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Long-Term Intermittent Hypoxia Increases O_2-Transport Capacity but Not V_{O2max}

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ABSTRACT

Prommer, Nicole, Katja Heinicke, Teresa Viola, Jorge Cajigal, Claus Behn, and Walter F. J. Schmidt. Long-term intermittent hypoxia increases O_2-transport capacity but not V_{O2max}. *High Alt. Med. Biol.* 8:225–235, 2007.—Long-term intermittent hypoxia, characterized by several days or weeks at altitude with periodic stays at sea level, is a frequently occurring pattern of life in mountainous countries demanding a good state of physical performance. The aim of the study was to determine the effects of a typical South American type of long-term intermittent hypoxia on V_{O2max} at altitude and at sea level. We therefore compared an intermittently exposed group of soldiers (IH) who regularly (6 months) performed hypoxic–normoxic cycles of 11 days at 3550 m and 3 days at sea level with a group of soldiers from sea level (SL, control group) at 0 m and in acute hypoxia at 3550 m. V_{O2max} was determined in both groups 1 day after arrival at altitude and at sea level. At altitude, the decrease in V_{O2max} was less pronounced in IH (10.6 ± 4.2%) than in SL (14.1 ± 4.7%). However, no significant differences in V_{O2max} were found between the groups either at sea level or at altitude, although arterial oxygen content (Ca_{O_2}) at maximum exercise was elevated ($p < 0.001$) in IH compared to SL by 11.7% at sea level and by 8.9% at altitude. This higher Ca_{O_2} mainly resulted from augmented hemoglobin mass (IH: 836 ± 103 g, SL: 751 ± 72g, $p < 0.05$) and at altitude also from increased arterial O_2-saturation. In conclusion, acclimatization to long-term intermittent hypoxia substantially increases Ca_{O_2}, but has no beneficial effects on physical performance either at altitude or at sea level.

Key Words: altitude; O_2 content; hemoglobin mass; blood volume; aerobic performance

INTRODUCTION

FREQUENT AND REGULAR CHANGES of altitude are common in many mountainous countries of the world. One major cause is a work place often situated above 3000 m at mines or military bases, which involve a great number of people. Many altitude sojourns last several days to weeks and are interrupted by resting periods at lowland.

This type of altitude change, here called long-term intermittent hypoxia, subjects the body to continuous adaptation and de-adaptation processes, resulting in unpredictable phys-

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iological reactions. It is not known yet whether the time at altitude is sufficient to provoke long-term adaptations or whether only acute reactions occur when ascending and descending. In particular, the impact on physical performance is of practical interest since most activities at altitude are physically demanding.

Until now, the influence of long-term intermittent hypoxia on maximal aerobic capacity (V_{O2max}) has not been examined at either sea level or altitude. Physical performance was studied once in a group of 29 sea-level recruited dwellers working at an altitude between 3800 and 4600 m for 7 days, interrupted by a resting period of 7 days at sea level (Richalet et al., 2002). A successive decrease in maximum performance at sea level reaching −12.3% after 31 months was determined, showing that long-term intermittent hypoxia causes physiological changes that do not seem to be of great benefit, at least at sea level. Data concerning aerobic performance at altitude are missing from the literature.

Regarding the results of studies investigating the impact of acute and chronic hypoxia on V_{O2max}, one would expect that long-term intermittent hypoxia increases V_{O2max} at sea level through chronic adaptation processes, resulting in higher arterial–venous oxygen difference (avD_{O2}; Moore et al., 1992) and higher hemoglobin mass (Schmidt et al., 2002). In addition, studies examining the recently developed training concept of live high, train low show an improvement of V_{O2max} (Levine and Stray-Gundersen, 1997) or physical performance (Saunders et al., 2004). Unchanged (Steinacker et al., 1996; Fulco et al., 1998) and even decreased V_{O2max} values are described in members of altitude expeditions staying several weeks to months above 5000 m (Cerretelli and Binzoni, 1990; Grassi et al., 1996).

The aim of the present study, therefore, was to examine the effect of long-term intermittent hypoxia on V_{O2max} and parameters influencing oxygen consumption such as ventilation, acid–base status, and blood status, both at altitude and at sea level. First results of this study published by Heinicke and colleagues (2003) allow the presumption that V_{O2max} may be increased after 6 months of long-term intermittent hypoxia, since red cell volume was found to increase significantly.

METHODS

Design of the study

The study was performed in the northern Chilean Andes in two regiments of the Chilean army located at sea level (Arica, 0 m) and at 3550 m (Putre). One group of soldiers participating in this study regularly performed hypoxic–normoxic cycles of 11 days at 3550 m and 3 days at sea level. At the time of investigation, this group had previously been exposed to intermittent hypoxia (IH) for 6 months. The two regiments were reached by a 2-h bus drive. The control group (SL) was comprised of soldiers who had also served 6 months in the army, but at sea level (Arica) only. The major advantage of choosing members of the army is their similarity concerning parameters such as age, nutrition, physical activity, and environmental conditions, which thus enables direct comparison.

To determine the effect of long-term intermittent hypoxia on V_{O2max} and its influencing parameters, maximal performance tests were performed by both groups at sea level and at 3550 m as follows:

SL: At sea level 1 week before going to altitude
At 3550 m on day 1 after arriving from sea level
IH: At sea level 1 day after descending from altitude
At 3550 m on day 1 after arriving from sea level

Data were collected from October to December 2000 with the permission of the ethics commission of the Facultad de Medicina de la Universidad de Chile, Santiago.

Test subjects

In total, 30 male subjects entered the study after giving their written informed consent to participate. All were allowed to withdraw from the study without any restrictions. The IH group and the SL group consisted of 15 soldiers each, all of whom were born in Santiago de Chile at 300 m above sea level. SL had no altitude experience before entering the study. All

30 subjects performed some physical activity, consisting of jogging twice a week for 1 h. IH trained only at sea level and had no special training sessions at altitude. For anthropometrical data, see Table 1.

Environmental conditions

The mean ambient pressure on the days of measurement at 3550 m was 501 ± 0.6 mmHg and 504 ± 0.5 mmHg for the SL and the IH groups, respectively. Inspiratory P_{O_2} was 104.7 ± 0.1 mmHg (SL) and 105.3 ± 0.1 mmHg (IH).

General methods

To determine $V_{O_{2max}}$ the subjects performed a maximal performance test using a cycle ergometer (Wilken Monark, Wilken, Berlin, Germany) as follows: after 5 min of warm-up at 40 W, the work load was successively increased by steps of 20 W/min until subjective exhaustion. Oxygen consumption and ventilatory parameters were determined using a portable spirometry system (Meta Max I, Cortex Biophysik, Leipzig, Germany). Heart rate (HR) was measured at 5-sec intervals throughout the test (Polar Accurex Plus, Polar Electro, Kempele, Finland).

Analytical methods

To determine hemoglobin concentration [Hb] and hematocrit (Hct), cubital venous blood samples were drawn after 15 min of seated rest prior to commencement of the maximal performance test and immediately after the subject had reached exhaustion. The blood samples were analyzed directly: [Hb] by using the ABL 520 gas blood system (Radiometer, Copenhagen, Denmark) and the Hct by microhematocrit centrifugation (EBA 21, Hettich, Tuttlingen, Germany) at 21,400 g, 15,000 rpm for 7 min.

Table 1. Anthropometric Data of the Test Subjects

Group	*IH* *n = 15*	*SL* *n = 15*
Age (yr)	18.8 ± 0.4	18.2 ± 0.7
Weight (cm)	65.7 ± 7.8	67.4 ± 8.0
Height (kg)	171.0 ± 5.3	172.0 ± 5.3
BMI	22.5 ± 1.9	22.0 ± 1.7

IH, subjects intermittently exposed to 3550 m; SL, subjects from sea level.

Total hemoglobin mass (tHb) was determined using the CO-rebreathing method at altitude on day 2 (IH) and at sea level before ascending to altitude (SL; see Heinicke et al., 2003). Blood volume (BV) was also calculated for day 2 at sea level (IH) and for day 2 at altitude (SL) using the following formula:

$$BV = (tHb \cdot 100) \cdot ([Hb] \cdot 0.91)^{-1}$$

Since tHb did not change within the days of measurements, the prevailing [Hb] could also be used to calculate BV for rest and exercise conditions at both altitudes. Plasma volume (PV) was calculated using the prevailing Hct values (see Heinicke et al., 2003). Part of the data describing tHb, BV, and PV of SL (i.e., group SL under resting conditions only) have been published previously by Heinicke et al. (2003).

Blood samples for determination of the blood gas and acid–base status before and immediately after the ergometer test were drawn from a hyperemic earlobe and analyzed using the ABL 520 system. Hemoglobin oxygen half-saturation pressure (P_{50}) was monitored under the prevailing in vivo conditions and subsequently corrected to standard conditions (pH 7.4) using the Bohr coefficient (−0.46) as described by Böning et al. (1978).

Plasma lactate concentration [Lac^-] was measured enzymatically (Accusport, Sports Resource Group, USA) before and 3 min after completion of the test. Arterial oxygen saturation (Sa_{O_2}) was measured continuously throughout the test using a finger pulse oximeter (9500 Onyx, Nonin Medical, Plymouth, MN, USA). The values reached at the end of every step were used for calculation.

In vivo buffer capacity ($BC = \Delta Lac^-/\Delta pH$) was calculated with and without correction for ventilation according to Böning and colleagues (2001).

Statistics

All data are presented as arithmetic mean values (x) with standard deviation (SD). Analysis of variance with repeated measurements was per-

formed to test the influence of altitude and differences in the group's response. To evaluate the significance of special differences between the IH and the SL groups at sea level and at altitude, an unpaired *t*-test was performed. A paired *t*-test was used to identify significant differences within each group at the different altitudes. A linear regression analysis was applied to evaluate whether the decrease in V_{O2max} in hypoxia depends on aerobic performance at sea level.

RESULTS

The results of the maximal performance tests at 0 and 3550 m of SL and IH are described next. HR and respiratory parameters were measured continuously during the whole test procedure, whereas [Hb], blood gas, and acid–base status were determined before and at the end of the test.

Respiratory data and heart rate during the maximal performance test

Under submaximal conditions, no differences in V_{O_2} were observed between groups at either altitude, whereas V_{O2max} (Table 2) decreased in a group-specific manner (ANOVA $p < 0.05$). Although the absolute V_{O2max} values did not differ between the groups at both altitudes (decrease from 46.7 ± 4.6 mL/kg/min to 41.7 ± 4.5 mL/kg/min in IH and from 49.7 ± 6.5 mL/kg/min to 42.5 ± 4.5 mL/kg/min in SL), IH showed a tendency to lower values at sea level (0 m: $p = 0.19$, 3500 m: $p = 0.66$). The altitude-related decrease, however, was significantly lower in IH (−5.0 mL/kg/min vs. −7.2 mL/kg/min; see Table 2).

In both groups ventilation (V_E) was increased at altitude during submaximal exercise, whereas maximal V_E was only higher at altitude in IH (Table 3). Comparing IH and SL, V_E was significantly higher in IH during submaximal exercise at both altitudes.

A similar but more significant picture was exhibited by the ratio V_E/V_{O_2} (Table 3), demonstrating a higher respiratory stimulus at altitude, especially in the IH group.

Analysis of the alveolar partial pressure for oxygen (P_{O2alv}, Table 4) revealed an increase during the tests, with markedly lower values at 3550 m. No significant differences, however, were apparent between the groups.

HR during submaximal exercise was higher at altitude in both groups (Table 3), whereas maximum heart rate was only significantly different in SL, who showed lower values at altitude.

Hematological data and acid–base status at rest and maximum exercise

[Hb] (Fig. 1A) and Hct (Table 2) were significantly increased at altitude in both groups. IH

TABLE 2. V_{O_2MAX}, HEMATOLOGICAL STATUS, AND BUFFER CAPACITY AT SEA LEVEL AND 3550 M

	IH		*SL*	
	0 m	*3550 m*	*0 m*	*3550 m*
V_{O_2max} (mL/kg/min)	$46.7^{\#} \pm 4.6$	41.7 ± 4.5	$49.7^{\#} \pm 6.5$	42.5 ± 4.5
ΔV_{O_2max} (mL/kg/min)		$-5.0 \pm 2.1^{*}$		-7.2 ± 2.9
ΔV_{O_2max} (%)		$-10.6 \pm 4.2^{(p = 0.058)}$		-14.1 ± 4.7
tHb-mass (g)		$836 \pm 103^{*}$	751 ± 72	
PV (mL)	$3334^{\#} \pm 459$	3089 ± 366	$3528^{\#} \pm 375$	3013 ± 358
Hct (%)	$46.6^{\dagger} \pm 3.1^{***}$	48.7 ± 4.0	$42.9^{\#} \pm 1.7$	46.7 ± 2.0
BC (mmol/L)	62.1 ± 14.9	59.2 ± 9.9	61.7 ± 15.3	75.0 ± 16.7
BC_{corr} (mmol/L)	48.7 ± 9.5	52.2 ± 7.2	49.2 ± 10.8	58.9 ± 9.6

ΔV_{O_2max}, decrease in V_{O_2max} at 3550 m either expressed as an absolute or relative term; tHb-mass, total hemoglobin mass measured at sea level in SL and at altitude in IH; PV, plasma volume; BC, in vivo buffer capacity; BC_{corr}, ventilation-corrected BC ($p_{CO_2} = 40$ mmHg).

Significant differences within a group at different altitudes are indicated by†, $p < 0.05$, $^{\ddagger}p < 0.01$, #, $p < 0.001$. Significant differences between the groups at identical altitude are indicated by *, $p < 0.05$, **, $p < 0.01$, ***, $p < 0.001$.

showed higher values under all conditions, especially at sea level. During exercise, [Hb] increased by approximately 10% in both groups (Fig. 1A).

tHb was 85 g (11.3%) higher in IH compared to SL (Table 2). BV (Fig. 1B) was identical in both groups at sea level and significantly decreased at altitude, particularly in SL (ΔBV in SL: -556 ± 184 mL; in IH: -238 ± 306 mL; $p < 0.01$). PV (Table 2) tended to be lower in IH at sea level compared to SL, but showed no differences at altitude.

The loss in BV during exercise (Fig. 1B) was similar in both groups (SL: -595 ± 180 mL, IH: -535 ± 176 mL) and was slightly attenuated at altitude (SL: -449 ± 161 mL, IH: -442 ± 135 mL).

Data for blood gas and acid–base status are presented in Table 4. All values were markedly influenced by altitude and additionally by exercise. Comparing the groups at altitude, partial pressure for oxygen in arterialized blood (Pa_{O_2}) reached significantly higher values in IH before and at the end of exercise. Resting alveolar–arterial oxygen difference (AaD_{O_2}) at 3550 m did not differ between the groups; however, at maximum exercise it was substantially lower in IH (SL: 25.3 ± 2.9 mmHg, IH: 20.3 ± 3.4 mmHg; Fig. 1C).

Sa_{O_2} was markedly reduced at altitude without significant differences between IH and SL. At the end of exercise at 3550 m, Sa_{O_2} was significantly higher in IH compared to SL (Fig. 1D). Resting partial pressure for carbon dioxide in arterialized blood (Pa_{CO_2}) was lower in IH at altitude, but no difference was apparent at maximum exercise. Regarding pH, higher values were found in IH under resting conditions at altitude and at the end of exercise at sea level.

Under in vivo conditions hemoglobin oxygen affinity (p_{50}) did not show any differences between groups at sea level. At altitude p_{50} tended to increase in both groups under resting conditions and was significantly higher in IH than in SL at the end of exercise (Table 4). When corrected to standard conditions (pH 7.4) p_{50} was significantly increased at altitude in both groups, whereas IH showed slightly higher values than SL at sea level and altitude.

$[Lac^-]$ increased similarly in both groups at altitude. In IH $[Lac^-]_{max}$ tended to be lower at sea level than at altitude, but did not differ significantly for SL (Table 4).

The in vivo buffer capacity was similar in both groups and was not affected by altitude (Table 2).

DISCUSSION

The present study was performed to examine the effects of long-term intermittent hypoxia in subjects regularly commuting between 3550 m and 0 m. Although this pattern of hypoxia concerns a great number of people, it is only rarely investigated and virtually no data are available on aerobic performance. Therefore, $V_{O_{2max}}$ and its influencing parameters were determined at altitude and at sea level. The key result is that despite 6 months of acclimatization no difference in $V_{O_{2max}}$ was found between intermittently exposed subjects either at altitude or at sea level. The altitude-related decrease, however, was less pronounced in the acclimatized group.

In contrast to long-term intermittent hypoxia, the impact on $V_{O_{2max}}$ due to acute and chronic hypoxia at altitude and at sea level has

Table 3. Cardiorespiratory Data Obtained During the Vita Maxima Tests at Sea Level and 3550 m

	IH_{0m}		SL_{0m}		IH_{3550m}		SL_{3550m}	
	100 W	*Max*	*100 W*	*Max*	*100 W*	*Max*	*100 W*	*Max*
V_E (L/min)	48# ± 6**	129# ± 18	39# ± 6	132 ± 12	59 ± 7*	150 ± 28	52 ± 6	140 ± 22
V_E/V_{O_2}	28.2# ± 2.3***	43.2# ± 5.3	24.5# ± 2.2	42.1# ± 5.4	35.1 ± 3.8*	55.2 ± 8.7*	32.0 ± 2.7	49.2 ± 5.6
HR (b/min)	130# ± 12	188 ± 7	128‡ ± 12	192# ± 8	137 ± 14	185 ± 6	137 ± 9	183 ± 7

V_E, ventilation; HR, heart rate; IH_{0m}, IH_{3550m}, SL_{0m}, SL_{3550} indicate groups at specific altitudes; Max, maximum exercise.

For statistical information see Table 2.

TABLE 4. ALVEOLAR AND BLOOD GAS STATUS AS WELL AS ACID–BASE BALANCE BEFORE AND AT MAXIMUM EXERCISE AT SEA LEVEL AND AT 3550M

	IH_{0m}		SL_{0m}		IH_{3550m}		SL_{3550m}	
	Rest	*Max*	*Rest*	*Max*	*Rest*	*Max*	*Rest*	*Max*
pO_{2alv} (mmHg)	106.6# ± 2.6	126.6# ± 2.3	100.2# ± 3.4	125.2# ± 2.3	65.6 ± 2.4	81.0 ± 3.3	63.0 ± 1.1	79.5 ± 1.9
Pa_{O_2} (mmHg)	89.6# ± 5.0*	88.2# ± 5.3	84.7# ± 5.9	89.7# ± 5.5	56.8 ± 4.3*	60.7 ± 4.5***	53.7 ± 2.9	54.2 ± 3.0
Ca_{O_2} (mL/100 mL)	20.8 ± 0.9***	21.8 ± 1.1***	19.3 ± 0.8	20.4 ± 0.9	20.4 ± 1.4**	20.2 ± 1.2***	18.8 ± 1.1	18.4 ± 1.0
Pa_{CO_2} (mmHg)	38.3# ± 2.3*	33.9# ± 3.1	40.5# ± 2.3	35.2# ± 4.4	30.3 ± 1.5***	27.3 ± 3.6	33.3 ± 1.4	28.5 ± 2.5
[Lac-] (mmol/L)	1.3 ± 0.7	11.0# ± 2.3	1.0 ± 0.2	12.5 ± 1.9	1.4 ± 0.2	14.1 ± 1.3	1.7 ± 0.8	13.7 ± 1.5
pH	7.416# ± 0.011	7.255 ± 0.37*	7.408# ± 0.019	7.214# ± 0.054	7.464 ± 0.014**	7.241 ± 0.034	7.443 ± 0.016	7.268 ± 0.048
HCO_3 (mmol/L)	24.0# ± 1.4	14.6# ± 1.5	25.1# ± 1.2	13.8 ± 2.2	21.4 ± 0.09*	11.4 ± 1.6	22.4 ± 1.0	12.7 ± 1.8
$P_{50in\text{-}vivo}$ (mmHg)	25.9 ± 0.4	32.0‡ ± 1.9	25.4‡ ± 0.7	33.6 ± 2.3	26.3 ± 0.9	34.1 ± 1.6*	26.5 ± 0.6	32.5 ± 1.5
$P_{50pH\text{-}7.4}$ (mmHg)	26.3# ± 0.4**	27.6# ± 0.8	25.6# ± 0.7	27.5+ ± 0.9	28.2 ± 0.8*	29.0 ± 0.6*	27.8 ± 0.6	28.3 ± 0.7

P_{O_2alfr}, alveolar partial pressure for oxygen; Pa_{O_2}, partial pressure for oxygen in arterialized blood; Ca_{O_2}, arterial oxygen content; Pa_{CO_2}, partial pressure for carbon dioxide in arterialized blood; [Lac^-], lactic acid concentration in arterialized blood; P_{50}, hemoglobin oxygen half-saturation pressure under prevailing ($P_{50\ in\ vivo}$) and standardized conditions ($P_{50\ pH\text{-}7.4}$).

For abbreviations and statistical information see Table 2.

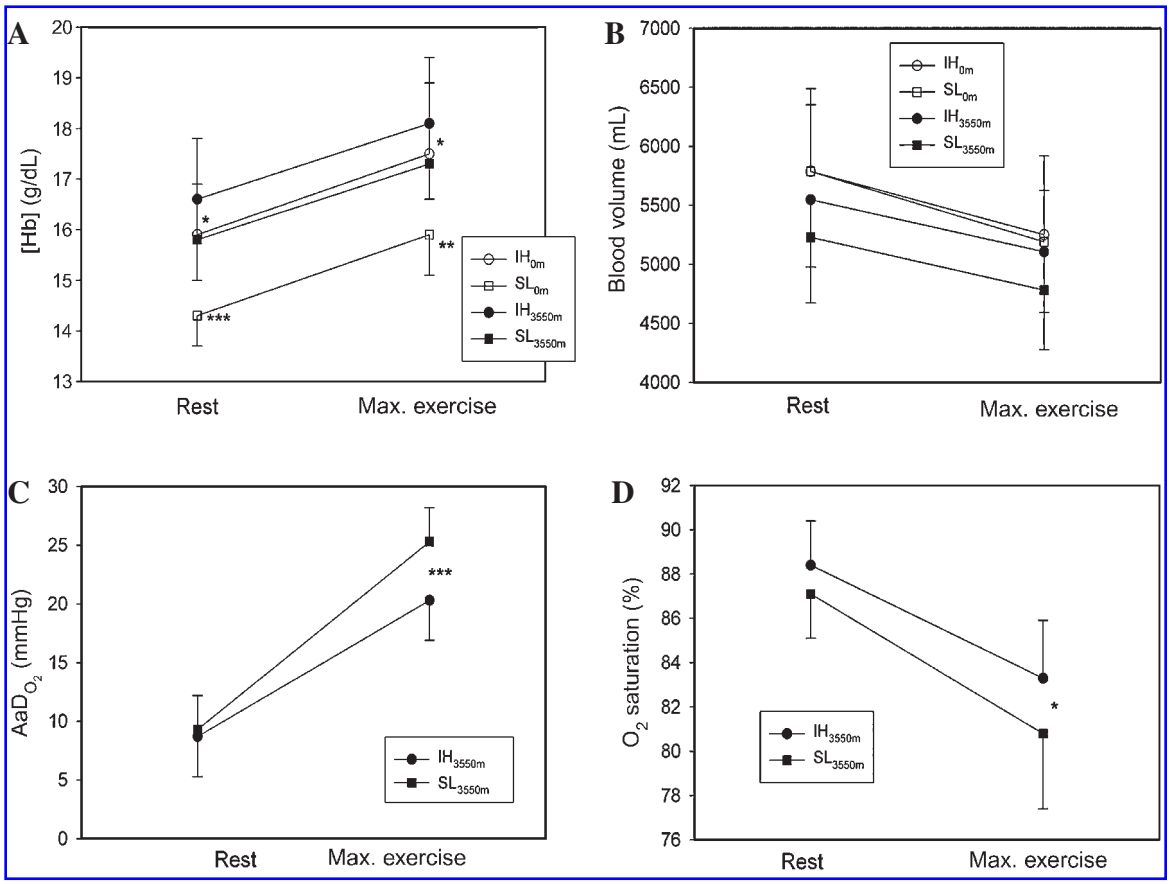

FIG. 1. Hemoglobin concentration ([Hb]): **A,** total blood volume; **B**, alveolar–arterial O_2 difference (AaD_{O_2}, and **C**, arterial O_2 saturation; (**D**) at rest and maximum exercise at sea level (**A, B**) and at 3550 m. Values are presented as mean ± SD. IH_{0m}, SL_{0m}, IH_{3550m}, and SL_{3550} indicate the intermittently exposed group and the sea-level group at the specific altitudes. Significant differences between IH and SL at sea level and at altitude are indicated by *, $p < 0.05$; **, $p < 0.01$; and ***, $p < 0.001$.

been investigated intensively. Several previous studies performing maximal performance tests at altitude have already shown consistently that $V_{O_{2max}}$ decreases above 700 to 900 m with increasing altitude in untrained subjects (Terrados et al., 1985; Grover et al., 1986). Similarly, in our study $V_{O_{2max}}$ was decreased at altitude in both IH and SL, by 11% and 14%, respectively. This is slightly lower compared to results of other studies at this altitude, yet still in the normal range (Fulco et al., 1998). As demonstrated in Fig. 2, there was a strong relationship between $V_{O_{2max}}$ at sea level and its decline at altitude in SL. This is in accordance to Fulco and colleagues (1998), showing a steeper decrease in subjects with higher $V_{O_{2max}}$ at sea level, suggesting that the oxygen transport system may be the limiting factor for better-performing subjects. The fact that this relationship cannot be shown for IH indicates that maximal performance in this group is limited by other mechanisms.

This assumption is supported by the finding that values for tHb were 11% higher in IH compared to SL (Table 2). According to the strong relationship between tHb and $V_{O_{2max}}$ (Gore et al., 1997), one should therefore expect an approximately 7 mL/kg/min higher $V_{O_{2max}}$ in IH. Surprisingly, no significant differences between IH and SL were obvious in $V_{O_{2max}}$ either at sea level or at altitude (Table 2). Contrary to expectations, IH tendentiously showed even lower values at sea level (~6%).

Comparable data for intermittently exposed subjects at altitude is not yet available. Richalet and colleagues (2002), however, found a progressive decrease in performance at sea level, reaching −12.3% after 31 months despite increased Hct values, in dwellers working at

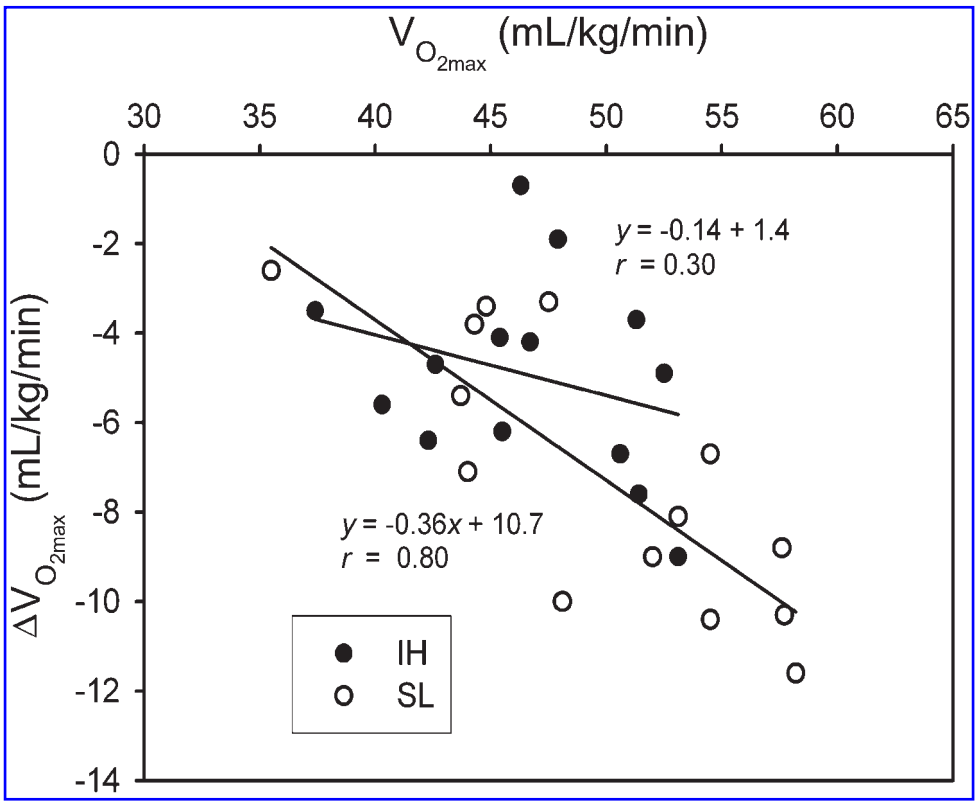

FIG. 2. Relationship between $V_{O_{2max}}$ determined at sea level and its percentage decrease at 3550 m. IH and SL indicate the intermittently exposed and the sea-level group, respectively.

altitudes between 3800 and 4600 m for 7 days, interrupted by a resting period of 7 days at sea level. This result supports our concept that performance in intermittently exposed subjects is not primarily limited by the arterial oxygen content (Ca_{O_2}).

To explain the reasons for similar $V_{O_{2max}}$ in IH compared to SL, the AaD_{O_2} and cardiac output (Q) will be discussed in detail. Because no data exist on long-term intermittent hypoxia, we will specifically refer to a study of Calbet and colleagues (2003), who showed no changes in $V_{O_{2max}}$ after chronic altitude adaptation (10 weeks at 5260 m) either in normoxia or in acute hypoxia.

Arterial–venous oxygen difference

Ca_{O_2} in arterialized blood was calculated using [Hb], Huefner's number (1.39), and Sa_{O_2}. Ca_{O_2} (Table 4) was significantly higher in IH at 3550 m, accounting for 6.3% just before and 8.9% at the end of the test compared with SL. Similarly, at sea level, Ca_{O_2} was elevated by 11.7% both before and at maximum exercise.

Because Sa_{O_2} did not differ between the groups either before or at the end of test (Fig. 1D), the significantly improved oxygen availability in IH at sea level must be due solely to an increased [Hb] of on average 1.6 g/dL. At altitude, the higher Sa_{O_2} in IH compared with SL at the end of the maximal performance test also contributes to the increased Ca_{O_2}. The elevated Sa_{O_2} in IH is due to an increased Pa_{O_2} (Table 4), which in turn can be explained by slightly higher alveolar ventilation (Table 3) and substantially smaller AaD_{O_2}. This beneficial decrease in AaD_{O_2} following altitude acclimatization is due to improved oxygen diffusion in the lung and can be attributed to an improved blood diffusing capacity, since membrane diffusing capacity has previously been shown to remain unchanged (Calbet et al., 2003). As a consequence of the fundamental advantage of higher oxygen availability in IH, one would again assume increased $V_{O_{2max}}$ compared with SL. Moreover, as Di Prampero and Ferretti (1990) have docu-

mented, the limitation of $V_{O_{2max}}$ is 70% dependent on oxygen availability.

Cardiac output

One further determining parameter of $V_{O_{2max}}$, Q, was not measured directly in this study, however, its behavior can be assumed by the results of Calbet and colleagues (2003). They showed a considerably reduced Q in chronic as well as in acute hypoxia, which was immediately restored under normoxic conditions even in the acclimatized subjects. The underlying mechanism may be the arterial P_{O_2} influencing central nervous functions or the heart directly.

Referring to our data, we conclude that a similar reduction in Q under hypoxia in both groups and a complete recovery in IH under normoxia at sea level occur. This is supported by the behavior of Pa_{O_2}, which did not differ between the groups at sea level and was lower at altitude in SL, suggesting an even more pronounced inhibition of Q.

In addition to the findings of Calbet and colleagues (2003), we may also state that a reduction in BV, and therefore in venous return, may contribute to the decrease in Q. We found a decrease in BV at altitude, which was more pronounced in SL (−318 mL) and further reduced during exercise in both groups by approximately 440 mL. These results also suggest that Q is not more diminished in IH than in SL.

Oxygen extraction

One remaining explanation for the unexpected low $V_{O_{2max}}$ in IH, especially at altitude, may be a decreased oxygen extraction from the tissue compared with SL. Reasons could be (1) increased O_2 affinity, (2) decreased tissue perfusion, or (3) impaired metabolic capacity.

Unfortunately due to circumstances of the study, only some of the mentioned parameters were measured directly; however, indirect parameters may help in evaluating their probability of existence.

1. The first hypothesis can be neglected since the resting oxygen dissociation curve (OCD) represented by $P_{50\text{in vivo}}$ does not differ between both groups (Table 4). During maximal exercise at altitude, the curve is shifted rightward in IH compared to SL, suggesting improved oxygen diffusion to the tissue (Böning et al., 1975). When considering oxygen affinity under standardized conditions, $P_{50\text{pH-7.4}}$ is generally higher in IH, proving a medium-term intraerythrocytic metabolic acclimatization, probably due to elevated diphosphoglycerate concentration (2,3-DPG), enhancing O_2 delivery.
2. One indicator of the assumed decreased tissue perfusion could be the high ventilation of IH (Table 3). According to Dempsey and colleagues (1996), high ventilation delimits exercise performance as soon as work intensity reaches values above 80% of $V_{O_{2max}}$. Following their arguments, this is due to a disproportionate rise in metabolic and circulatory costs of respiratory muscles, which then leads to circulatory competition between diaphragm and working extremities. Therefore, blood circulation is inadequate in both components (working muscles and diaphragm), thus provoking exhaustion. A deteriorated distribution of cardiac output between working and inactive muscle tissue has also been reported following altitude adaptation by Calbet and colleagues (2003). They showed that the amount of blood flow directed to noncontracting tissue was 37% higher in chronic hypoxia compared with acute hypoxia, therefore reducing the amount of flow to the exercising muscles.

   On the other hand, Hoppeler and colleagues (1990) and Howald and colleagues (1990) document improved muscle perfusion at rest and during exercise following altitude sojourns above 5000 m as a result of increases in muscle capillary density due to a loss of muscle mass. Another factor leading to improved capillarity may be the hypoxia-induced HIF-1 VEGF cascade, which has also been shown by Hoppeler and Vogt (2001). Both findings imply a reduction in muscle diffusion distances which should facilitate oxygen transport to mitochondria, counteracting the negative effects of increased Hct on blood flow (e.g., Miyamoto, 2005) and distribution mismatch (Calbet et al., 2003).
3. In addition to the lower contracting muscle perfusion, oxygen extraction may also dete-

riorate as a result of a decrease in muscle mitochondria volume density. In fact, Favier and colleagues (1995) report a 19% decrease in mitochondrial density in altitude residents from 3400 to 3600 m. This crucial point is confirmed by Hoppeler and colleagues (2003), who state that the mitochondrial content of muscle is reduced in all subjects who spend long time periods at high altitude.

All these variations in muscle structure and function arising from altitude acclimatization would confirm our hypothesis of a deteriorated metabolic capacity in IH, which is mirrored by the low V_{O2max} at sea level. When commuting to altitude, however, the higher oxygen availability allows utilizing a higher fraction of metabolic capacity and therefore reduces the altitude-related decrease in V_{O2max}.

Acid–base status

A decrease in V_{O2max} is frequently attributed to increased acidosis and reduced buffer capacity. In this study, however, buffer capacity is similar in both groups (Table 2), and there is no evidence that pH (Table 4) is a determining factor of performance in IH. Similar observations were made by Juel and colleagues (1990) and Street and colleagues (2001), who also disproved any correlation between blood pH and termination of exercise.

Lower [Lac^-] and corresponding higher pH after exercise have often been documented following return from altitude sojourns (Green et al., 1989; Grassi et al., 1996) and are also supported by the results found in IH. Although no definite explanations are available as yet, it is assumed that alterations of metabolism as a consequence of reduced carbohydrate availability and increased fat oxidation could be a reason. Furthermore, a decline or delay of lactic acid release from the muscle cell to the blood (Böning et al., 2001), an improved consumption of lactic acid (Bender et al., 1989), and an improved transport capacity for [Lac^-] and H^+ across the erythrocyte membrane (Juel et al., 2003) have also been discussed. Moreover, higher PV at sea level (Table 2) also contributes to reduced [Lac^-].

CONCLUSION

In conclusion, acclimatization to long-term intermittent hypoxia does not increase V_{O2max} either at sea level or at altitude. This seems to be surprising since total hemoglobin mass, hemoglobin concentration, and arterial oxygen content are all elevated, and therefore oxygen diffusion to the tissue should be in favor. It is assumed that these advantages are abolished by decreased perfusion of the tissue due to deteriorated blood distribution to the working skeletal muscle and by a reduction of muscle mitochondrial volume density, respectively.

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