984), and desaturation is more marked during short-term work (Dempsey, 1987).

Being experienced competitive cyclists, and having performed 2-3 practice trials prior to the experimental conditions, subjects were generally able to execute the 5-min performance test appropriately. In some cases, though, changes in motivation or a learning effect seem to have influenced the results. In particular (Table 2): a) the low performance of subject #2 under the "mild hypoxemia" condition could be attributed to reduced motivation on this his last test; b) the increasing performance of subject #4 with each successive test suggests a learning effect more than a condition effect; and c) the low performance of subject #5 in the "normoxemic" test could be due to his participation in an important athletic contest one day following the experiment, and not his real inability to perform better. The suggestion that in all the aforementioned cases the subjects did not achieve maximum performance is supported by the relatively low physiological values of HR, RER, $\dot{V}E$, and respiratory rate at the end of exercise. Carry-over effects like the above are a problem that performance studies with repeated measures designs have to deal with; however, taking steps such as following a counterbalanced design, pretraining the subjects prior to introducing them to the experimental treatments, and allowing sufficiently long breaks between the treatments, minimizes or eliminates carryover effects (Bordens and Abbott, 1988). In the present study all the above steps were taken so that any systematic bias was avoided.

Ear oximeter. The protocol of the present study required that %SaO₂ be read immediately in order to control the saturation levels continuously throughout the performance test. For that purpose ear oximetry was used since, as it has been shown, the ear oximeter is a valid and reliable tool to monitor %SaO₂ continuously during exercise without the insertion of an arterial catheter (Godfrey et al., 1971; Ries et al. 1985, Powers et al., 1989). For most accurate readings, adequate perfusion of the skin of the ear was assured by using a vasodilator cream, and a Hewlett-Packard (HP) 47201A ear oximeter was used which is the most accurate and reliable among the commercially available ear oximeters. The HP ear oximeter gives readings that are very closely correlated ($r=0.90$) with SaO₂ values measured simultaneously directly from arterial blood, over a wide range of oxygenation (Smyth et al., 1986; Cymerman et al., 1989). It has been estimated that blood SaO₂ values above 75% are underestimated by less than 2% by the HP oximeter (Smyth et al., 1986).

In conclusion, in the present study it was demonstrated that maximal performance capacity is significantly reduced in highly trained cyclists working under an arterial oxyhemoglobin saturation level of 87%, but not under a milder desaturation level of 90%. It is speculated that compensatory mechanisms such as enhanced oxygen extraction by the muscle, exercise-induced hemoconcentration, and some increase in muscle blood flow opposed the decreased CaO₂ and, hence, kept $\dot{V}O_2$ unchanged in both hypoxemic conditions. Thus, the reduction in maximal performance capacity may be related to the worsening of the metabolic acidosis elicited by hypoxemia. In particular, the insignificant impact of the 90% level of hypoxemia on maximal performance capacity may be due to the relatively minor contributory effect of this %SaO₂ level on metabolic acidosis, whereas 87%SaO₂ impairs maximal performance significantly, because it exerts a marked effect on the worsening of metabolic acidosis.

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APPENDIX I

REVIEW OF LITERATURE

OXYGEN DELIVERY AS A DETERMINANT OF MAXIMAL AEROBIC CAPACITY

There has been a long-standing debate whether maximal oxygen consumption ($\dot{V}O_{2\max}$), and hence maximal aerobic performance, is limited by the capacity of the oxygen transport system to deliver O_2 to exercising muscle or by the capacity of the muscle to utilize O_2 . Although this issue is still quite controversial, substantial evidence is available now to favor the oxygen delivery to muscle as the essential limiting factor (Wagner, 1988; Ekblom, 1986; Saltin, 1985). This position is inferred from studies where $\dot{V}O_{2\max}$ and/or physical performance have been observed to increase with increasing O_2 partial pressure in inspired air (Bannister and Cunningham, 1954; Kaijser, 1970; Ekblom et al., 1975; Welch and Pedersen, 1981; and others) and after blood transfusion (Buick et al., 1980; Ekblom et al., 1976; Thomson et al., 1982; Williams et al., 1981; and others), whereas it decreases in hypoxia (for review see Welch, 1987), after breathing carbon monoxide (Ekblom and Huot, 1972; Horvath et al., 1975) and after acute anemia (Woodson et al., 1978). Moreover, when specific muscle blood flow is increased by restricting exercise to isolated muscle groups in man, $\dot{V}O_{2\max}$ is also increased well beyond values observed for the same muscle group during whole body exercise (Andersen and Saltin, 1985; Rowell et al., 1986), further supporting the above notion. DiPrampo (1985) has calculated that in two-legged exercise, about 75% of $\dot{V}O_{2\max}$ is set by O_2 transport with the remaining fraction being about equally partitioned between diffusion and perfusion from capillary to cell, and mitochondrial capacity to utilize O_2 . Lawler et al. (1988) theoretically calculated that differences in oxygen delivery can account for 72.1% of the observed differences in the $\dot{V}O_{2\max}$ of trained individuals between hypoxia and normoxia. With respect to hypoxia, however, the higher muscle $[H^+]$ seen under hypoxic conditions compared with the same exercise under normoxic conditions has also been posed as an interacting limiting factor for $\dot{V}O_{2\max}$ (Kaijser, 1970; Lawler, et al; 1988).

RESPIRATORY FACTORS LIMITING PERFORMANCE

It has been traditionally thought that the ventilatory system does not limit performance in normal healthy individuals exercising at sea level. There has been substantial evidence supporting the belief that the capacity and the homeostatic regulatory capability of the pulmonary system is sufficient to achieve and sustain adequate levels of alveolar ventilation and complete alveolar to pulmonary capillary to arterial gas exchange even during maximum short-term exercise or heavy long-term exercise (Dempsey et al, 1980; Wasserman et al., 1981). However, in several newer studies a substantial decline in arterial oxygen saturation has been observed in healthy highly trained individuals during intense exercise, challenging the above concept. The possible mechanisms by which the ventilatory system may fail in its function and thus may limit exercise capacity are the following:

Lung mechanics: The tidal flow:volume loop during exercise has been appraised as informative about possible mechanical ventilatory limitation. As exercise intensity increases, frequency and tidal volume increase and the flow:volume loops expand accordingly. In normal relatively sedentary adult subjects performing exhausting exercise the flow:volume loop rarely approaches its maximum limit during inspiration or expiration (Olafsson and Hyatt, 1969); on the contrary, in fitter healthy young individuals tidal flow:volume at maximal exercise usually "touches" the maximum volitional limit at least on expiration (Grimby et al., 1971; Klas and Dempsey, 1989;), thus limiting expiratory flow and, consequently, ventilation. Effort to further increase the maximal volumes may lead to hyperinflation of the lungs and, thus, to shortening of the inspiratory muscles, to increased elastic work of breathing, reduced efficiency, and greater vulnerability to fatigue (Roussos et al., 1979).

Energetics: It is possible that the demand for energy, and thus blood flow, imposed by the respiratory muscles during heavy, especially prolonged, exercise reduces the amount of O_2 available to the locomotor muscles sufficiently to limit their $\dot{V}O_2$ and exercise capacity. At low and moderate levels of ventilation ($\dot{V}E$), the fraction of $\dot{V}O_2$ consumed by the respiratory muscles ($\dot{V}O_{2\text{ resp}}$) is relatively small (Bartlett et al., 1958), but at levels of ventilation above

100 l·min⁻¹, $\dot{V}O_2$ resp varies from 2 to 8 ml O₂ per liter $\dot{V}E$ (Bye et al., 1983). Thus, according to some authors (Frontera and Adams, 1986; Dempsey et al., 1990) maintaining a large $\dot{V}E$ costs about 10-15% of the total $\dot{V}O_2$ at maximal exercise, while some others have calculated this cost to account for 20% (Shephard, 1966) or even 25% (Bye et al., 1983) of the total $\dot{V}O_{2\max}$. Furthermore, it has been argued (Otis, 1954) that, in theory, a level of ventilation could be reached above which any further increase in $\dot{V}O_2$ would be consumed entirely by the respiratory muscles.

Respiratory muscle fatigue: Respiratory muscle fatigue, defined as the inability of the inspiratory muscles to maintain their maximum capacity for pleural pressure development, could occur during exercise and limit performance. It does not seem likely to occur in short-term exercise of 2-4 minutes at $\dot{V}O_{2\max}$, since the capacity for pressure developed by inspiratory muscles at rest is reached at maximal exercise of short duration in fit subjects (Dempsey et al., 1990). Moreover, the observations that: 1) ventilation remained unchanged when inspiratory and expiratory muscles were "unloaded" during short-term heavy exercise in untrained subjects (Gallagher and Younes, 1989), and 2) diaphragmatic pressure (P_{di}) changes, produced via supramaximal phrenic nerve stimulation at rest, remained unchanged after maximum progressive exercise (Levine and Henson, 1988), provide further evidence against inspiratory muscle fatigue during short-term heavy to maximum exercise. However, when sufficient ventilatory demands are imposed over sufficiently long periods, fatigue may occur at least in some inspiratory muscles. Thus, there are some indications of respiratory muscle fatigue during long-term endurance exercise especially in the highly trained athletes who are capable of maintaining very high metabolic rates and, therefore, high ventilation and respiratory muscle pressures for prolonged time. Maximum volitional P_{di} was reduced following a marathon (Loke et al., 1982), and, also, endurance performance times were improved in athletes working at high exercise intensities (85% and 90% $\dot{V}O_{2\max}$) when their inspiratory muscles were "unloaded" by He:O₂ breathing (Dempsey et al., 1988). Moreover, substantial increase in blood lactate was found after ten minutes of maximum ventilatory effort

with maintenance of alveolar PCO_2 (Cobley et al., 1981). Lastly, studies investigating ventilatory endurance in trained and untrained subjects suggest that ventilatory muscle training may occur during endurance exercise training (Martin and Stager, 1981; Leith and Bradley, 1976). In a recent study (Fairbairn et al., 1991) it was found that four weeks of respiratory muscle endurance training increased the respiratory muscle endurance of highly trained cyclists but had no effect on their maximal exercise ventilation or their maximal cycling performance.

Pulmonary gas exchange: The aforementioned respiratory factors which may set the ventilation at a lower level, in combination with other mechanisms (venoarterial shunt, worsening of ventilation-perfusion inequality, diffusion limitation, and increased extravascular lung water) may inhibit an efficient gas exchange in the lung, leading to arterial hypoxemia and increased alveolar to arterial oxygen difference. Arterial hypoxemia, sufficient to impair performance, has been demonstrated in healthy highly trained individuals exercising at sea level.

INCIDENCE OF EXERCISE-INDUCED ARTERIAL HYPOXEMIA IN HIGHLY TRAINED ATHLETES AT SEA LEVEL

The challenging of the traditional concept which asserts that during exercise the arterial oxygen tension (PO_2) and hemoglobin oxygen saturation (SaO_2) remain close to the resting values over a wide range of work rates began with some scattered observations reported early in the literature. It was in 1919 when Harrop noted that exhausting exercise could reduce the oxygen saturation of arterial blood in normal individuals to 85%. In 1958, Holmgren and Linderholm observed decreases of 16.5 mmHg and 24.6 mmHg in mean arterial oxygen tension (PO_2) after heavy and exhaustive work, respectively, in well-trained junior cyclists. Some years later, Rowell et al. (1964) reported similar results showing a decrease in hemoglobin oxygen saturation (SaO_2) from a resting mean value of 95.7% to a mean of 85.2% at the end of a 3-min exhausting run in four highly trained endurance athletes. However, for

many years the above observations did not receive the deserved attention most probably because the old belief was quite strong and continuously confirmed chiefly by studies using light to moderate work rates unable to demonstrate any decline in arterial PO_2 and SaO_2 (Barr et al., 1964; Hesser and Matell, 1965; Bjurstedt and Wigertz, 1971).

In the last decade, however, increasing interest has been taken in the above issue with a number of studies focusing on the arterial hypoxemia observed during heavy exercise in well trained individuals with a high $\dot{V}O_{2max}$.

A very thorough study on exercise-induced hypoxemia (EIH) was performed by Dempsey et al. (1984). In this study, the incidence of EIH and its determinants were examined on sixteen highly trained runners ($\dot{V}O_{2max} = 72 \pm 2 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) while performing a progressive short-term exercise test on a treadmill. It was found that eight of the sixteen subjects showed reductions in arterial PO_2 of 21-35 mmHg, resulting to an arterial PO_2 of less than 75 mmHg and to less than 60 mmHg in two cases. Percent arterial oxyhemoglobin saturation ($\%SaO_2$) showed a reduction from a resting mean of 97.2% to a mean of 91.9% during exercise.

Hopkins and McKenzie (1989) investigated the relationship among the hypoxic ventilatory response, exercise ventilation, and EIH during heavy exercise in elite athletes from a variety of sports backgrounds. The mean arterial PO_2 and $\%SaO_2$ at the end of a 5-min running test at $\dot{V}O_{2max}$ were 78 mmHg and 92%, respectively. Eight of the 12 subjects participating in the study showed $SaO_2 < 92\%$ indicating development of EIH.

Powers et al. (1988a) attempted to quantify the occurrence of EIH in healthy adults at sea level with particular reference to elite endurance athletes. EIH in this study was defined as a $\%SaO_2$ of $\leq 91\%$ during exercise, and it was found to occur in 52% of the highly trained endurance athletes tested, notably showing high reproducibility ($r = 0.95$, $p < 0.05$). It did not occur in any of the untrained or the moderately trained subjects. The incidence of EIH among highly trained individuals was further documented by more studies where trained and untrained subjects were used and $\%SaO_2$ values during exercise were measured (Williams et

al., 1986; Powers et al., 1988a, 1988b, 1989). In a recent report, Dempsey et al. (1990) asserted that significant EIH (SaO_2 84-92%) was achieved in about 40% of highly trained young athletes and about 15-20% of a group of elderly, fit subjects studied to date.

The development of hypoxemia is more common and severe among athletes with $\dot{V}\text{O}_{2\text{max}} > 65 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ (Dempsey et al., 1984, 1990; Williams et al., 1986; Powers et al., 1988a, 1988b, 1989). It seems that such athletes have developed adaptations in muscle tissue and cardiovascular function which surpass those of the less-adaptive pulmonary system (Rasmussen and Ryan, 1990; Dempsey, 1986). Williams et al. (1986) examined the relationship between $\dot{V}\text{O}_{2\text{max}}$ and $\%\text{SaO}_2$ in highly trained endurance athletes and untrained individuals exercising at 95% $\dot{V}\text{O}_{2\text{max}}$ for 3 minutes and demonstrated that the level of arterial saturation was inversely related to the subject's $\dot{V}\text{O}_{2\text{max}}$. The correlation coefficients were $r = -0.68$, $r = -0.74$, and $r = -0.72$ ($p < 0.05$) for minutes 1 through 3, respectively. Cymerman et al. (1989) found an even higher correlation ($r = -0.81$, $p < 0.02$) between $\dot{V}\text{O}_{2\text{max}}$ and $\%\text{SaO}_2$ during maximal exercise in a group of subjects with a wider range of $\dot{V}\text{O}_{2\text{max}}$ (41.3 to 63.3 $\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$).

It seems that exercise-induced desaturation occurs under certain exercise conditions. The *work load* has to be heavy both in absolute and relative terms. Dempsey et al. (1982) after studying the incidence of EIH in highly trained runners reported that it usually occurs at an exercise intensity higher than 85% $\dot{V}\text{O}_{2\text{max}}$ or at a $\dot{V}\text{O}_2$ of approximately 4 $\text{l}\cdot\text{min}^{-1}$. Powers et al. (1984) monitored $\%\text{SaO}_2$ during incremental arm and leg exercise to exhaustion and found that $\%\text{SaO}_2$ began to fall at work rates above 70% $\dot{V}\text{O}_{2\text{max}}$ with the greatest reduction occurring at work rates greater than 90% $\dot{V}\text{O}_{2\text{max}}$ in both types of exercise. The *type of exercise* may also play a role in the development of EIH, since it was observed that the mean $\%\text{SaO}_2$ at work rates above 90% was higher during arm than during leg work (Powers et al., 1984). Thus, Powers and Williams (1987) alleged that only work involving large muscle groups appears to elicit marked decrease in arterial oxygen tension and hemoglobin saturation with the greatest changes in these factors occurring during treadmill running, whereas

Dempsey et al. (1982) feel that the type of exercise is not so important, since grade walking or level running of sufficient intensity can elicit similar degrees of hypoxemia in a given subject. The *duration of exercise*, though, seems to be critical. Dempsey (1987) reported that significant arterial hypoxemia during heavy prolonged work is seen only rarely. Only three of sixteen runners studied throughout prolonged heavy treadmill exercise developed a consistent reduction in arterial PO_2 . Moreover, when ten runners performed both a short-term exercise task at $\dot{V}O_{2max}$ (2-4 minutes) and prolonged heavy work at $74 \pm 3\% \dot{V}O_{2max}$ for 60-90 minutes, it was observed that during prolonged work only three of the ten runners showed arterial $PO_2 < 80$ mmHg, only one < 70 mmHg, and the rest of them were in the normoxic range, whereas during short-term work eight of ten runners had an arterial $PO_2 < 80$ mmHg, seven of ten < 75 and three < 70 mmHg. Further, since four of seven subjects who developed hypoxemia in short-term maximum work remained in the normoxic levels during prolonged work, it was shown that hypoxemia during short-term exercise was a poor predictor of arterial oxygenation during long-term work (Dempsey, 1987). Lastly, Dempsey et al. (1982) considered also the *immediate exercise history* as an important factor mediating the development of exercise-induced hypoxemia, as some runners who showed sustained hypoxemia during 4-5 min high intensity work at $80-85\% \dot{V}O_{2max}$ of sudden onset, did not develop hypoxemia when the same work load was preceded by many minutes of less intense work and then prolonged. Despite the aforementioned conditions under which EIH is more probable to occur, divergent responses to similar exercise stimuli are often observed, accounted for by individual differences in susceptibility to EIH.

POSSIBLE MECHANISMS UNDERLYING EXERCISE-INDUCED HYPOXEMIA

The mechanisms underlying exercise-induced arterial hypoxemia have not been elucidated yet. However, several potential causes including venoarterial shunt, ventilation-perfusion inequality (VA/Q), hypoventilation, diffusion limitation, and increased extra-vascular lung water have been proposed.

Venoarterial shunt: Intrapulmonary shunting occurs when pulmonary arterial blood goes into the pulmonary veins without passing through the pulmonary capillary bed and postpulmonary venoarterial shunt occurs when small amounts of arterial blood [$\sim 1\text{--}1.5\%$ of the total cardiac output in healthy subjects (Bachofen et al., 1973)] pass via the bronchial venous blood flow and the Thebesian veins directly into the systemic circulation without coursing through ventilated areas of the lung. The result in all the above cases is that poorly oxygenated blood enters the systemic circulation causing a slight decrease in arterial PO_2 . However, the effect of the venoarterial shunt on the decline of PO_2 during exercise does not seem to be large, since breathing hyperoxic gas (Dempsey et al., 1984; Powers et al., 1989) or oxygen (Gale et al., 1985; Torre-Bueno et al., 1985) during exercise has been shown to reverse EIH, indicating that the shunted blood which does not see the increased alveolar oxygen tension is very little.

Ventilation-perfusion inequality: Ventilation-perfusion inequality occurs when some alveoli that are ventilated with air are not perfused with pulmonary capillary blood or, conversely, when some alveoli that are well perfused are not well ventilated. This generally occurs because, due to gravity, the base of the lung receives a greater blood flow than the apex. During low intensity exercise, pulmonary blood flow and alveolar ventilation to the apex appear to increase relatively more than to the base, tending to a more uniform distribution of VA/Q within different areas of the lung. During heavy exercise ($\dot{\text{V}}\text{O}_2 \geq 3 \text{ l}\cdot\text{min}^{-1}$) a minor increase in VA/Q inequality has been found (Gale et al., 1985; Torre-Bueno et al., 1985; Hammond et al., 1986), which, however, is not sufficient to explain alone the widening alveolar-to-arterial O_2 tension difference, and hence arterial hypoxemia, seen during maximal exercise (Hammond et al., 1986). In all the above studies, approximately one third of the observed alveolar-to-arterial O_2 tension difference was due to VA/Q mismatch, and two thirds to alveolar-end-capillary diffusion limitation.

Hypoventilation: Development of arterial hypoxemia has been also related to diminished hyperventilatory response to heavy exercise. In several studies (Dempsey et al.,

1982; Dempsey et al., 1984; Powers et al., 1984; Young and Woolcock, 1978) it has been observed that individuals who demonstrated the greatest arterial hypoxemia exhibited the lowest ventilatory response during heavy exercise. The extremely high metabolic rates achieved by elite athletes during heavy exercise require tremendous ventilatory rates to ensure arterial blood gas homeostasis; it seems, however, that mechanical limits and metabolic cost may restrict the production of sufficient compensatory hyperventilation. Indeed, when helium breathing was used to mechanically unload the respiratory muscles, the hyperventilatory response increased substantially and hypoxemia was partially corrected (Dempsey et al., 1984; Powers et al., 1986). Thus, it appears that ventilatory response to heavy exercise may play a role in the genesis of arterial hypoxemia. Hopkins and McKenzie (1989), however, failed to find any correlation between hypoxic ventilatory response at rest and maximal exercise ventilation or SaO_2 .

Diffusion limitation: Diffusion equilibrium of alveolar gas with end-pulmonary capillary blood may be limited during high intensity exercise due to either insufficient alveolar ventilation to ensure adequate alveolar oxygenation and diffusion gradient, or to diminished red blood cell transit time in the pulmonary capillary secondary to the increase in pulmonary blood flow (Dempsey et al., 1982). Highly trained athletes with metabolic demands of 4-5 l/min and cardiac outputs of 30-35 l/min may exceed the morphological limit of the pulmonary capillary blood volume during heavy exercise so that mean red blood cell transit time in the pulmonary capillary may be as low as 0.25 sec, which is far less than the 0.35 sec required for complete equilibration (Dempsey et al., 1984). Thus, it appears that diffusion limitation secondary to reduced red blood cell transit time in the pulmonary capillary may lead to a reduced arterial PO_2 and hemoglobin saturation.

Increased extra-vascular lung water: There is some indirect evidence from animal and human studies implying that extravascular lung water increases during exercise, thus contributing to diffusion limitation. It has been found, for example, that lung lymph flow increases in exercising sheep in parallel with cardiac output (Coates et al., 1984), and, also,

that following heavy exercise there is an increase in residual and closing lung volumes and a relative tachypnea in humans (Maron et al., 1979; Younes et al., 1984), suggesting small airway closure, presumably secondary to fluid accumulation in the lung. Dempsey (1987), on the other hand, thinks that in the healthy lung, even during extreme exercise, it is unlikely for the accumulated extra-vascular lung water to proceed to the stage of alveolar flooding so as to impair gas exchange severely. Nevertheless, to date, findings are inconclusive.

EXERCISE-INDUCED ARTERIAL HYPOXEMIA IN HORSES

An analogy of human arterial desaturation is found in the very highly trained thoroughbred horse; substantial exercise-induced arterial hypoxemia (SaO_2 84-92%) was present in all such animals studied to date (Dempsey et al., 1990), beginning at workloads requiring only 65-75% of their $\dot{V}\text{O}_{2\text{max}}$ (Bayly et al., 1989) or at $\dot{V}\text{O}_2$ values approximating 50-65 $\text{l}\cdot\text{min}^{-1}$ (Dempsey et al., 1985). However, the physiological basis of arterial hypoxemia during heavy exercise in the horse is somewhat different: The horse, unlike the human, develops substantial CO_2 retention which must be linked to the compulsory nasal breathing and the obligatory association of breathing and striding frequency (Bayly et al., 1989; Attenburrow, 1982). Thus, because of the extraordinarily high $\dot{V}\text{CO}_2$ and $\dot{V}\text{O}_2$, adequate hyperventilatory response to maximal exercise in the horse is not achieved, which in turn contributes to the development of the accompanying hypoxemia. Moreover, unlike humans, VA/Q relationships in the horses are generally found not to deteriorate with heavy exercise (Wagner et al., 1989). However, hypoxemia in horses appears to have little effect on O_2 transport during exercise because of the liberation of red blood cells from their splenic reserve (Thomas and Fregin, 1981).

EFFECT OF EXERCISE-INDUCED HYPOXEMIA ON $\dot{V}\text{O}_{2\text{max}}$ AND AEROBIC PERFORMANCE

The consequence of exercise-induced arterial hypoxemia on aerobic work capacity has been studied recently by Powers et al. (1989) who prevented the development of arterial

hypoxemia in highly trained athletes by using hyperoxic gas. The authors found that increase in %SaO₂ from a mean of 92% to a mean of 96% led to a significant 6-8% increase in $\dot{V}O_{2\max}$. Earlier studies investigating the effect of arterial hypoxemia caused by acute exposure to hypoxia on aerobic work capacity have also reported significant decreases in $\dot{V}O_{2\max}$ with decreasing levels of hypoxemia. Pugh (1967) found that $\dot{V}O_{2\max}$, measured during 4 min of exercise to exhaustion on a cycle ergometer, decreased approximately 10% when maximal exercise %SaO₂ was reduced from 95% at sea level to 86% at an altitude of 2270 m. Kaijser (1970) comparing aerobic performance at different barometric pressures (P_B) (760, 630, and 560 mmHg) found that a higher than 3% decrease in SaO₂ and arterial oxygen content (CaO₂) should occur before performance time to exhaustion and maximal oxygen uptake are affected. Squires and Buskirk (1982) studied the effects of acute exposure to simulated altitudes of 914-2286 m (equivalent to barometric pressures of roughly 680-570 mmHg) on the $\dot{V}O_{2\max}$ of fit subjects, including %SaO₂ at maximal exercise and concluded that a greater than 3.5% reduction in arterial saturation is required before a significant detrimental effect on aerobic capacity is observed. The above conclusion confirmed the finding by Horvath et al. (1975) that a significant reduction in $\dot{V}O_{2\max}$ occurs when SaO₂ is lowered approximately 4% from control values by carbon monoxide replacement of O₂ from the hemoglobin binding sites. The small discrepancies in the results of the above studies can be explained by differences in protocols, in the levels of hypoxemia studied, and in the trained state of the participating subjects. Lawler et al. (1988) have demonstrated that the more highly trained the individuals are, the larger the impairment in sea level $\dot{V}O_{2\max}$ and maximal power output they suffer during acute hypoxia.

Cymerman et al. (1989) correlated $\dot{V}O_{2\max}$ at different simulated altitudes (P_B of 760, 464, 347, 289, and 240 mmHg) with %SaO₂ measured at the time of $\dot{V}O_{2\max}$ and found a strong positive correlation ($r = 0.96$) between $\dot{V}O_{2\max}$ and %SaO₂ measured at the time of $\dot{V}O_{2\max}$. Generally, it seems that $\dot{V}O_{2\max}$ and aerobic performance drops off with decreasing partial pressure of inspired oxygen (for review see Welch, 1987), but the precise relationship

is obscure particularly in the range of mild hypoxia where only few studies have been performed.

Possible mechanisms for altered performance: What is the explanation for the impairment in $\dot{V}O_{2\max}$ and exercise performance when arterial saturation levels decrease? The crucial factors implicated in maximal oxygen delivery and utilization are maximal cardiac output (Q_{\max}) and maximal arteriovenous oxygen difference [(a-v) O_2]. Oxygen delivery to contracting skeletal muscle is the product of arterial oxygen content and local blood flow. When SaO_2 is reduced, either artificially or due to pulmonary insufficiency, CaO_2 is decreased which may lead to decreased oxygen delivery, decreased capillary-to-mitochondrial diffusion gradient, decreased (a-v) O_2 and, consequently, to a reduction in maximal oxygen utilization. Inversely, hyperoxia used to prevent exercise-induced hypoxemia increases $\dot{V}O_{2\max}$ 1) by increasing CaO_2 and thus enhancing the potential for expanding arteriovenous O_2 content difference, and 2) by augmenting mean capillary PO_2 in such an extent that capillary-to-mitochondrial diffusion is enhanced, further widening the (a-v) O_2 (Powers et al., 1989).

However, oxygen delivery may not decrease with changes in CaO_2 . There is evidence (Hogan and Welch, 1986) that blood flow to active muscles increases in mild hypoxia, so that oxygen delivery remains relatively constant. Indeed, during submaximal exercise no effect is seen on $\dot{V}O_2$ unless hypoxemia is severe (Welch, 1987). There are also studies, however, which have found that splanchnic (Rowell et al., 1984) and skin blood flow (Rowell et al., 1982) are not further reduced when moderate hypoxia is added to submaximal exercise, implying that under such conditions muscle blood flow could not increase to keep O_2 delivery constant. During maximal exercise, Q_{\max} is not different in acute hypoxia and normoxia (Hartley et al., 1973; Stenberg et al., 1966). Thus, even though the exercising muscle may have the capacity to vasodilate and increase its flow during hypoxic conditions, since cardiac output cannot increase proportionately, only a minor increase in muscle blood flow can be achieved secondary to further vasoconstriction of the already vasoconstricted, due to maximal exercise, inactive tissues (Welch, 1987).

Exercise-induced hemoconcentration can present an additional increase in oxygen delivery, opposing the reduction in CaO_2 caused by hypoxemia. Thomson et al. (1974) have reported that hemoconcentration induced by prolonged exercise to exhaustion caused a 1.0-1.5 g/100 ml rise in hemoglobin concentration leading to a 0.2 ml/100 ml increase in CaO_2 .

Increasing metabolic acidosis, due to maximal exercise, may also compensate partially for the decreased CaO_2 in hypoxemia by facilitating oxygen unloading from hemoglobin to tissues. The combined effects of increased CO_2 production, decreased pH, increased temperature, and changes in 2,3-DPG occurring during exercise favor a rightward shift in the HbO_2 dissociation curve. It appears that in short-term exercise the Bohr effect (increase in PCO_2 with concomitant decrease in pH) dominates the shift of the curve, whereas in prolonged exercise the temperature effect is predominant (Thomson et al., 1974). Moreover, increased 2,3-DPG synthesis stimulated by short-term exhaustive exercise can contribute significantly to the reduction of hemoglobin affinity for oxygen observed in this type of exercise accounting for ~ 20-50% of the variability in P_{50} (Klein et al., 1980). 2,3-DPG appears to decrease oxygen affinity directly by binding to deoxyhemoglobin and tending to "hold" it in this state, and indirectly by decreasing intracellular pH due to its inability to cross the red cell membrane (Klocke, 1972). Nevertheless, the effect of the rightward shift in the HbO_2 dissociation curve on arterial blood desaturation is considered relatively small (Thomson et al., 1974; Klein et al., 1980).

APPENDIX II

TABLE A1. Power outputs equivalent to 50% and 90% of subjects' $\dot{V}O_{2\max}$.

Subject No.	PO 90 % (Watts)	PO 50 % (Watts)
1	405	201
2	385	188
3	398	192
4	360	171
5	434	215
6	320	154
7	392	184
Mean	384.9	186.4
±SE	13.69	7.49

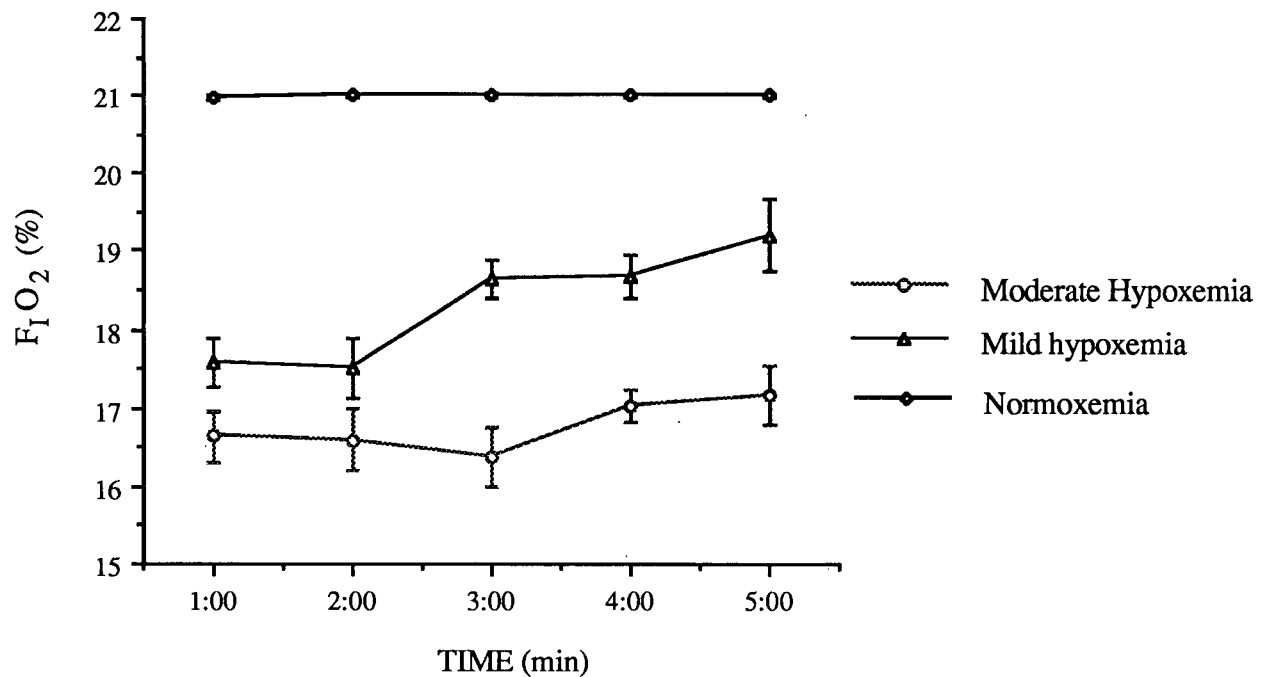


Fig. A1. Mean (\pm SE) inspired oxygen fraction ($F_I O_2$) during the 5-min performance cycle test in the three experimental conditions (normoxemia, mild, and moderate hypoxemia).

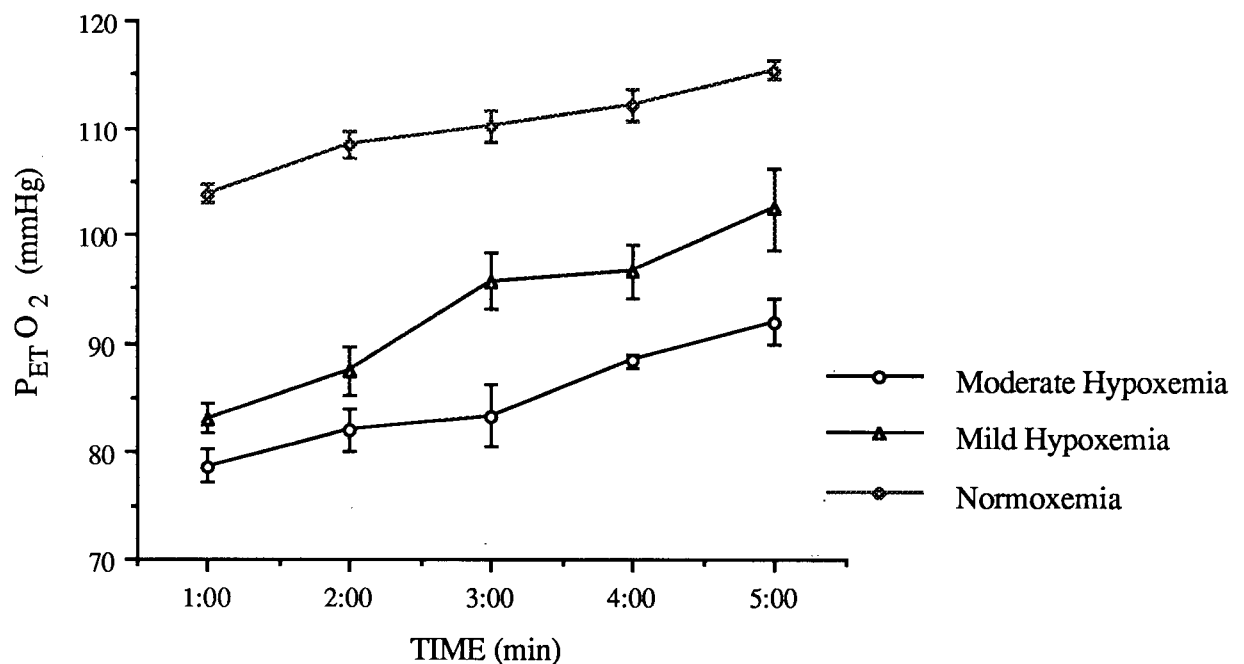


Fig. A2. Time course of mean (\pm SE) end-tidal partial pressure of O_2 ($P_{ET} O_2$) response in a group of young elite cyclists ($n=7$) during a 5-min cycle ergometer test to exhaustion under normoxemia and induced mild and moderate hypoxemia.