ORIGINAL RESEARCH

Acute Mountain Sickness Is Not Repeatable Across Two 12-Hour Normobaric Hypoxia Exposures

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Objective.—The purposes of this experiment were to determine the repeatability of acute mountain sickness (AMS), AMS symptoms, and physiological responses across 2 identical hypoxic exposures.

Methods.—Subjects ($n = 25$) spent 3 nights at simulated altitude in a normobaric hypoxia chamber: twice at a partial pressure of inspired oxygen ($P_{I_{O_2}}$) of 90 mmHg (4000 m equivalent; “hypoxia”) and once at a $P_{I_{O_2}}$ of 132 mmHg (1000 m equivalent; “sham”) with 14 or more days between exposures. The following variables were measured at hours 0 and 12 of each exposure: AMS severity (ie, Lake Louise score [LLS]), AMS incidence (LLS ≥ 3), heart rate, oxygen saturation, blood pressure, and the fraction of exhaled nitric oxide. Oxygen saturation and heart rate were also measured while subjects slept.

Results.—The incidence of AMS was not statistically different between the 2 exposures (84% vs 56%, $P > .05$), but the severity of AMS (ie, LLS) was significantly lower on the second hypoxic exposure (mean [SD], 3.1 [1.8]) relative to the first hypoxic exposure (4.8 [2.3]; $P < .001$). Headache was the only AMS symptom to have a significantly greater severity on both hypoxic exposures (relative to the sham exposure, $P < .05$). Physiological variables were moderately to strongly repeatable (intraclass correlation range 0.39 to 0.86) but were not associated with AMS susceptibility ($P > .05$).

Conclusions.—The LLS was not repeatable across 2 identical hypoxic exposures. Increased familiarity with the environment (not acclimation) could explain the reduced AMS severity on the second hypoxic exposure. Headache was the most reliable AMS symptom.

Key words: high altitude, reproducibility, acclimation, acclimatization, previous history

Introduction

Acute mountain sickness (AMS) is a relatively common form of altitude illness that can occur after rapid ascents to altitudes above 2500 m or during exposures to (normobaric or hypobaric) hypoxia in a laboratory.¹ Humans vary significantly in their abilities to acclimatize to hypoxia, and researchers often use AMS as a marker of inadequate acclimatization or acclimation.¹ Despite much research, the etiology of hypoxia intolerance is not well understood,² and identifying persons who are susceptible to AMS before hypoxia exposure is difficult (eg, Barry and Pollard³).

Repeatability is an assessment of consistency within persons over a series of measurements.⁴ Although a previous history of AMS is frequently stated to be a strong risk factor for the recurrence of AMS,^{3,5} evidence for the repeatability of AMS is not conclusive. Multiple studies reported associations between AMS history and AMS recurrence,^{6–8} however, these studies also reported moderate numbers of false positives (positive AMS history, negative AMS diagnosis) and false negatives (negative AMS history, positive AMS diagnosis), thus questioning the extent to which AMS is repeatable. Three prospective studies reported that AMS was repeatable,^{9–11} but hypoxic exposures were not necessarily comparable in 2 of the studies because of vasopressin use on 1 exposure¹² and a high likelihood of acclimatization on 1 exposure.¹⁰ Furthermore, the sample sizes were small (<20) in 2 of the studies,^{9,10} and all 3 lacked sham conditions to blind subjects to the conditions.

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The physiological processes responsible for individual differences in AMS susceptibility have yet to be determined, and a reliable physiological predictor of AMS remains elusive.¹³ Currently, results are inconsistent for associations between AMS and physiological variables such as blood oxygen saturation (SpO_2),^{14,15} heart rate (HR),¹⁶ blood pressure (BP),^{16,17} and the fraction of exhaled nitric oxide ($\text{F}_{\text{E}_{\text{NO}}}$).^{18,19} Establishing the repeatability of AMS in conjunction with the repeatability of these physiological variables should clarify which variables are associated with AMS and which are not.

This experiment was designed to determine the repeatability of AMS, AMS symptoms, and objective physiological variables across 2 identical normobaric hypoxia exposures. To prevent bias in self-reported AMS symptoms, a sham exposure was included in the experimental design and subjects were blinded to the experimental conditions. We hypothesized that individual physiological responses to hypoxia would be repeatable across the 2 identical hypoxic exposures and that each of the physiological variables would be associated with AMS.

Methods

SUBJECTS

Twenty-six healthy nonsmoking subjects (17 male; 9 female) were recruited, all of whom resided at low altitude (ie, <200 m above sea level) and had not ascended above 2500 m (excluding commercial flights in pressurized airliners) in the 2 months preceding each exposure. Subjects were asked about their caffeine use, and those who acknowledged withdrawal symptoms from abstinence were excluded because caffeine intake was restricted and symptoms of caffeine withdrawal can mimic symptoms of AMS.²⁰ On their first visits to the laboratory, subjects were familiarized with the procedures and the testing environment. The Clinical Research Ethics Board of the University of British Columbia approved this study, and each subject provided written informed consent before participating.

EXPERIMENTAL DESIGN

This experiment utilized a single-blind, sham-controlled design. Subjects slept 3 nights in a normobaric hypoxia chamber (Colorado Altitude Training, Louisville, CO) located approximately 100 m above sea level at the University of British Columbia's Vancouver Campus. The chamber (approximate volume of 15.6 m³) was a transparent box housed in a large room with natural lighting. The temperature was controlled at 22°C ± 3°C,

but humidity was not controlled. Subjects were exposed to hypoxia on 2 occasions (H1 and H2) with partial pressure of oxygen ($\text{P}_{\text{I}_{\text{O}_2}}$) of 90 mmHg (4000 m equivalent)²¹ and to a sham condition on 1 occasion (SH) with $\text{P}_{\text{I}_{\text{O}_2}}$ of 132 mmHg (1000 m equivalent),²¹ with a minimum of 14 days between each exposure. The $\text{P}_{\text{I}_{\text{O}_2}}$ was measured with the chamber's built-in sensors, and airflow into the chamber was modified as necessary by the chamber to maintain the desired hypoxic dose. An exhaust fan vented the chamber to limit CO₂ accumulation.

Subjects entered the chamber in the evening and remained in the chamber for 12 hours before exiting the next morning. Two subjects occupied the chamber simultaneously for most exposures, but a single subject occupied the chamber for 6 exposures owing to scheduling conflicts. Subjects were randomly divided into 3 groups, with each group experiencing SH on the first, second, or third exposure. Making the chamber slightly hypoxic for the SH exposure was necessary to mimic the sound of the hypoxic exposures. The SH $\text{P}_{\text{I}_{\text{O}_2}}$ did not lower the subjects' SpO_2 values relative to baseline (although it would lower the partial pressure of oxygen in arterial blood) and AMS does not occur at 1000 m.¹ Subjects were blinded to the conditions, but the researchers were not because SpO_2 values needed to be monitored as a safety precaution.

To limit confounding effects on various measurements, subjects were asked to refrain from the intake of food and drink for 2 hours, caffeine for 12 hours, alcohol for 24 hours, and food rich in nitrates for 48 hours before entering the chamber.²² Subjects ingested water ad libitum in the chamber and were offered a standard meal after 1 hour. While in the chamber, subjects rested (ie, performed no physical activity).

PHYSIOLOGICAL MEASUREMENTS

All variables were measured in room air before subjects entered the chamber (hour 0) and inside the chamber before subjects exited (hour 12). Subjects were awoken 30 minutes before exiting the chamber to allow for data collection.

Hypoxia tolerance was assessed using the Lake Louise score (LLS) questionnaire,²³ which required subjects to rate 5 symptoms of AMS (headache, gastrointestinal symptoms, fatigue, dizziness, and sleep difficulty) on a scale of 0 (not present) to 3 (severe). A LLS of 3 or greater with a headache score of 1 or greater was considered a positive diagnosis (AMS+), and a LLS not meeting these criteria was considered a negative diagnosis (AMS-).²³

While subjects were supine, HR and SpO_2 were measured from the ear lobe with a tabletop pulse oximeter (Avant 9600; Nonin Instruments, Plymouth, MN). Both variables were recorded continuously for 5 minutes, and the mean of each recording was analyzed. With the subjects still supine, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured with a BPM-200 automated blood pressure monitor (BpTRU; Coquitlam, BC, Canada). The average of 3 measurements was analyzed. Mean arterial pressure (MAP) was estimated as $2/3 \text{ DBP} + 1/3 \text{ SBP}$. The F_{ENO} was measured using a NIOX MINO handheld electrochemical analyzer (Aerocrine AB, Solna, Sweden) according to the manufacturer's recommendations and the established guidelines.²⁴ The F_{ENO} was measured once at hour 0 and once at hour 12. Normobaric hypoxia does not affect the accuracy of this device.²⁵

Nocturnal HR and SpO_2 were measured continuously while subjects slept using pulse oximetry (as described above). Six-hour blocks of data (corresponding to hours 5 to 11, the hours during which subjects were most likely to be sleeping) were analyzed for each subject during each exposure. From these data, the 6-hour means for HR and SpO_2 were calculated, and the proportion of time elapsed below SpO_2 thresholds (ie, time below 70% SpO_2 , time below 75% SpO_2 , and so forth) were calculated.

DATA ANALYSIS

Data analysis was performed using SPSS version 21.0 (IBM, Armonk, NY), and alpha was set to 0.05 for all statistical tests.

The severity of AMS and the severity of each individual AMS symptom during each condition (at hour 12) were compared with a one-way analysis of variance (ANOVA) and Friedman tests, respectively. Post hoc analysis was performed with Bonferroni-corrected paired samples *t* tests and Wilcoxon signed rank tests, respectively. The exact McNemar's test was used to compare the incidence of AMS and its symptoms across exposures. The percent agreement²⁶ was calculated as a measure of repeatability. To determine if familiarity with the chamber affected the LLS, tests for linear trends were performed (independent variable, condition; dependent variable, LLS).

The effect of the condition on each continuous physiological variable was determined using a two-way repeated measures ANOVA (time [0 and 12 hours] vs condition [H1, H2, SH]). Post hoc analysis was performed with Bonferroni-corrected paired samples *t* tests within each exposure and across exposures at hour 12. The effect of condition on mean nocturnal HR and SpO_2

was determined with one-way repeated measures ANOVA and a similar post hoc analysis. The repeatability of each physiological variable was measured with an intraclass correlation (ICC), and the association between physiological variables and AMS was tested with independent *t* tests.

Results

SUBJECT CHARACTERISTICS

Twenty-five subjects (9 female and 16 male) completed this experiment, and 1 male subject withdrew from the study after completing 2 exposures. The mean (SD) age of subjects was 24.6 years (6.2 years), mean height was 175 cm (8.4 cm), and mean weight was 72 kg (12 kg). One subject's F_{ENO} data were excluded from analysis because she exhaled more than 100 parts per billion (ppb), approximately 5 times larger than the mean, and high F_{ENO} can indicate the presence of asthma,²⁷ which was an exclusion criterion for the F_{ENO} component of the study. After 8 subjects had begun the experiment, BP measurements were added as outcome variables ($n = 17$ for these variables). Consecutive exposures were separated by a median of 21 days (14–108 days), and H1 and H2 were separated by a median of 28 days (14–138 days).

NORMOBARIC CHAMBER CONDITIONS

A mean P_{IO_2} of 90 mmHg (87–93 mmHg) was maintained for all hypoxic exposures, and a mean P_{IO_2} of 132 mmHg (129–135 mmHg) was maintained for sham exposures. The partial pressure of carbon dioxide (P_{CO_2}) was not measured during each exposure; however, multiple measurements made during the study demonstrated that the chamber maintained the P_{CO_2} below 2.6 mmHg in hypoxic and sham conditions.

REPEATABILITY OF AMS AND ITS SYMPTOMS

The incidence and severity of AMS were much greater in both hypoxic exposures (H1 and H2) compared to the SH exposure (Table 1, Figure 1). The severity of AMS was significantly lower (–35%) in H2 relative to H1 ($P < .001$; Table 1), but the difference in the incidence of AMS from H1 to H2 (also –35%) was not statistically significant ($P = .065$). Agreements for the incidence and severity of AMS on H1 and H2 were low (Table 1).

The incidence and severity of all 5 individual symptoms comprising the LLS were significantly greater in H1 relative to SH, but only the incidence and severity of headache symptoms were significantly greater in H2 relative to SH (Table 1). Agreements for the incidence and severity of AMS symptoms were variable (Table 1).

Table 1. Incidence and severity of acute mountain sickness and its individual symptoms in 1 sham and 2 normobaric hypoxia exposures

Symptom	Incidence				Severity			
	SH ^a	H1 ^a	H2 ^a	Agreement ^b	SH ^c	H1 ^c	H2 ^c	Agreement ^b
Headache	3 (12)	21 (84) ^d	19 (76) ^d	16 (68)	0 (0–1)	2 (0–3) ^d	1 (0–2) ^d	8 (32)
Gastrointestinal	0 (0)	6 (24) ^d	1 (4) ^e	20 (80)	0 (0)	0 (0–2) ^d	0 (0–1) ^e	20 (80)
Fatigue	4 (16)	14 (56) ^d	5 (20) ^e	16 (64)	0 (0–1)	1 (0–2) ^d	0 (0–2) ^e	14 (56)
Dizziness	2 (8)	9 (36) ^d	6 (24)	18 (72)	0 (0–1)	0 (0–2) ^d	0 (0–2)	17 (68)
Sleep difficulty	18 (72)	24 (96) ^d	22 (88)	23 (92)	1 (0–2)	2 (0–3) ^d	1 (0–3)	12 (48)
AMS	1 (4)	21 (84) ^d	14 (56) ^d	14 (56)	1.2 (1.0)	4.8 (2.3) ^d	3.1 (1.8) ^{d,e}	4 (16)

^a The number (percentage) of subjects who had each symptom and acute mountain sickness (AMS).

^b The number (percentage) of subjects who had the same response on first hypoxia exposure (H1) and second hypoxia exposure (H2).

^c For individual symptoms, the median (range) is reported; for AMS, the mean (SD) is reported.

^d Significant difference from the sham exposure (SH).

^e Significant difference between the 2 hypoxic conditions.

The incidence and severity of headache were not statistically different between H1 and H2 (Table 1).

The decrease in LLS across SH exposures was not statistically significant ($P = .066$), but the linear trend for a decrease in sleep difficulty scores was statistically significant ($P = .025$; Figure 2).

REPEATABILITY OF PHYSIOLOGICAL RESPONSES TO HYPOXIA

As shown in Table 2, SpO_2 was significantly decreased by hypoxia; HR, DBP, and MAP were significantly increased by hypoxia; and $\text{F}_{\text{E}_{\text{NO}}}$ and SBP were unaffected by hypoxia. At hour 12, the means of each physiological variable were not statistically different in H1 and H2

(Table 2). The ICC of physiological variables at hour 12 ranged from 0.39 to 0.84, indicating moderate to strong repeatability in normobaric hypoxia (Table 2).

Nocturnal HR was greater on H1 (63.2 [10.6] beats/min) and H2 (60.1 [11.5] beats/min) relative to SH (52.5 [9.1] beats/min; $P < .001$ for both comparisons); and nocturnal HR was greater on H1 compared to H2 ($P = .005$). Relative to SH (97.5% [1.5%]), nocturnal SpO_2 was lower on H1 (79.4% [4.6%]; $P < .001$) and H2 (80.2% [4.7%]; $P < .001$); however, nocturnal SpO_2 was similar on H1 and H2 ($P = .14$). The ICC of nocturnal HR and nocturnal SpO_2 were 0.86 and 0.68, respectively ($P < .05$ for both).

PREDICTING AND DIAGNOSING AMS

Twelve subjects were AMS+/AMS+, 2 subjects were AMS–/AMS–, 9 subjects were AMS+/AMS–, and 2 subjects were AMS–/AMS+ on H1 and H2, respectively; therefore, the AMS diagnosis on H1 had a sensitivity of 86%, a specificity of 18%, a positive predictive value of 56%, and a negative predictive value of 50% for the AMS status on H2.

The AMS+ and AMS– subjects' data were only compared on H2 because the distribution of subjects was unbalanced on H1 (ie, 21 AMS+, 4 AMS– on H1). None of the physiological variables was significantly associated with AMS (Table 3). The mean proportion of time elapsed below each SpO_2 threshold was similar for AMS+ and AMS– subjects, and nocturnal SpO_2 was not associated with LLS (Figure 3).

Discussion

This is the first experiment to assess AMS repeatability with a single blind, sham-controlled design. Contrary to

Figure 1. The Lake Louise score at hour 0 (open bars) and hour 12 (solid bars) of the sham, first hypoxic, and second hypoxic exposures ($\text{P}_{\text{I}_{\text{O}_2}}$ was 132 mmHg, 90 mmHg, and 90 mmHg, respectively). *Denotes a 12-hour mean that was significantly greater than the 0-hour mean of the same condition ($P < .05$). †Denotes a 12-hour mean that was significantly greater than the 12-hour sham mean ($P < .05$). §Denotes a 12-hour mean that was significantly greater than the 12-hour mean of the second hypoxia exposure ($P < .05$). Error bars represent 1 SD of the mean, and $n = 25$.

Figure 2. The mean Lake Louise score (left) and sleep difficulty item score (right) from hour 12 of sham conditions that randomly occurred on the first ($n = 8$), second ($n = 8$), or third ($n = 9$) exposure of the study. Error bars represent 1 SD of the mean. †Denotes a statistically significant linear trend for decreasing sleep difficulty scores ($P = .025$). The linear trend for the Lake Louise Score was not statistically significant ($P = .066$).

our hypotheses, the severity of AMS (measured with the LLS) was lower on the second hypoxic exposure relative to the first, and none of the physiological variables was associated with AMS. As hypothesized, however, physiological variables were moderately to strongly repeatable across H1 and H2. We suggest that familiarization with

the environment may be responsible for the decrease in AMS symptom severity across hypoxic exposures.

The difference in the AMS incidence between H1 and H2 was not statistically significant; however, that the severity of AMS was significantly lower in H2 still suggests that AMS was not repeatable in this experiment.

Table 2. Physiological responses to one 12-hour sham exposure and two 12-hour hypoxia exposures

Variable	Condition	n	Time		Change (%) ^a	ICC ^b
			Hour 0	Hour 12		
HR, beats/min	SH	25	62.4 (10.3)	55.2 (11.3) ^c	−11.5	0.84 ^e
	H1	25	62.3 (9.54)	64.5 (12.5) ^d	+3.5	
	H2	25	63.3 (9.88)	62.0 (13.5) ^d	+2.1	
SpO ₂ , %	SH	25	97.9 (1.15)	98.0 (1.02)	+0.0	0.39 ^e
	H1	25	98.3 (1.32)	84.7 (4.67) ^{c,d}	−13.9	
	H2	25	98.1 (1.20)	84.8 (5.18) ^{c,d}	−13.6	
F _E NO, ppb	SH	24	21.6 (8.16)	21.8 (7.65)	+0.9	0.78 ^e
	H1	24	21.6 (10.8)	22.0 (8.66)	+1.9	
	H2	24	22.1 (9.03)	23.8 (9.17)	+7.7	
SBP, mmHg	SH	17	109.2 (11.1)	106.7 (10.6)	−2.3	0.65 ^e
	H1	17	108.1 (9.12)	109.1 (7.85)	+0.9	
	H2	17	105.2 (8.10)	107.8 (8.74)	+2.5	
DBP, mmHg	SH	17	64.7 (5.35)	64.5 (7.29)	−0.3	0.57 ^e
	H1	17	63.9 (5.26)	69.0 (4.78) ^{c,d}	+8.0	
	H2	17	62.3 (4.40)	67.0 (7.33) ^c	+7.5	
MAP, mmHg	SH	17	79.6 (6.49)	78.4 (7.76)	−1.5	0.66 ^e
	H1	17	78.8 (5.53)	82.2 (5.34) ^{c,d}	+4.3	
	H2	17	76.6 (4.69)	80.6 (6.51) ^c	+5.2	

Data are presented as mean (SD).

HR, heart rate; SpO₂, oxygen saturation; F_ENO, fraction of exhaled nitric oxide; ppb, parts per billion; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure.

^a The percent change is calculated for hour 12 relative to hour 0 of the same exposure.

^b Intraclass correlations (ICC) are calculated for mean values measured at hour 12 of the first hypoxia exposure (H1) and second hypoxia exposure (H2).

^c Statistically different from hour 0 in the same exposure after Bonferroni correction ($P < .008$).

^d Statistically different from hour 12 of sham exposure (SH) after Bonferroni correction ($P < .008$).

^e Statistically significant ICC at hour 12 of H1 and H2 ($P < .05$).

Table 3. Physiological responses to the second 12-hour normobaric hypoxia exposure in subjects with and subjects without acute mountain sickness

Variable	n	Time (hour)	AMS–	AMS+	T statistic	P value
HR, beats/min	25	0	60.9 (9.1)	65.1 (10.4)	–1.05	.31
HR, beats/min	25	5–11	57.0 (10.1)	62.5 (12.3)	–1.19	.25
HR, beats/min	25	12	58.4 (12.0)	64.9 (14.4)	–1.20	.24
SpO ₂ , %	25	0	98.2 (1.1)	98.0 (1.3)	0.46	.65
SpO ₂ , %	25	5–11	79.8 (4.0)	80.6 (5.3)	–0.40	.69
SpO ₂ , %	25	12	85.5 (2.8)	84.2 (6.5)	0.65	.52
F _E NO, ppb	24	0	24.8 (10.4)	19.8 (7.4)	1.37	.19
F _E NO, ppb	24	12	25.7 (9.9)	22.1 (8.5)	0.97	.34
SBP, mmHg	17	0	105.0 (7.5)	105.3 (8.8)	–0.06	.95
SBP, mmHg	17	12	106.8 (8.7)	108.4 (9.1)	–0.34	.74
DBP, mmHg	17	0	60.7 (4.6)	63.2 (4.2)	–1.14	.27
DBP, mmHg	17	12	65.0 (6.7)	68.1 (7.7)	–0.82	.42
MAP, mmHg	17	0	75.4 (5.5)	77.2 (4.3)	–0.73	.48
MAP, mmHg	17	12	79.2 (5.3)	81.5 (7.1)	–0.68	.50

Data are presented as mean (SD).

AMS–, without acute mountain sickness; AMS+, with acute mountain sickness; HR, heart rate; SpO₂, oxygen saturation; F_ENO, fraction of exhaled nitric oxide; ppb, parts per billion; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure.

The severity of AMS is more sensitive to changes than the incidence of AMS, making it a better index for repeatability: for any decrease in LLS, whether a change in AMS incidence would occur is dependent on 1) the threshold LLS for a positive AMS diagnosis, and 2) the mean severity of AMS induced by the experimental conditions. The lack of repeatability suggests that it may be inappropriate to categorize subjects as AMS susceptible or AMS resistant after 1 hypoxia exposure.

Headache, the cardinal symptom of AMS,²⁸ was the only symptom with a significantly greater incidence and severity in H1 and H2 relative to SH. The incidence and severity of headache were not statistically different in H1 and H2, suggesting that headache symptoms may be influenced less by familiarization than other AMS symptoms. Sleep difficulty was the only other symptom that occurred commonly on H2, but the elevated sleep-difficulty scores in SH suggest that the chamber (independent of hypoxia) was responsible for much of the difficulty sleeping.

The decrease in LLS from H1 to H2 was not likely due to hypoxia acclimation. Although 5 days above 3000 m in the 2 months preceding an ascent to 4559 m decreased the risk of AMS,⁷ to our knowledge, sustained acclimation multiple weeks after a single 12-hour exposure to hypoxia has not been demonstrated (in awake or sleeping subjects). A washout period similar to the one employed in this study (ie, 12–14 days) was previously used to prevent carryover effects between 2 longer (22-hour) hypoxic exposures (barometric pressure

446 mmHg; 4300 m equivalent).²⁹ That objective physiological responses were similar to H1 and H2 also suggests subjects were not acclimated to hypoxia on the second hypoxic exposure.

Our data suggest that familiarization to the environment affects the LLS, and our results reaffirm the subjective nature of the LLS. An unfamiliar sleeping environment and the anticipation of unpleasant symptoms (the potential symptoms of AMS were a required element of the consent forms) may have been responsible for the greater LLS on H1. MacNutt et al³⁰ suggested that a greater “psychological tolerance” of altitude (acquired from previous ascents) could explain the reduced AMS symptoms observed in subjects reascending to altitude. Although our subjects did not ascend to altitude, they may have been anxious about the experiment. In support of this suggestion, sleep quality improved significantly with the number of previous exposures to the chamber, and mean HR, SBP, DBP, and MAP were slightly lower in H2 compared with H1 (at hour 12), possibly indicating reduced anxiety. Although familiarization with the environment has been postulated to be a potential confounding variable in studies of this sort,²⁹ this study is the first to demonstrate that familiarization with the testing environment affects self-reported LLS.

That AMS severity was not repeatable is in disagreement with previous studies,^{9–11} but between-study comparisons are difficult for a number of reasons. Firstly, only 1 previous study¹¹ used the LLS questionnaire, and

Figure 3. Nocturnal oxygen saturation (SpO₂) of subjects during the second hypoxic exposure. (A) The relationship between the mean SpO₂ and the Lake Louise score on the second hypoxic exposure. (B) The percentage of time elapsed below thresholds of SpO₂ for subjects with acute mountain sickness (AMS+ [open bars]) and subjects without acute mountain sickness (AMS- [solid bars]). Error bars represent 1 SD of the mean, and $n = 25$.

methods of assessing AMS (eg, Hackett's score³¹) used in the other studies will likely have different psychometric properties compared to the LLS that will affect repeatability. Secondly, the methods used to calculate or confirm AMS repeatability differed substantially across studies, preventing a direct comparison of quantitative repeatability statistics. Thirdly, methodological differences make direct comparisons problematic because 2 studies occurred at high altitude,^{10,11} 1 study utilized a hypobaric chamber,⁹ and our study was conducted in a normobaric chamber. It is possible that there would be a greater effect of familiarization in a chamber experiment than in a high-altitude experiment because sleeping in a chamber would be a novel experience for the subjects, whereas sleeping in a high-altitude setting could be similar to sleeping in a low-altitude setting in many ways. Finally, we included the SH exposure to reduce subject bias, which was not done in any of the previous studies.

Pulse oximetry is frequently used in field studies of AMS, but pulse oximetry has not been conclusively

demonstrated to be a reliable diagnostic tool for AMS.³² Mean HR (wakeful) was highly repeatable in this study, but similar to previous studies (eg, Wagner et al³³), HR was not associated with AMS. The mean SpO₂ (wakeful) had the lowest repeatability, and it was also not associated with AMS. Our SpO₂ results are in agreement with some studies,^{15,33} but not with others that showed AMS+ subjects to have lower SpO₂ values than AMS- subjects.^{14,34} The low repeatability of wakeful SpO₂ may explain mixed results in the literature. As HR is strongly affected by physical exertion and SpO₂ is strongly influenced by voluntary breathing patterns,³⁵ Windsor³² proposed that pulse oximetry data collected during sleep may be more informative than data collected during wakefulness; however, our results demonstrated that, although nocturnal HR and SpO₂ were repeatable, neither variable was associated with AMS. This finding conflicts with previous studies that reported a lower mean nocturnal SpO₂ in AMS+ subjects relative to AMS- subjects.^{36,37}

In addition to pulse oximetry, we tested BP and F_{E_{NO}} for associations with AMS. Blood pressure was not associated with AMS, but our sample size was relatively small ($n = 17$) for these comparisons. The ICCs of SBP, DBP, and MAP were lower than those measured in normoxia,³⁸ possibly because of the small range of each variable in our data.³⁹ The F_{E_{NO}} was unaffected by normobaric hypoxia, a finding that supports previous studies,^{19,25,40} and the high repeatability of F_{E_{NO}} agrees with data collected in normoxia.⁴¹ The AMS+ subjects had a lower mean F_{E_{NO}} than the AMS- subjects, which, although not statistically significant ($P = .065$), is consistent with previous studies.^{19,42}

STUDY LIMITATIONS

There are several limitations to this experiment that should be considered when interpreting our results. Firstly, we cannot rule out the possibility that a consistent history of AMS symptoms across multiple (> 2) independent exposures to hypoxia would be useful for predicting AMS on future exposures. Secondly, as with any study with a small to moderate sample size, we also cannot rule out the possibility of type I errors. Thirdly, the duration of the exposures were a compromise between feasibility and the typical time course of AMS, and increasing the exposure length may affect the repeatability of AMS. Finally, it is unclear whether our results can be generalized to high altitude settings. Subjects were exposed to normobaric hypoxia instead of hypobaric hypoxia, and the 2 modes of hypoxia may differ in terms of their capacities to induce AMS.^{43,44} Exposure to normobaric hypoxia also requires subjects to

be confined to a small space that is unfamiliar and potentially uncomfortable, possibly making this mode of hypoxia different from a true altitude exposure.⁴⁵ Similarly, the normobaric hypoxia chamber used in this study was not able to maintain a CO₂ concentration equal to the atmospheric concentration of CO₂. The higher ambient CO₂ would not likely have a large effect on ventilation,⁴⁶ and the repeated measures design and inclusion of a sham condition should have controlled for any effects that the slight hypercapnia would have on the subjects; however, this difference is still a limitation to our study.

Conclusions

We demonstrated that AMS severity (measured with the LLS questionnaire) was not repeatable in response to 2 identical 12-hour normobaric hypoxia exposures, and that the AMS status on H1 was not a reliable predictor of the AMS status on H2. The measured physiological responses to normobaric hypoxia were moderately to strongly repeatable, but none was associated with AMS status. Finally, a greater focus on headache may be warranted in future AMS studies: headache was repeatable across hypoxic conditions, and headache was the only AMS symptom with an elevated severity (relative to sham) on the second hypoxic exposure.

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