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ORIGINAL RESEARCH

Sleeping in Moderate Hypoxia at Home for Prevention of Acute Mountain Sickness (AMS): A Placebo-Controlled, Randomized Double-Blind Study

Christoph Dehnert, MD; Astrid Böhm; Igor Grigoriev; Elmar Menold; Peter Bärtsch, MD

From the University Hospital, Medical Clinic, Internal Medicine VII, Sports Medicine, Heidelberg, Germany.

Objective.—Acclimatization at natural altitude effectively prevents acute mountain sickness (AMS). It is, however, unknown whether prevention of AMS is also possible by only sleeping in normobaric hypoxia.

Methods.—In a placebo-controlled, double-blind study 76 healthy unacclimatized male subjects, aged 18 to 50 years, slept for 14 consecutive nights at either a fractional inspired oxygen (F_{IO_2}) of 0.14 to 0.15 (average target altitude 3043 m; treatment group) or 0.209 (control group). Four days later, AMS scores and incidence of AMS were assessed during a 20-hour exposure in normobaric hypoxia at $F_{IO_2} = 0.12$ (equivalent to 4500 m).

Results.—Because of technical problems with the nitrogen generators, target altitude was not achieved in the tents and only 21 of 37 subjects slept at an average altitude considered sufficient for acclimatization (>2200 m; average, 2600 m). Therefore, in a subgroup analysis these subjects were compared with the 21 subjects of the control group with the lowest sleeping altitude. This analysis showed a significantly lower AMS-C score (0.38; 95% CI, 0.21 to 0.54) vs 1.10; 95% CI, 0.57 to 1.62; $P = .04$) and lower Lake Louise Score (3.1; 95% CI, 2.2 to 4.1 vs 5.1; 95% CI, 3.6 to 6.6; $P = .07$) for the treatment subgroup. The incidence of AMS defined as an AMS-C score greater than 0.70 was also significantly lower (14% vs 52%; $P < .01$).

Conclusions.—Sleeping 14 consecutive nights in normobaric hypoxia (equivalent to 2600 m) reduced symptoms and incidence of AMS 4 days later on exposure to 4500 m.

Key words: acclimatization, acute mountain sickness, hypoxia, prevention, ventilation

Introduction

Ascent to altitudes above 2500 m frequently causes acute mountain sickness (AMS), a syndrome characterized by headache, nausea, dizziness, and insomnia, and ascent to higher altitudes can also occasionally cause potentially lethal high altitude pulmonary edema (HAPE) or high altitude cerebral edema (HACE).[1] The major determinants of the prevalence of these illnesses are altitude, individual susceptibility, rate of ascent, and degree of acclimatization caused by preceding exposures.[2] Slow ascent that would help to reduce severity and incidence of these illnesses is often not possible because of time constraints or financial reasons. Therefore, in a given setting of rapid ascent, preacclimatization or intake of drugs such as acetazolamide[3] or nifedipine[4] are often the only options to avoid or reduce the chance of experiencing AMS or HAPE.

There have been successful attempts to reduce AMS[5] and to improve the rate of ascent on climbing Mt Everest[6] by exposure to hypobaric hypoxia in the weeks preceding the altitude exposure. These studies, however, involved few subjects, were uncontrolled, and used procedures that interfere with regular daily activities. Furthermore, it was shown that staging ascent for 6 days at 2200 m reduces AMS severity at 4300 m by 44%,[7] but a placebo-controlled, double-blind study found only a minor, clinically irrelevant preventive effect on AMS at the same altitude after 8 days of sleeping 7.5 hours in normobaric hypoxia corresponding to an average altitude of 2600 m.[8]

Exposure to hypoxia during sleep is an attractive possibility of acclimatization because it does not interfere with normal daily activities. It is likely that the short duration of total nights accounts for the mostly negative

The study is registered on ClinicalTrial.gov with the title: "Prevention of Acute Mountain Sickness by Intermittent Hypoxia" (NCT 00559832).

Corresponding author: Christoph Dehnert MD, Medical Clinic, University Hospital Heidelberg, Internal Medicine VII, Sports Medicine, Im Neuenheimer Feld 410, D–69120 Heidelberg, Germany (e-mail: christoph.dehnert@gmx.de).

results in the study of Fulco et al.[8] Therefore, we hypothesized that sleeping 14 instead of 8 consecutive nights in a well-tolerated hypoxic environment at home using nitrogen-enriched air would significantly reduce severity and incidence of AMS most likely by inducing ventilatory acclimatization. This hypothesis was tested during a 20-hour exposure in a normobaric hypoxia room at an ambient P_{O_2} corresponding to 4500 m.

Methods

SUBJECTS AND STUDY DESIGN

We recruited 84 healthy, nonsmoking male subjects who did not take any medication and who had not stayed above 2000 m during the last 2 months before the study. Seventy-six of them were found eligible, agreed to participate, and were randomly assigned to one of the study groups. Three dropped out during the study and 73 finished the study protocol (Figure 1). They had a mean age of 26.5 years (range, 18 to 48 years) and a mean body mass index of 23.6 kg/m^2 (range, 19.1 to 35.2 kg/m^2). History of AMS was not assessable in all but 3 subjects because of lack of appropriate altitude exposures. Subjects were randomly assigned in blocks of 6 to normoxic or hypoxic treatment, which consisted of sleeping for 14 consecutive nights at home under a tent that was ventilated by either normoxic (control group) or hypoxic (treatment group) air. A few days before the

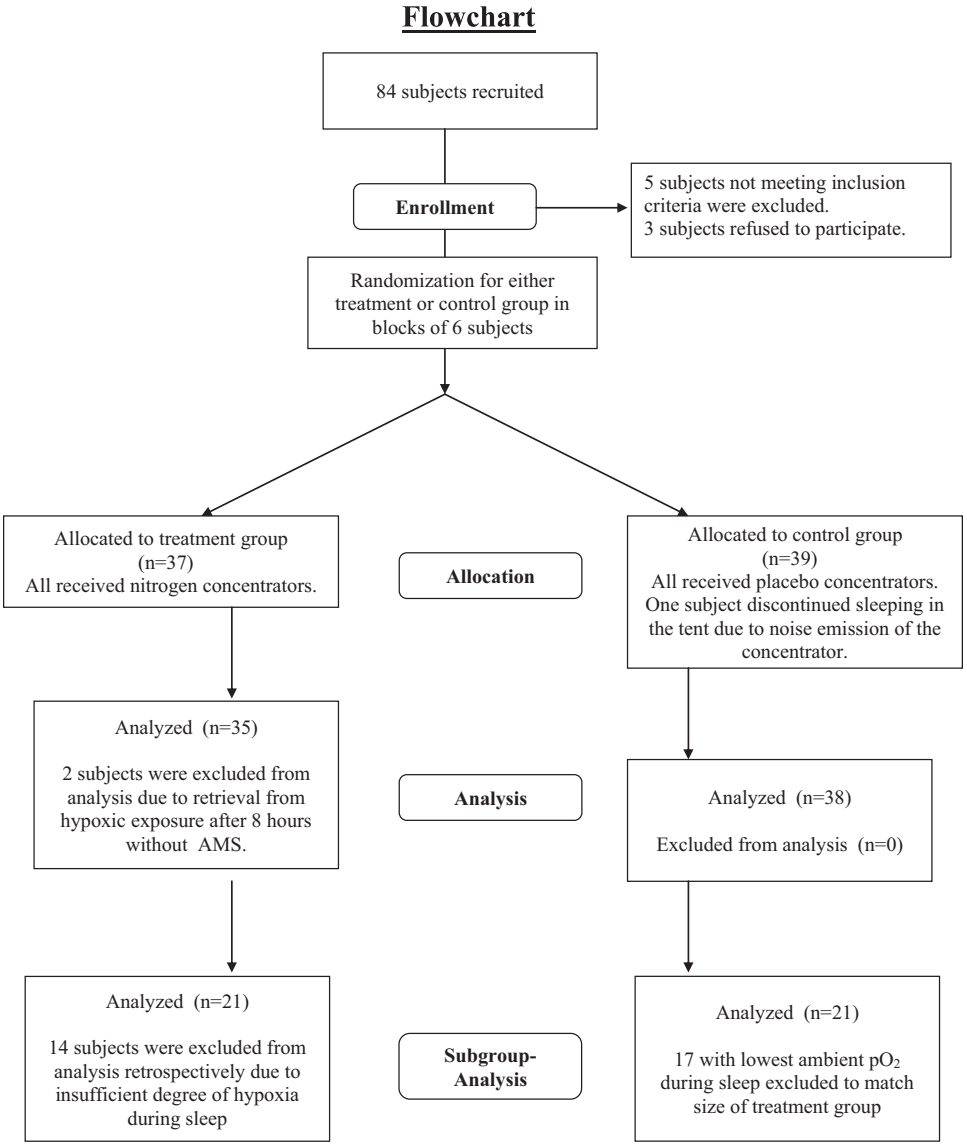

Figure 1. Cohort flow diagram. Flowchart of enrolment and randomization of the subjects and overview of data analysis.

intervention they were exposed in a hypoxia room for 4 hours at a fractional inspired oxygen (F_{IO_2}) of 0.12, which results in a P_{O_2} equivalent to 4500 m. During the last half hour of this exposure, ventilation, respiratory gases, pulse oximetry, and capillary blood gas analysis were performed. AMS was assessed before leaving the hypoxia room. The intervention period of 14 nights was followed by 4 nights without treatment, because 4 to 5 days are often needed for travelling to high altitude regions in various places of the world. Thereafter, subjects spent 20 hours (from 2 PM to 10 AM on the next day) at 12% O_2 in the hypoxia room in groups of 3 subjects. Subjects were not allowed to take any medication throughout the study. The same measurements that were performed during the first exposure in the hypoxia room were repeated after 4 and 20 hours or at the time of early termination of the final exposure. Five subjects terminated this exposure after 8 to 16 hours of exposure because of unacceptable symptoms of AMS. Written informed consent was obtained from the subjects, and the study was approved by the Ethics Committee of the Medical Faculty of the University of Heidelberg. The study was registered on the ClinicalTrial.gov site with the title "Prevention of Acute Mountain Sickness by Intermittent Hypoxia" (NCT 00559832).

The statistical power analysis yielded a sample size of 40 subjects. When analyzing the data of the first 40 subjects, we discovered that many subjects had not been exposed to the intended degree of hypoxia because of technical problems discussed in the section describing the devices. Avoiding the identified causes for failure to reach sufficient hypoxia, the study was repeated in another group of 40 subjects.

MEASUREMENTS IN THE HYPOXIA ROOM

Exposure to hypoxia took place in a laboratory unit located at 100 m above sea level equipped with 3 beds, a shower, and a toilet. Ambient P_{O_2} and P_{CO_2} were held at 12% and below 0.3%, respectively, during the exposures by regulation of nitrogen admixture and airflow (System Linde Gas, Unterschleißheim, Germany).

AMS was assessed by the Lake Louise Score[9] and the AMS-C subscore of the Environmental Symptom Questionnaire.[10] Subjects were considered to have AMS when the AMS-C score was ≥ 0.7 and the Lake Louise Score (questionnaire and clinical examination) was ≥ 5. This criterion for AMS had been applied in a previous study,[11] the results of which were used for the power calculation of this investigation. When one score was borderline and the other fulfilled the criterion score, subjects were also classified as having AMS as shown in Table 1. The classification regarding questionable cases

Table 1. Individual data of all subjects

Subgroup	*AMS*	*LL score*	*AMS-C score*	*Altitude (m)*	*Hx/Nx*
Treatment group (n = 21)					
	1	6	0.679	3201	Hx
	1	8	1.388	3146	Hx
	0	2	0.187	2886	Hx
	0	1	0.000	2792	Hx
	0	1	0.269	2725	Hx
	0	0	0.000	2724	Hx
	0	4	0.366	2669	Hx
	0	4	0.462	2651	Hx
	1	5	0.752	2633	Hx
	1	6	0.580	2597	Hx
	1	5	1.105	2591	Hx
	0	3	0.149	2584	Hx
	0	2	0.090	2576	Hx
	0	3	0.202	2510	Hx
	0	0	0.000	2469	Hx
	0	4	0.184	2453	Hx
	0	3	0.573	2428	Hx
	0	1	0.000	2269	Hx
	1	5	0.694	2262	Hx
	0	0	0.000	2212	Hx
	0	3	0.269	2211	Hx
	1	6	0.778	2106	Hx
	0	0	0.000	2067	Hx
	0	5	0.258	2000	Hx
	0	4	0.184	1960	Hx
	1	5	0.737	1927	Hx
Subjects excluded (n = 26)					
	1	6	0.727	1865	Hx
	0	4	0.402	1851	Hx
	0	2	0.328	1759	Hx
	1	8	1.800	1746	Nx
	1	5	1.755	1743	Hx
	0	4	0.796	1607	Nx
	0	0	0.000	1560	Nx
	1	9	1.610	1497	Hx
	0	1	0.000	1085	Nx
	0	3	0.254	1044	Nx
	0	4	0.164	1012	Nx
	0	2	0.323	983	Hx
	1[a]	10	2.101	969	Hx
	1[b]	8	3.196	884	Nx
	0	4	0.438	873	Nx
	0	3	0.090	814	Nx
	1	5	0.494	734	Nx
	1	5	0.164	671	Nx
	0	3	0.090	652	Nx
	1[b]	12	3.317	627	Nx
	0	3	0.320	569	Nx
Control group (n = 21)					
	1	4	0.732	545	Nx
	0	3	0.511	456	Nx
	1	6	0.612	448	Nx
	1[b]	14	4.260	438	Nx

Table 1. (*continued*)

Subgroup	*AMS*	*LL score*	*AMS-C score*	*Altitude (m)*	*Hx/Nx*
	1	5	1.176	401	Nx
	1	6	1.022	401	Nx
	0	3	0.169	397	Nx
	0	3	0.338	394	Nx
	0	2	0.000	366	Nx
	1	6	2.324	344	Nx
	1	5	1.326	323	Nx
	1	5	0.759	295	Nx
	0	2	0.292	276	Nx
	0	2	0.000	274	Nx
	1	8	1.996	252	Nx
	0	3	0.184	250	Nx
	0	1	0.194	239	Nx
	1	8	2.073	235	Nx
	1	5	1.082	174	Nx
	1[b]	14	4.022	161	Nx
	0	2	0.000	146	Nx
Subjects excluded (n = 5)					
	0	4	0.000	No record[c]	Nx
	1	5	1.108	No record	Nx
	1	8	2.146	No record	Nx
	0	0	0.000	No record	Hx
	0	3	0.320	No record	Hx

Individual data on acute mountain sickness (AMS) classification (0 = no AMS, 1 = AMS), Lake Louise (LL) score, AMS-C score, altitude equivalent of average hypoxic exposure (altitude), allocation to study group (Hx, hypoxia; Nx, normoxia), and group assignment for subgroup analysis.

[a] Indicates termination of study after 16 hours.

[b] Indicates termination of study after 8–10 hours.

[c] "No record" means no or insufficient recording available.

of AMS was performed before the examiners were unblinded. Sleep quality in the laboratory and at home was assessed by the question of the Lake Louise Score regarding sleep: 0 = slept as well as usual, 1 = did not sleep as well as usual, 2 = woke up many times, poor night's sleep, 3 = could not sleep at all.

Ventilation and end-tidal P_{O_2} and P_{CO_2} were measured with a breath-by-breath analyzer (ZAN600; ZAN Messgeräte GmbH, Oberthulba, Germany) in quietly resting subjects for 30 minutes and were averaged over the last 10 minutes. Saturation was measured by pulse oximetry (3900Biox; Datex Ohmeda, Helsinki, Finland) via finger clips simultaneously and averaged over the same time. Capillary blood gases were obtained after measuring ventilation and analyzed by Rapidpoint 405 (Bayer Healthcare AG, Leverkusen, Germany). Examiners supervising subjects and performing measurements were blinded with regard to treatment and were therefore not involved in distributing the hypoxic tents.

EXPOSURE IN HYPOXIC TENTS

Tents and oxygen generators (Integra TEN; Sequal, San Diego, CA) modified to produce nitrogen-enriched air were obtained from a company selling such devices to athletes for sleeping or training in hypoxia. Air and nitrogen flow, respectively, were regulated via O_2 (KE 25; GS Yuasa Corporation, Kyoto, Japan) and CO_2 sensors built in a control unit that was placed inside the tents. In 3 of 6 nitrogen concentrators ("placebo generators"), nitrogen supplementation was blocked and they always supplied room air independent of the selected altitude on the control panel. Subjects had no information regarding the level of hypoxia because the display on the control unit showing the ambient O_2 concentration was hidden while the display of the altitude remained visible for selection of the altitude. Furthermore, a flowmeter on the generator showing the nitrogen flow to the tents was also covered by a metal plate. Subjects were asked to sleep for 8 hours each night, starting with an altitude of 2500 m (15.4% O_2) and increasing the altitude every night by about 100 m (decrease O_2 by 0.2%) until 3300 m (14% O_2) was reached. This altitude was kept constant for the last 7 days, resulting in an overall average exposure of 3043 m per night. The O_2 and CO_2 signals were continuously registered on notebook computers and were used after the study to calculate the O_2 and CO_2 concentration in the tents throughout each night. In addition, oxygen saturation (Spo_2) was measured by pulse oximeters and recorded continuously. All recorded signals were saved in a hidden file on a notebook computer. Recordings of 5 subjects indicated in Table 1 were missing or incomplete. The person responsible for distributing the nitrogen generators and setting up the devices in the homes of the subjects was in charge of randomization and was not involved in clinical testing. Because the temperature in the tents rises by about 2°C above ambient temperature and humidity increases substantially during sleep, this environment was not tolerated well during late spring and early summer when the first part of the study took place.

Analysis of CO_2 production in the tents revealed a good compliance regarding the time spent in the tents (7.4 ± 0.8 h/night), although the target F_{IO_2} was hardly ever reached. It is unlikely that the recorded F_{IO_2} data were erroneous because gas sensors were checked and calibrated regularly. Furthermore, the simultaneously recorded Spo_2 from the subjects are compatible with the respective altitudes as shown in Figure 2. We suspected that the tents had not been closed completely because of the warm weather during a large part of the first study period and that the capacity of the generators was not sufficient to compensate this dilution. Because

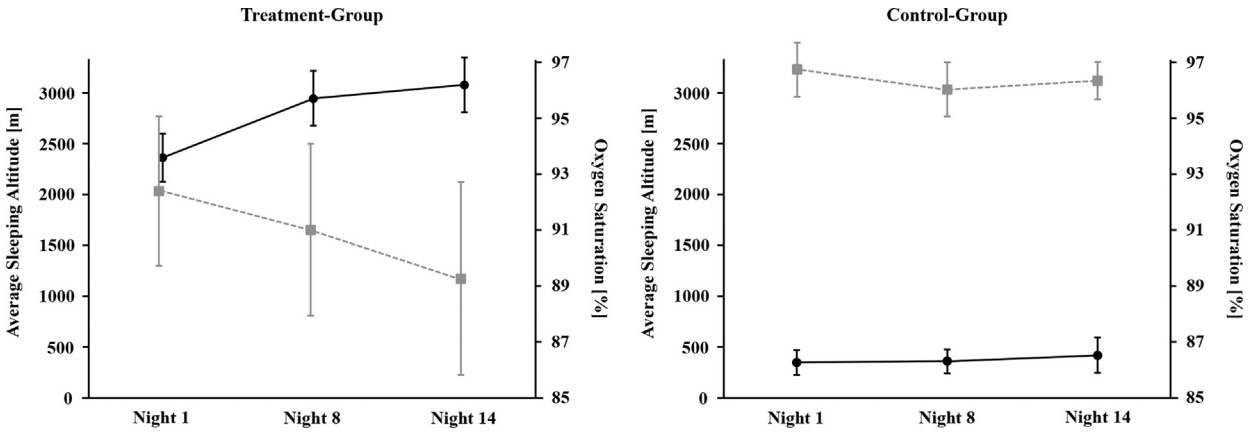

Figure 2. Average sleeping altitude ± SD (black circles) and average oxygen saturation ± SD (gray squares) during exposure in the tent for the treatment group (left) and the control group (right). Oxygen saturation decreases with increasing sleeping altitude in the treatment group, whereas in the control group it remains within normal range throughout the whole study.

of the failure to reach the planned level of hypoxia, we repeated the study during winter and early spring and eliminated the biggest sized tent (for a double bed) from the study. Despite these precautions, we did not reach the desired level of altitude in most cases, as shown in Table 1. In addition, analysis of gas recordings in the placebo group revealed that 2 of the placebo apparatuses were supplying some nitrogen-enriched air during the second part of the study, which was attributable to a defect in the valve blocking the nitrogen supplementation. This resulted in 6 subjects sleeping at an average Po_2 equivalent to an altitude above 900 m. Mean altitude equivalents of the ambient Po_2 and AMS scores of all 73 subjects are shown in Table 1. We additionally recorded Spo_2 during the nights in the tents. At 3000 m subjects' Spo_2 averaged slightly below 90%, which is a reasonable value for this altitude, while the Spo_2 of those sleeping below 500 m was on average 96% (Figure 2).

STATISTICAL ANALYSIS

The calculation of the sample size was based on an estimated AMS prevalence of 50% found in a comparable study.[11] We calculated a sample size of 20 subjects per group for detecting a reduction of the incidence of AMS from 50% to 20% with a power of 80% ($\alpha = 0.05$). The frequency of AMS between treatment groups is compared by χ^2 test. Values between the groups with and without AMS are compared by Mann-Whitney *U* tests, and 2-sided probability values are reported. Values are reported as mean values and 95% CI, unless otherwise stated. Correlation analysis was performed by linear regression analysis (Pearson correlation). The level of statistical significance was set at $P < .05$ (2-sided) for all tests.

The aim of the study was to compare subjects who acclimatized while sleeping at approximately 3000 m for 2 weeks with subjects who slept close to sea level. Therefore, we also performed a subgroup analysis of those subjects who slept at an altitude that might induce acclimatization during a repeated exposure of 8 hours. A recent study demonstrated that first the symptoms attributable to hypoxia start occurring between 2134 m and 2438 m within 9 hours.[12] We selected 2134 m as a cutoff level for the treatment group, assuming that an altitude that causes symptoms attributable to hypoxia will also induce some altitude acclimatization during a similar duration exposure. Therefore, the results of the 21 subjects who slept on average above 2134 m (range, 2211 to 3291 m; mean, 2599 m) were compared with those of an equal-sized group who had slept at the highest inspiratory Po_2 (lowest altitude), which turned out to be below an equivalent altitude of 550 m. At this altitude significant acclimatization to high altitude can be excluded because Honigman et al[13] showed that even residency up to 900 m had no preventive effect on AMS.

Results

ANALYSIS OF ALL SUBJECTS

There was no significant difference in age, body mass index, and history of AMS between treatment groups. Individual data on exposure and AMS scores of all subjects are shown in Table 1. The overall incidence of AMS was 42%, without significant differences between treatment and control groups regarding the criterion score and the symptom scores. There was a trend to less AMS in those assigned to sleep in hypoxia, with 34% AMS (12 of 35 subjects) vs 50% (19 of 38 subjects) in

the control group ($P = .25$). The respective symptom scores were 3.6 (95% CI, 2.8 to 4.5) and 4.9 (95% CI, 3.9 to 6.0; $P = .13$) for the Lake Louis Score and 0.50 (95% CI, 0.32 to 0.68) and 0.99 (95% CI, 0.62 to 1.36; $P = .17$) for the AMS-C score. Linear regression analysis between mean "altitude" of the hypoxic exposure and Lake Louise or AMS-C scores is statistically significant with $P = .04$ and $P = .01$, respectively, but yields only r^2 values of 0.06 and 0.09, respectively, indicating that only 6% and 9% of the variability of the respective scores can be explained by differences in normobaric hypoxia during sleep. Exponential regression models did not result in better correlation coefficients.

It is well documented that residency above 900 m has some preventive effect on AMS.[13] The lack of a good correlation between the degree of hypoxia and AMS scores may be explained by a lack of acclimatization during the short exposure time (14 nights of 8 hours each) at intermediate altitudes between 1000 and 2000 m. Therefore, we also performed a subgroup analysis based on criteria that came close to the initial intention.

SUBGROUP ANALYSIS

AMS scores of those 21 subjects who on average slept at an ambient P_{O_2} corresponding to an altitude above 2134 m vs those 21 subjects who slept at the lowest altitudes (ie, <550 m) are shown in Figure 3. The treatment group had a significantly lower AMS-C score, whereas the reduction of the Lake Louise Score ($P = .07$) and the reduction of the incidence of AMS, both defined by cutoff scores from 58% to 29% ($P < .06$), were of borderline statistical significance. Based on these numbers and assuming that they would be similar and become significant in a larger sample, we estimate the number needed to treat (NNT) to be 3.4 and the relative risk reduction to be 0.50. Using only the AMS-C score ≥ 0.70 as criterion, the incidence of AMS significantly decreases from 52% to 14% ($P < .025$). When AMS is defined by AMS-C score only, the NNT is 2.6 and the relative risk reduction is 0.73.

To test whether sleeping in moderate hypoxia had an effect on ventilation and blood gases, we compared the data measured after 4 hours of exposure to 12% O_2 before and after treatment. The results are shown in Table 2. There was no difference in ventilatory acclimatization between treatment groups. We only observed insignificant trends to higher Pa_{O_2}, Sp_{O_2}, and ventilation without changes in Pa_{CO_2} in those who slept in moderate hypoxia. No changes occurred in the placebo group. Table 3 shows that irrespective of treatment modalities, AMS is associated with a significantly lower Pa_{O_2} and Sp_{O_2}, whereas Pa_{CO_2} shows a tendency to be higher in those without AMS despite a trend also to higher ventilation.

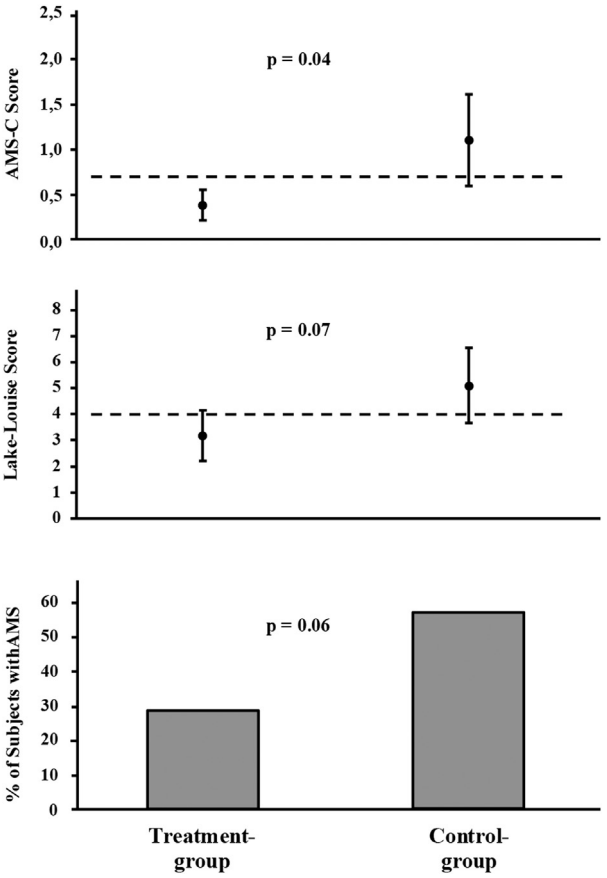

Figure 3. Mean values and 95% CI of AMS-C score (top) and Lake Louise score (middle) as well as incidence of acute mountain sickness (AMS; bottom) in 21 subjects of the treatment group and 21 subjects of the control group; dashed lines indicate cutoff level for diagnosis of acute mountain sickness with respective score.

We further analyzed the sleep quality of the 42 subjects involved in the subgroup analysis. After the first 3 nights, sleep quality in the tent expressed as an average sleep score for days 4 to 14 was significantly impaired compared with a control night before the intervention in both groups. Mean scores in the treatment group were 0.43 (95% CI, 0.27 to 0.59) during vs 0.05 (95% CI, 0.00 to 0.14) before the treatment and 0.45 (95% CI, 0.22 to 0.67) vs 0.10 (95% CI, 0.00 to 0.22), respectively, in the control group. The data demonstrate that there was only a mild impairment of sleep that was the same in both groups during treatment. Furthermore, sleep score was considerably less than when sleeping at 12% O_2, which resulted in scores of 1.35 (95% CI,

Table 2. Effect of treatment on blood gases and ventilation

Variable	*Group*[a]	*Before treatment*	*After treatment*
Pa_{O_2} (mm Hg)	Treatment	41.3 (39.7 to 42.9)	43.8 (42.1 to 45.5)
	Control	42.5 (38.9 to 46.2)	42.5 (40.1 to 44.8)
Sp_{O_2} (%)	Treatment	78.5 (75.4 to 81.7)	81.2 (78.7 to 83.7)
	Control	79.6 (75.9 to 83.3)	78.6 (75.0 to 82.1)
Pa_{CO_2} (mm Hg)	Treatment	34.7 (32.6 to 36.8)	34.8 (33.2 to 36.4)
	Control	34.2 (31.9 to 36.4)	34.9 (33.6 to 36.2)
V_E (L/min)	Treatment	4.9 (4.2 to 5.5)	5.4 (5.0 to 5.7)
	Control	5.3 (4.7 to 5.9)	5.2 (4.7 to 5.7)

Mean values and 95% CI of capillary blood gas analysis, pulse oximetry (Sp_{O_2}), and ventilation (V_E) after a 4-hour exposure at 12% O_2 before and 4 days after treatment.

[a] Treatment group (n = 21), control group (n =21).

0.86 to 1.84) for the treatment group and 1.77 (95% CI, 1.39 to 2.15) for the control group.

Discussion

This randomized, placebo-controlled, double-blind study demonstrates that sleeping in moderate normobaric hypoxia equivalent to an average altitude of 2600 m for 14 consecutive nights significantly reduces the severity and the incidence of AMS assessed by AMS-C scores during a subsequent exposure to normobaric hypoxia (equivalent to 4500 m) that took place 4 days after the last night spent in hypoxia. Absence of AMS was associated with higher Sp_{O_2} values, likely as a result of ventilatory acclimatization after the nightly exposures to hypoxia.

Although our conclusions are based on a subgroup analysis, we consider them valid because the selection of subjects for the subgroup analysis was based on criteria that are in accordance with the primary purpose of the study, which was to compare subjects who did and did not sleep at levels of hypoxia that have been shown to induce acclimatization and prevent AMS during a prolonged continuous stay at high altitude. Despite not reaching the intended average level of hypoxia (equivalent to an altitude of 3043 m), we demonstrated significant effects on AMS assessed by the AMS-C score. This score is used in many studies as the only parameter to assess AMS,[14] particularly in those looking at the effects of various forms of preexposure to hypoxia for prevention of AMS at Pikes Peak (4300 m).[15] The reduction of AMS assessed by the Lake Louise Score was of borderline significance. In a larger sample with greater statistical power, the differences in Lake Louise Scores would most likely become statistically significant because AMS-C and Lake Louise Score are closely related.[16]

Our study provides further insight into earlier work on this issue and suggests that a longer duration of exposure might be necessary to induce a sufficient degree of acclimatization. An earlier double-blind, placebo-controlled study showed that sleeping 7 consecutive nights at normobaric hypoxia equivalent to 2220 to 3100 m had no significant overall effect on AMS assessed by AMS-C scores after rapid ascent to 4300 m despite improving Sp_{O_2} and symptoms of AMS immediately after waking.[15]

Table 3. Blood gases and ventilation in relation to acute mountain sickness

Variable	*Time (h)*	*With AMS*	*Without AMS*	*P value*
Pa_{O_2} (mm Hg)	4	42.4 (40.5 to 44.3)	44.2 (43.1 to 45.3)	0.05
	20	46.7 (44.6 to 48.8)	48.0 (46.9 to 49.1)	0.40
Sp_{O_2} (%)	4	78.1 (76.2 to 79.9)	81.5 (79.9 to 83.1)	0.02
	20	81.3 (79.1 to 83.5)	84.9 (83.7 to 86)	0.03
Pa_{CO_2} (mm Hg)	4	34.1 (33.0 to 35.2)	35.3 (34.3 to 36.2)	0.11
	20	31.3 (29.9 to 32.6)	32.8 (32.0 to 33.7)	0.06
V_E (L/min)	4	4.6 (4.2 to 5.1)	5.2 (4.9 to 5.5)	0.08
	20	5.6 (4.7 to 6.5)	5.8 (5.4 to 6.2)	0.31

Mean values ± 95% CI of capillary blood gas analysis, pulse oximetry (Sp_{O_2}) and ventilation (V_E) after 4 and 20 hours exposure at 12% O_2 in 31 subjects with and 42 subjects without AMS. Probability value (2-sided) refers to the Mann-Whitney *U* test.

The data of the present study indicate that extending the nightly hypoxic exposure will result in a significant reduction of AMS.

Previous uncontrolled studies used more severe hypobaric hypoxia (4300 m and higher) that lasted 4 and more hours per day for effective acclimatization and prevention of AMS.[5,6] Such a procedure is not compatible with a normal professional life and depends on the availability of hypobaric chambers. Our study shows that a preventive effect on AMS can be achieved by a degree and mode of application of normobaric hypoxia that does not interfere with daily activities and that is quite well tolerated. Interestingly, subjective judgment of sleep quality was similar between the intervention and control groups and indicated minimal disturbance, which can be attributed to increased humidity and temperature inside the tents as well as to the noise of the generator (about 30 dB). Subjects usually placed the generator in an adjacent room. One subject, however, dropped out of the study because he did not tolerate the noise.

We suspect that some subjects had not completely closed their tents because of the humidity and high temperatures and that the generators could not provide enough nitrogen to compensate for the leak. Thus, these subjects did not reach the intended simulated altitude and insufficient capacity of the generators may be a concern with this method, particularly with the use of bigger tents. Insufficient supply of nitrogen would, however, easily be detected outside a study setting because the display on the oxygen sensor inside the tent would be visible and indicate the oxygen concentration. Users should be told to let the generator run for 1 to 2 hours at the desired level of hypoxia before bedtime to check whether the desired altitude is reached inside the closed tent. Alternatively one could set up a continuous registration of P_{O_2} throughout the night on a nearby computer. Manufacturers of such devices should be asked to provide links and programs for control recoding on personal computers. In addition, users need to realize that the tent must be completely closed and that small air conditioners for use in the tents have become available if humidity and temperature become uncomfortable.

The reduction in the incidence of AMS is comparable with the reduction reported from other studies using 500 to 750 mg of acetazolamide per day for prevention of AMS.[17] Because the effect of our intervention was tested in normobaric hypoxia, we cannot exclude that the outcome might be somewhat different with exposure to real high altitude, in which additional factors like hypobaria and exertion may play a role. We are confident with regard to hypobaria that its influence is minimal because we repeatedly[11] observed the same symptoms[18] with a comparable prevalence in normobaric hypoxia as we do at an altitude of 4559 m.[2] Exercise and exertion, which were not involved in our testing, may enhance AMS.[19] On the other hand, we exposed subjects within minutes to hypoxia equivalent to 4500 m, whereas mountaineers usually take a few days to reach this altitude, even on Kilimanjaro. Thus, the immediate exposure may compensate for the lack of exercise as an AMS risk factor in our setting.

Blood gas analysis and pulse oximetry shown in Table 3 demonstrates that subjects with AMS had a lower S_{PO_2} and a trend toward a lower P_{aO_2} and ventilation, which were all more pronounced after 4 hours than after 20 hours of exposure (ie, at a time when symptoms of AMS develop). Measurements obtained after 4 hours of hypoxia before and after the intervention show that ventilation, P_{aO_2}, and S_{PO_2} are all higher in those who slept in hypoxia, whereas they remain unchanged in the control group. The changes in the treatment group are, however, not statistically significant because of the small sample on measurements with large interindividual variability. Nevertheless, they are compatible with the hypothesis that ventilatory[20] acclimatization occurred during sleeping in moderate hypoxia and that it was partly conserved over 4 days, contributing to a better oxygenation with reexposure and thus attenuating AMS. Others have shown that ventilatory response to hypoxia increases when sleeping 15 nights at a normobaric hypoxia equivalent to an altitude of 2650 m.[21] Carryover effects for increased ventilation and S_{PO_2} in hypoxia were reported to last for several weeks,[22] and prevention of AMS with acclimatization was shown to persist at least 8 days.[23] In addition, other effects of acclimatization, which were not assessed in our study, such as increasing O_2 content by decreasing plasma volume, may have contributed to the attenuation of AMS, although an increase of total hemoglobin mass can be excluded with this type of exposure.[24]

In summary, symptoms of AMS during acute exposure to hypoxia equivalent to an altitude of 4500 m are significantly reduced for at least 4 days after sleeping 14 consecutive nights in normobaric hypoxia equivalent to an altitude of 2600 m. Thus, acclimatizing at home during sleep may be an alternative for those who consider taking drugs for prevention of AMS when travelling to high altitude.

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References

1. Hackett PH, Roach RC. High-altitude illness. *N Engl J Med*. 2001;345:107–114.

2. Schneider M, Bernasch D, Weymann J, Holle R, Bärtsch P. Acute mountain sickness: influence of susceptibility, pre-exposure and ascent rate. *Med Sci Sports Exerc*. 2002;34:1886–1891.
3. Swenson E, Teppema LJ. Prevention of acute mountain sickness by acetazolamide: as yet an unfinished story. *J Appl Physiol*. 2007;102:1305–1307.
4. Bärtsch P, Maggiorini M, Ritter M, Noti C, Vock P, Oelz O. Prevention of high-altitude pulmonary edema by nifedipine. *N Engl J Med*. 1991;325:1284–1289.
5. Beidleman BA, Muza SR, Fulco CS, et al. Intermittent altitude exposures reduce acute mountain sickness at 4300 m. *Clin Sci (Lond)*. 2004;106:321–328.
6. Richalet J-P, Bittel J, Herry J-P, et al. Use of a hypobaric chamber for pre-acclimatization before climbing Mount Everest. *Int J Sports Med*. 1992;1(suppl 1):S216–S220.
7. Beidleman BA, Fulco CS, Muza SR, et al. Effect of six days of staging on physiologic adjustments and acute mountain sickness during ascent to 4300 meters. *High Alt Med Biol*. 2009;10:253–260.
8. Fulco CS, Muza SR, Beidleman BA, et al. Effect of repeated normobaric hypoxia exposures during sleep on acute mountain sickness, exercise performance, and sleep during exposure to terrestrial altitude. *Am J Physiol Regul Integr Comp Physiol*. 2011;300:R428–R436.
9. Roach RC, Bärtsch P, Hackett PH, Oelz O. The Lake Louise acute mountain sickness scoring system. In: Sutton JR, Houston CS, Coates G, eds. *Hypoxia and Molecular Medicine* Burlington, VT: Queen City Printers; 1993:272–274.
10. Sampson JB, Cymerman A, Burse RL, Maher JT, Rock PB. Procedures for the measurement of acute mountain sickness. *Aviat Space Environ Med*. 1983;54:1063–1073.
11. Bailey DM, Roukens R, Knauth M, et al. Free radical-mediated damage to barrier function is not associated with altered brain morphology in high-altitude headache. *J Cereb Blood Flow Metab*. 2006;26:99–111.
12. Muhm JM, Rock PB, McMullin DL, et al. Effect of aircraft-cabin altitude on passenger discomfort. *N Engl J Med*. 2007;357:18–27.
13. Honigman B, Theis MK, Koziol-McLain J, et al. Acute mountain sickness in a general tourist population at moderate altitudes. *Ann Intern Med*. 1993;118:587–592.
14. Bärtsch P, Roach R. Acute mountain sickness and high-altitude cerebral edema. In: Hornbein TF, Schoene RB, eds. *High Altitude: An Exploration of Human Adaptation.* New York, NY: Marcel Dekker; 2001:731–776.
15. Fulco CS, Beidleman BA, Muza SR. Effectiveness of pre-acclimatization strategies for high altitude exposure. *Exerc Sport Sci Rev*. 2013;41:55–63.
16. Maggiorini M, Müller A, Hofstetter D, Bärtsch P, Oelz O. Assessment of acute mountain sickness by different score protocols in the Swiss Alps. *Aviat Space Environ Med*. 1998;69:1186–1192.
17. Dumont L, Mardirosoff C, Tramèr MR. Efficacy and harm of pharmacological prevention of acute mountain sickness: quantitative systematic review. *BMJ*. 2000;321:267–272.
18. Schommer K, Menold E, Subudhi AW, Bärtsch P. Health risk for athletes at moderate altitude and normobaric hypoxia. *Br J Sports Med*. 2012;46:828–832.
19. Roach RC, Maes D, Sandoval D, et al. Exercise exacerbates acute mountain sickness at simulated high altitude. *J Appl Physiol*. 2000;88:581–585.
20. Rahn H, Otis AB. Man's respiratory response during and after acclimatization to high altitude. *Am J Physiol*. 1949;157:445–462.
21. Townsend NE, Gore CJ, Hahn AG, et al. Living high-training low increases hypoxic ventilatory response of well-trained endurance athletes. *J Appl Physiol*. 2002;93:1498–1505.
22. Katayama K, Fujita H, Sato K, Ishida K, Iwasaki K, Miyamura M. Effect of a repeated series of intermittent hypoxic exposures on ventilatory response in humans. *High Alt Med Biol*. 2005;6:50–59.
23. Lyons TP, Muza SR, Rock PB, Cymerman A. The effect of altitude pre-acclimatization on acute mountain sickness during reexposure. *Aviat Space Environ Med*. 1995;66:957–962.
24. Schmidt W, Prommer N. Effects of various training modalities on blood volume. *Scand J Med Sci Sports*. 2008;18(suppl 1):57–69.