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INTERMITTENT HYPOXIA DOES NOT AFFECT ARTERIAL OXYGEN SATURATION AT REST DURING SHORT-TERM EXPOSURE TO SIMULATED ALTITUDES UP TO 4000 M*

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Abstract

Introduction: Intermittent hypoxia (IH) is assumed to prevent acute mountain sickness by inducing aspects of acclimatization. Although several studies have considered IH for prophylaxis of acute mountain sickness, no systematic results are available.

Objective: To investigate the effects of IH on resting physiological parameters during exposure to different simulated altitudes up to 4000 m.

Methods: Nine healthy male volunteers (26 ± 4 years) were exposed to different levels of normobaric hypoxia corresponding to altitudes of 1000 m, 2000 m, 3000 m, and 4000 m (random order, single blinded). After 20 minutes at rest ventilation, arterial oxygen saturation, heart rate, and blood lactate concentration were measured. After a pre-acclimatization program (IH: 7 x 1 hour at rest, corresponding altitude 4500 m) the identical test procedure was repeated. A two-way ANOVA with repeated measures was used to detect effects of IH and altitude. *P*-values < 0.05 (two-tailed) were considered to indicate statistical significance.

Results: Arterial oxygen saturation decreased with altitude, but there was no effect of IH. Blood lactate concentrations were lower after IH irrespective of altitude.

Conclusions: The present results do not indicate that the applied IH protocol improved arterial oxygen saturation during subsequent exposures to altitudes up to 4000 m. However the reduced blood lactate concentrations may suggest an AMS-prophylactic effect of IH by reducing catecholamine levels during subsequent high-altitude exposures.

Key words: *high altitude, pre-acclimatization, normobaric hypoxia, ventilation*

Introduction

Exposures to high altitude are associated with a decline in endurance performance [1] and the risk for high altitude illnesses of which acute mountain sickness (AMS) is the most common [2]. AMS is characterised by unspecific symptoms like headache, dizziness, nausea, vomiting, loss of appetite, fatigue and insomnia [3]. Although usually benign and self-limiting the presence of AMS markedly compromises the feeling of well being, reduces the chance to reach the summit and to return safely, and may progress to life-threatening high altitude pulmonary (HAPE) or cerebral edema (HACE) [2]. Among other factors the degree of altitude acclimatization determines the risk to develop AMS with a lower risk in well acclimatized compared to non acclimatized persons [4].

Adaptations in ventilatory regulation (ventilatory acclimatization) play an important role in the complex altitude acclimatization process leading to a progressive increase in ventilation and arterial oxygen saturation (SaO_2) within the first hours to days during an acute continuous hypoxic exposure [5]. The increase in hypoxic ventilatory response (HVR) has been shown to be an essential mechanism of early ventilatory acclimatization [6]. Therefore pre-acclimatization strategies increasing the HVR may have the ability to reduce the risk for AMS during a subsequent hypoxic exposure by improving SaO_2.

Intermittent hypoxia (IH) is defined as repeated exposures to hypoxia interspersed by normoxic periods [7] including a broad variety of IH protocols defined by the degree of hypoxia, the duration of the single hypoxic exposures, the relation between hypoxic and normoxic periods and the duration of the whole IH application. Several studies reported positive effects of IH at sea level, e.g. an optimized running economy in athletes [8,9] or improved exercise tolerance in elderly persons and patients [10,11]. Furthermore IH applying repeated (7 to 12 times) short-term exposures (0.5 to 2 hours) to normobaric or hypobaric hypoxia (inspired fraction of oxygen of 11 to 13% or 4500 m) increases the HVR [12-19]. Therefore a pre-acclimatization program using repeated short-term hypoxic exposures may prevent AMS by inducing ventilatory

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acclimatization [20]. Previous studies dealing with the AMS prophylaxis by IH applied hypoxic exposures of longer duration and did not provide systematic results on IH effects [21,22]. Therefore the present study was conducted to add systematic findings to the present knowledge on altitude-dependent effects of pre-acclimatization by IH applying repeated short-term hypoxic exposures.

Methods

Study participants

Nine healthy male volunteers (age 26 ± 4 years, height 179 ± 4 cm, body mass 75 ± 5 kg, all non smokers) participated in the study. All study participants had their residence ≤ 850 m and had no exposure > 2500 m during the previous 4 weeks. Written consent was obtained from each individual. The study was conducted at the Department of Sport Science of the University Innsbruck (Austria) at an altitude of 600 m and was approved by the Institutional Review Board of the Department of Sport Science (University Innsbruck).

Study protocol and measurements

The pre tests (pre) were performed in a normobaric altitude chamber (Hypoxico Altitude Training Systems, Köln, Germany) under 4 different simulated altitudes. The simulated altitudes and the corresponding inspired fractions of oxygen (F_IO_2) were: 800 m (0.204), 2000 m (0.176), 3000 m (0.155), and 4000 m (0.135). F_IO_2 was continuously controlled during each test (Multiwarn II, Dräger, Lübeck, Germany). Each subject started with the test at 800 m. The order between the 3 following tests was randomly balanced in a single-blind fashion to eliminate possible training and acclimatization effects by the testing procedure. The 4 tests were completed within 2 days and with 2 tests per day and a recovery period of at least 4 hours between tests. Mean ambient temperature and humidity during the tests conditions were kept between 23 and 26 degree Celsius and 36 and 44% respectively.

After a 20-minute lasting resting exposure in the chamber SaO_2 was measured by finger pulsoxymetry (Onyx 9550, Nonin, Plymouth, USA). The mean of the minimum and the maximum values observed during a 30 second period was included into the analyses. Ventilatory parameters (Oxycon mobile, Viasys Healthcare, Höchberg, Germany) and heart rate (HR; Polar chest belt) were monitored continuously and mean values over 1 minute were included into the analyses. Capillary blood samples from the hyperaemized ear lobe were drawn to determine blood lactate concentration (Biosen C-line, EKF-Diagnostic, Barleben, Germany).

After a wash-out period of at least 6 days the IH pre-acclimatization program started. The program consisted of 7 resting sessions within 7 consecutive days (one session per day) lasting 1 hour each. The participants were exposed to normobaric hypoxia (Hypoxico Altitude Training Systems, Köln, Germany) with an F_IO_2 of 0.126 corresponding to an altitude of 4500 m. This protocol was chosen because it is proven to increase HVR [16-19]. The subjects had no further altitude exposure >2500 m during the pre-acclimatization program.

One day after the last session of the IH pre-acclimatization program the post tests (post) were conducted. All measurements took place at approximately the same time of day (± 1 hour) as in the pre tests. The order of the simulated test altitudes, the test procedure and the measurements were the same as in the pre tests.

Statistics

Statistical analyses were conducted by PASW Statistics 18 (IBM, Vienna, Austria). The missing value of 1 participant for blood lactate concentration at the simulated altitude of 4000 m was replaced by the mean of the group ($n = 8$). Normality in the distribution of data was tested by the Kolmogorov-Smirnov's test. Differences in the measured parameters among the experimental conditions were analyzed using two-way ANOVA with repeated measures (pre-post x altitude). If significances were found, paired students' t-tests with Bonferroni correction were carried out to find the source of difference. P-values < 0.05 (two-tailed) were considered to indicate statistical significance. Values are presented as means ± SD.

Results

We detected no altitude-dependent effect of IH in any of the measured parameters. SaO_2 decreased and heart rate tended to increase with altitude, but there was no effect of IH on these parameters. There was a significant effect of IH on blood lactate concentrations which were reduced after IH (Table 1). Post hoc analysis revealed a significant reduction in blood lactate concentration from pre to post at a simulated altitude of 3000 m (Fig. 1).

Discussion

To our knowledge this was the first study comparing effects of IH on resting physiological parameters at different altitudes. We detected no altitude dependent effect of the applied IH protocol. Moreover, there was no general IH effect on ventilation and SaO_2 but IH tended to reduce resting blood lactate concentration.

In regard to the ventilatory data our results are in agreement with other studies at moderate altitude (up to 2500 m). Katayama et al. used the same IH protocol leading to an increase in HVR but reported no increase in resting ventilation and SaO_2 at a simulated altitude of 2500 m [17]. In contrast to our findings

Table 1. *Selected cardiorespiratory, ventilatory, and metabolic parameters during short-term exposure to different simulated altitudes before (pre) and after (post) intermittent hypoxia. P-values refer to general effects of simulated altitude (ALT), general effects of intermittent hypoxia (IH), interactions between simulated altitude and intermittent hypoxia (ALTxIH). Values are means±SD.*

		Simulated altitude				*P*-values		
		1000 m	2000 m	3000 m	4000 m	ALT	IH	ALTxIH
Arterial oxygensaturation (%)	pre	98 ± 1	94 ± 2	92 ± 2	85 ± 4	<0.01	0.60	0.22
	post	98 ± 1	93 ± 2	91 ± 3	86 ± 3			
Heart rate (1/min)	pre	67 ± 5	69 ± 9	72 ± 8	73 ± 10	0.44	0.07	0.77
	post	63 ± 7	70 ± 10	70 ± 7	71 ± 4			
Minute ventilation (l/min)	pre	14 ± 2	13 ± 3	13 ± 4	12 ± 2	0.51	0.35	0.10
	post	13 ± 4	14 ± 2	12 ± 2	14 ± 2			
Breathing frequency (1/min)	pre	18 ± 4	16 ± 3	15 ± 4	15 ± 4	0.18	0.85	0.07
	post	16 ± 4	17 ± 3	16 ± 5	15 ± 4			
Blood lactate con-centration (mmol/l)	pre	1.0 ± 0.3	1.1 ± 0.3	1.3 ± 0.4	1.3 ± 0.5	0.32	0.03	0.58

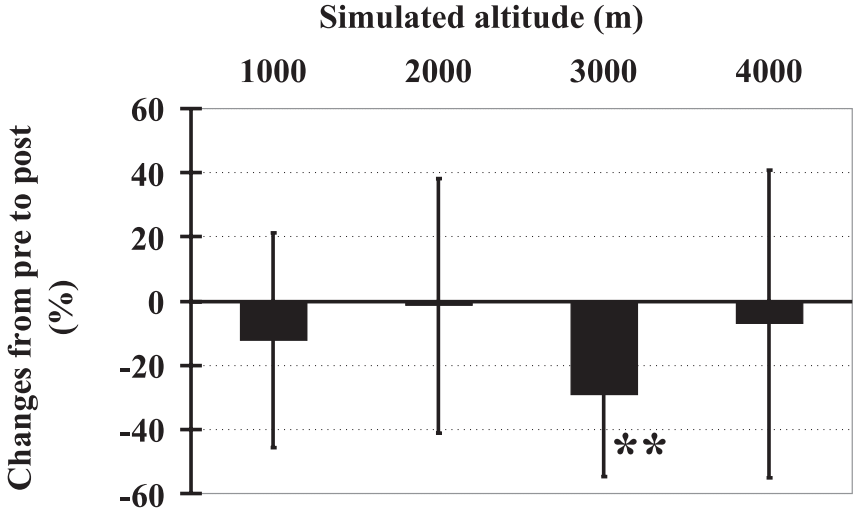

Fig. 1. *Relative changes in resting blood lactate concentration during short-term exposure to different simulated altitudes before (pre) and after (post) intermittent hypoxia*

Values are means ± SD. $P = 0.03$ for a general effect of intermittent hypoxia
** $P < 0.01$ for changes from pre to post at the specific simulated altitude

studies testing at altitudes >4000 m showed significant increases in resting ventilation and SaO_2. Beidleman et al. reported an increase in SaO_2 from 80 to 85% at a simulated altitude of 4300 m related to an increase in ventilation that was indicated by a fall in end-tidal pressure of carbon dioxide [21]. Also Katayama et al. showed a marked increase in SaO_2 and ventilation at 4500 m (hypobaric chamber) after IH [16]. In contrast to these results we could not find similar effects at simulated altitudes up to 4000 m. A possible reason for the diverging results might be the difference in the simulated altitude or, more likely, in the degree of individuals' hypoxemia. Our participants showed SaO_2 values of about 85% (at 4000 m) whereas mean SaO_2 was 80% at 4300 m and about 67% at 4500 in the studies from Beidleman et al. and Katayama et al. respectively [16,21]. The reasons for the low SaO_2 values in these studies can not be explained by our data but may be caused by a low ventilatory response to hypoxia of the tested individuals. Furthermore a more pronounced ventilation perfusion mismatching in the lung or/and a possible interstitial pulmonary edema could have contributed to reduced SaO_2 values [23]. Regardless of these speculations, one could assume that an increased HVR did not (sufficiently) stimulate ventilation due to the lower degree of hypoxemia in our

persons compared to the other studies. From a practical point of view, measured SaO_2 values in our subjects can be considered as representative when compared to previous measurements in our laboratory [24]. Unfortunately we did not perform measurements at altitudes >4000 m in this study and therefore we can not provide information on possible effects of the applied IH protocol when more pronounced hypoxemia is provoked. However persons with very low SaO_2 values during an acute hypoxic exposure (e.g. HAPE susceptible individuals) may benefit from repeated 1-hour exposures whereas persons with normal values did not [20]. Based on these observations it can be speculated that positive ventilatory effects of the applied IH protocol are only detectable when baseline SaO_2 is very low (e.g. caused by a low individual HVR) or the level of environmental hypoxia is high (e.g. simulated altitudes > 4000 m).

A further explanation may be at least partly provided by different time points of the measurements during the exposure to hypoxia. In our study we determined ventilation and SaO_2 after about 20 minutes in hypoxia. At this time the hypocapnia independent hypoxic ventilatory decline (HVD), which occurs during the first 5 to 30 minutes of a sustained hypoxic exposure, counteracts the initial HVR and reduces ventilation [25]. In contrast Beidleman et al. performed the corresponding evaluations after 20 to 22 hours in hypoxia when HVD has disappeared and ventilatory acclimatization progresses [21,25].

In accordance with other studies we detected small but significant reductions in blood lactate concentration after IH [10,11,26]. Blood lactate concentrations are related to epinephrine levels during acute high-altitude exposure [27]. Since an association between increased catecholamine levels at high altitude and AMS development has been supposed, the reduction in blood lactate concentrations might represent a mechanism for a reduced AMS risk after IH [28,29]. However, it remains unclear if this effect persists during a longer-lasting hypoxic exposure and if it is able effectively to reduce the AMS risk. The post-hoc analysis revealed a significant reduction in blood lactate concentrations only at an altitude of 3000 m (figure 1). Thus, it is speculated that sympathetic activation is too low at altitudes up to 2000 m, whereas at 3000 m it is sufficient for a positive impact of the pre-acclimatization program. However at 4000 m the effects of IH were not homogenous enough to reach statistical significance.

Limitations of the study

The present study has several limitations. First, the small sample size leads to a relative low statistical power. Therefore we can not exclude that possible IH effects are existent but were not identified. Second, the hypoxic exposures of the study participants lasted only a short time period and all evaluations were done once at the end of this period. Therefore, a) individual time courses in the acute responses could not be regarded and b) the present results cannot be generalized to several hours to days lasting hypoxic exposures which are common when AMS occurs, e.g. during mountaineering. Future research with sufficient statistical power should address these topics.

In conclusion, the present results did not indicate increased resting ventilation and improved SaO_2 during subsequent exposures to altitudes up to 4000 m by the applied IH protocol. However, the reduced blood lactate concentrations may suggest an AMS-prophylactic effect of IH by reducing catecholamine levels during subsequent high-altitude exposures.

Declaration of interest

The authors report no conflicts of interest.

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