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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 $\geq$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 Pollard[3]).

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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 exposure[12] 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.

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 ($F_{E_{NO}}$).[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 abstention 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 m^3) was a transparent box housed in a large room with natural lighting. The temperature was controlled at $22^{\circ}C \pm 3^{\circ}C$, but humidity was not controlled. Subjects were exposed to hypoxia on 2 occasions (H1 and H2) with partial pressure of oxygen ($P_{I_{O_2}}$) of 90 mmHg (4000 m equivalent)[21] and to a sham condition on 1 occasion (SH) with $P_{I_{O_2}}$ of 132 mmHg (1000 m equivalent),[21] with a minimum of 14 days between each exposure. The $P_{I_{O_2}}$ 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 CO_2 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 $P_{I_{O_2}}$ 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]