Acute mountain sickness, chemosensitivity, and cardiorespiratory responses in humans exposed to hypobaric and normobaric hypoxia

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HYPobaric hypoxia (HH) lowers the PO2 by reduction of barometric pressure (Pb), which in turn reduces end-tidal CO2 levels (fCO2). Normobaric hypoxia (NH) lowers the PO2 by reducing the fraction of inspired oxygen (FiO2) through addition of exogenous nitrogen (N2) without altering Pb. While acute mountain sickness (AMS) is a self-limiting illness experienced by some when exposed to hypoxia for a period of ~6–10 h, in others, symptoms develop as soon as 1 h after hypoxia exposure. The diagnosis of AMS is made if recent high-altitude ascent (>2,500 m) is accompanied by a headache and one or more of the following symptoms: nausea/vomiting, insomnia, general fatigue, and dizziness. At a given hypoxic dose, several groups have reported greater AMS severity in HH relative to NH (17, 34, 41). Since the severity of AMS appears greater in HH than in NH, it has been proposed that a synergistic effect between hypoxia and hypobaria might be responsible for the discrepancy in response (8, 17).

HYPOBaria and hypoxia along with the “specific response to hypobaria” as described by Savourey et al. (39) seem to be a recurring explanation as to why HH exposure causes more severe AMS than NH. Furthermore, a recent series of Point-Counterpoint articles has shown a lack of consensus on...
the equivalence of NH and HH, whereas a recent commentary has also indicated that further comparison of HH and NH is necessary (26, 27, 29). As such, the purpose of this research was to compare hypobaric and normobaric hypoxia at an iso-oxic dose to isolate the effects of lowering barometric pressure vs. lowering the fraction of inspired oxygen. We compared responses over the course of 6-h exposures to HH, NH, hypobaric normoxia (HN), and a sham normobaric normoxia (NN) condition. We hypothesized that exposure to HH would generate greater AMS severity and a lower posttest hypoxia (NN) condition. We hypothesized that those with a higher ventilatory CO2 threshold and a lower ventilatory sensitivity to CO2 as measured before the exposure would demonstrate increased AMS severity.

**METHODS**

**Ethical approval.** This study was approved by the University of British Columbia Clinical Ethics Review Board and conformed to the standards of the Declaration of Helsinki. All subjects provided written consent after receiving verbal and written descriptions of the project. **Recruitment and familiarization.** Subjects (n = 12) were nonsmoking men, 18–47 yr of age, with no history of travel to altitude (>2,500 m) within the prior 2 mo, and no history of cardiorespiratory disease. All subjects were sea-level residents. Subject familiarization allowed subjects to enter the environmental chamber a priori to reduce anxiety on test days. Anthropometric data were collected and basic spirometry testing conducted in accordance with standardized procedures (25). Subjects were also familiarized with the control of breathing tests.

**Study design.** Subjects refrained from alcohol and heavy exercise for 12 h before exposure. They were asked not to modify their caffeine intake, which could influence the rating of hypoxia-related headaches. Subjects commuted to the chamber for the familiarization and 4 test days. Exposures were conducted in a pseudo-randomized crossover, single-blind fashion, allowing a minimum 14-day washout between hypoxic exposures and a 7-day washout between normoxic exposures. Inside the chamber, measurements were taken at 5 min, 30 min, and hourly for 6 h. Subjects took part in sedentary activities in between tests, and light snacks were provided ad libitum. Outside the chamber, subjects underwent the control of breathing tests before and after the 6-h exposure.

**Environmental chamber.** The chamber (Perry Baromedical, Florida) was equipped with CO2, O2, Pb, humidity, and temperature sensors (Analogx Sub-EIR1 5R, Stokesley, North Yorkshire) and a radio communication system (AMCOM 11 2820-4003, Gathersburg, MD). In the NH and NN exposures, the chamber was compressed to 760 Torr as opposed to using the actual geographical altitude (440 m/2721 Torr) as the start point. For the NH exposure, the main lock was hypoxicated by addition of exogenous nitrogen to decrease the FiO2 from 20.93% to 10.5%. In NH, hypobaric normoxia (i.e., HN), the main lock was decompressed to 427 Torr and, to maintain a normoxic environment, exogenous oxygen (FiO2, of 39.5%) was added. Subjects entered the main lock via an entry lock, which was depressurized at 450 m/min (in the case of HH and HN) or hypoxic (in the case of NH) to equilibration with the main lock, with subjects breathing a normoxic gas mix. In the normobaric exposures, the entry lock was slightly depressurized (to 1,500 m) then repressurized to blind subjects by providing the middle-ear sensation of "descent." During all testing, an investigator remained inside the main lock and tended to subjects undergoing measurements at specific time points. Gas partial pressures and simulated altitudes are presented in Table 1. Our target hypoxic dose calculations included the effects of water vapor and are represented as the inspired PO2 (PiO2). There was a minor amount of CO2 accumulation in the chamber where ambient PCO2 was ~1 ± 0.1 Torr across all four conditions.

**Chemosensitivity to CO2.** The Duffin hyperoxic and hypoxic CO2 rebreathe method, described in detail elsewhere (4), was used. Subjects, supine on a massage table, listened to relaxing music with no prominent rhythm. Wearing nose clips and eyeshades, subjects breathed through a mouthpiece (9060 series, Hans Rudolph, Shawnee, KS) connected to a filter and heated pneumotach (3813 Athletic series, Hans Rudolph, Shawnee, KS) measuring flow upon which Ve and VT were determined. The mouthpiece was connected to a three-way valve (ER2870, Hans Rudolph, Shawnee, KS). The valve was attached to a 10-liter rebreathe bag. The end-tidal PO2 (PETCO2) was maintained to either a hypoxic (50 Torr) or hyperoxic tension (150 Torr) by means of a computer-controlled solenoid valve. For hyperoxic tests, the bag contained 6.5% CO2, 26% O2, and balance N2. In the hypoxic test, the bag contained 6.5% CO2, 6% O2, and balance N2. Before the start of the test, subjects were coached through a 5-min hyperventilation to reduce and maintain their end-tidal PCO2 (PETCO2) between 19 and 25 Torr; at this time, the three-way valve was opened to room air. After the hyperventilation, subjects maximally exhaled, and the valve was switched from room air to the rebreathe bag, where subjects were asked to take three large breaths to equilibrate the gas in their lungs with the gas in the rebreathe bag. During basal ventilation, PETCO2 progressively increased until the subject reached his ventilatory response threshold (VRT), the point upon which ventilation increased beyond basal ventilation. The magnitude of the increase in ventilation was termed slope sensitivity or S1. Test termination occurred once Ve reached 100 l/min, the PETCO2 reached 60 Torr, or if the subject experienced severe discomfort. Analog data were collected (NI USB-6229, National Instruments, Austin, TX), and customized software (LabVIEW 10.0, National Instruments) was used to display real-time ventilatory parameters and end-tidal gases over time. Upon completion of the test, Ve was graphed against PETCO2, on a breath-by-breath basis expressed as l·min⁻¹·mmHg⁻¹. From these data, the CO2 VRT and S1 were established. The hyperoxic VRT and S1 estimate the central chemoreceptor threshold and sensitivity, whereas the hypoxic VRT and S1 represent the peripheral chemoreceptor threshold and sensitivity. The hyperoxic test was conducted first, followed by the hypoxic test once ventilation returned to resting values. The same-day coefficient of variation for the HCVR method is 17.9% (range 8.3–26.3%) (35), whereas for the Duffin test it is 18–32% for CO2 sensitivity and 3–3.8% for the CO2 threshold (11).

**HVR.** The HVR was measured on the familiarization day, before and after exposures with procedures based on methods from our research group (13, 15). Supine subjects wore nose clips and breathed through a mouthpiece and heated pneumotach connected to a one-way, non-rebreathing valve (2700 series, Hans Rudolph, Shawnee, KS) while listening to music. Resting ventilation was measured for 5 min to establish baseline PETCO2 values. At the onset of the HVR test, the FiO2 was lowered from 20.93% to ~5% over 5 min by addition of 100% N2 to the inspired air via a custom-made 25-liter mixing chamber. Isocapnia was maintained using a manually controlled gas regulator. End-tidal gases were analyzed breath-by-breath using O2 and CO2 analyzers (Vacumed Fast Response Edition 17625 and 17630, Richard NA et al. • A Comparison of Hypobaric and Normobaric Hypoxia • J Appl Physiol doi:10.1152/japplphysiol.00319.2013 www.jappl.org

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**Table 1. Gas partial pressures and simulated altitudes**

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PB, barometric pressure; FIO2, inspired O2 fraction; PETCO2, inspired PO2.
Subjects were removed from the chamber when a LLS of not sleep in the chamber; therefore, scores were graded out of 12. Scores to comparable questionnaires when used in a terrestrial altitude has been validated in hypobaric chambers (37) and yields similar the Lake Louise score (LLS), to quantify AMS severity (33). The LLS Chart, ADInstruments, Colorado Springs, CO). 

Cardiorespiratory parameters. Inside the chamber, cardiorespiratory variables were measured upon entry (referred to as the 5-min time point) at 30 min and hourly until exit. Blood pressure was measured using an automated blood pressure cuff with the subject sitting feet flat on the ground; three readings were averaged (BPM 200, BpTRU, Coquitlam, BC, Canada). Heart rate (HR) and SpO2 were measured using right earlobe pulse oximetry (CANL-425SV-A, Med Associates, St. Albans, VT) and ventilation by means of a mouthpiece connected to a one-way valve and pneumotach. Analog data were digitized (PowerLab 8/35, ADInstruments, Colorado Springs, CO) and viewed in real time using commercially available software (LabChart, ADInstruments, Colorado Springs, CO). 

AMS. Subjective hypoxia symptoms were measured hourly using the Lake Louise score (LLS), to quantify AMS severity (33). The LLS has been validated in hypobaric chambers (37) and yields similar scores to comparable questionnaires when used in a terrestrial altitude environment (19). The sleep question was omitted since subjects did not sleep in the chamber; therefore, scores were graded out of 12. Subjects were removed from the chamber when a LLS of >9 was reached, a steady SpO2 of <70%, or upon request. A physician was present during all hypoxic and hypobaric exposures and was responsible for medical supervision of the subjects.

Statistical analysis. Descriptive statistics (means ± SD) were calculated for cardiorespiratory parameters, AMS scores, and control of breathing measures. Values for all data were expressed as means ± SD; ventilatory parameters were expressed as l/min. Data were also examined for normality using a Kolmogorov-Smirnov test. Friedman’s test was completed followed by a post hoc Wilcoxon test for nonparametric comparisons. A two-way, repeated-measures ANOVA was undertaken for cardiorespiratory variables, AMS, and control of breathing measures for the previously mentioned time points and for each of the four conditions (HH, NH, NN, NN). Bonferroni’s test was used as a post hoc test to compare means (i.e., the different times or environmental conditions) when a main effect was seen. When comparing pre- and posttest for control of breathing test within the same condition, a one-way ANOVA was used and a Tukey’s post hoc test was conducted. A P value of <0.05 was deemed statistically significant. Pearson’s r correlations (two-tailed) were conducted between LLS scores and cardiorespiratory variables, and with pre- and posttest HVR and rebreathing data scores for each exposure. Unpaired t-tests were used to compare AMS+ and AMS− subjects when necessary. Our sample size was based on power calculations established from a study with similar outcomes (16).

RESULTS

Eleven subjects completed the 4 exposure days; one subject was unable to complete all exposures because of schedule conflicts. Subjects’ descriptive statistics are seen in Table 2.

Chemosensitivity to CO2. The pre-chamber VRT for all of the hyperoxic Duffin tests (45.9 ± 1.6 Torr) were higher than for the hypoxic tests (41.1 ± 2.2 Torr; P < 0.0001). The S1 was lower in the hyperoxic tests (3.9 ± 2.5 l·min−1·Torr−1) than in the hypoxic tests (5.8 ± 1.7 l·min−1·Torr−1; P < 0.01). Nonparametric statistics were used for the hyperoxic and hypoxic S1 analyses. In all pre-chamber tests, the mean within-subject coefficient of variation for the VRT and S1 in the hyperoxic tests was 0.036 and 0.50. In the hypoxic tests, the coefficient of variation was 0.056 for the VRT and 0.28 for the S1. 

Hyperoxic VRT. The hyperoxic VRT decreased from pre- to postexposure in HH and NH (P < 0.0001). The differences between the pre-chamber test and the post-chamber test (∆VRT) were determined. The ∆VRT was larger in NH than in NN and NN (P < 0.01), but no difference was seen between HH and the other conditions. Finally, the post-chamber hyperoxic VRT correlated negatively to LLS (i.e., lower VRT in AMS+ than in NH) (r = 0.37; P < 0.05). 

Hyperoxic S1. A difference was only seen in NH when the change in slope sensitivity was compared pre- to postexposure. There was a nonsignificant increase in hyperoxic S1 (P = 0.084) in HH that was variable between subjects (range −12% to 70%) (Fig. 2).

Table 2. Subjects’ descriptive statistics

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BMI, body mass index; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 s; BP, blood pressure; HR, heart rate; AMS+ and AMS−, acute mountain sickness susceptible and resistant, respectively.
A Comparison of Hypobaric and Normobaric Hypoxia • Richard NA et al.

Fig. 1. Comparison of the CO2 ventilatory response threshold (VRT) measured before hypoxic chamber entry compared with the VRT measured post-chamber exposure in each environmental condition [hypobaric hypoxia (HH), normobaric hypoxia (NH), hypobaric normoxia (HN), and normobaric normoxia (NN)] within all subjects. Pre, VRT measured before chamber entry; Post, VRT measure taken after chamber exposure. Significant difference: **P < 0.01; ***P < 0.001; ****P < 0.0001.

Hypoxic VRT. The hypoxic VRT decreased following the two hypoxic exposures (P < 0.01 and P < 0.001, preexposure and postexposure, respectively) (Fig. 1). When the difference between the preexposure test and the postexposure test (VRT preexposure minus VRT postexposure) is compared, the hypoxic ΔVRT was larger in NH than in HN and NN (P < 0.01). Similarly, the difference in preexposure to postexposure ΔVRT in HH was larger than in HN and NN (P < 0.05).

Hypoxic S1. The hypoxic S1 analysis showed an increase pre- to postexposure in HH and NH (P < 0.05) (Fig. 2). A decrease in S1 postexposure was seen in NN (P < 0.05).

Hypoxic ventilatory response. The mean HVR for all pre-exposure measures was 0.55 ± 0.2 l·min⁻¹·% SpO₂⁻¹ and was 0.51 ± 0.2 l·min⁻¹·% SpO₂⁻¹ after HH and 0.69 ± 0.4 l·min⁻¹·% SpO₂⁻¹ after NH exposure; there were no significant differences (P = 0.14). The HVR did not differ significantly when compared pre- and postexposure, between or within conditions. Comparison of postexposure HVR and scores again showed no statistical significance to the LLS, and no difference was observed between AMS+ and AMS− subjects. The pre-exposure HVR coefficient of variability was 0.44.

Cardiorespiratory parameters. The following analyses used the 5-min and 30-min time points and averaged the values for the last 5 h, referred to as the 5-h mean time point. Data were also analyzed at each hourly time point but did not differ from the 5-h mean. Figure 3 represents V̇E, HR, and SpO₂ at their representative time points. The 5-min V̇E during HH and NH was significantly higher than during the two normoxic conditions (P < 0.05). The 5-h mean V̇E in NH was higher than HN (P < 0.05) and NN (P < 0.01). The V̇E in NH (P < 0.05) was only higher than NN at the 5-h time point (Table 3). No differences were seen between AMS+ and AMS− subjects, nor were any correlations observed between V̇E and LLS. No differences from the above-mentioned were seen when V̇E was normalized for body surface area (BSA). No differences were demonstrated for f₀ in all conditions at all time points. A correlation was observed between f₀ at 5-h mean and LLS, with AMS+ subjects having a higher rate of breathing in HH (r = 0.4; P < 0.05) and NH (r = 0.43; P < 0.05). V̇E was higher in NH than in NN at 5 min (P < 0.05) and 30 min (P < 0.05) and greater than NN at 5-h mean (P < 0.05) (Table 3). A correlation was observed between LLS and V̇E. The AMS+ subjects had a lower 5-h mean V̇E in both the HH and the NH condition (HH; r = 0.39, P < 0.05; NH; r = 0.48, P < 0.05). Blood oxygen saturation was significantly lower in both hypoxia conditions (HH, NH, HN, NN) within all subjects. Significant differences were observed between AMS+ and AMS− subjects. The pre-exposure HVR coefficient of variability was 0.44.
in the hyperoxic rebreathing test and after HH and NH expo-
conditions. The S1 parameter was increased after NH exposure
between HH and NH. The VRT was lowered in both the
spiratory parameters and the severity of AMS were similar
SpO2, %
††significantly lower than the 5-min time point; NN and HN; **significantly higher than NN; †significantly higher than HN;
V˙E, l/min
Table 3.
Main findings. We examined whether differences existed in
severity of AMS, cardiorespiratory parameters, or control of
breathing between HH and NH. Hypobaric normoxia was
included to assess the role of reduced Pb alone. The cardiorespiratory parameters and the severity of AMS were similar
between HH and NH. The VRT was lowered in both the
hyperoxic and hypoxic Duffin rebreath test following HH and
NH exposure but did not differ between the two hypoxic conditions. The S1 parameter was increased after NH exposure in
the hyperoxic rebreathing test and after HH and NH expo-
sure in the hypoxic rebreathing test. Differences in the HVR
were absent pre- and postexposure or between HH and NH. These findings suggest that, given an equivalent hypoxic dose,
our measure of cardiorespiratory parameters, chemosensitivity,
and AMS symptoms in HH are similar to NH over a 6-h exposure. The paucity of differences in control of breathing between
AMS+ and AMS− subjects advance that regulation of ventilation alone is not the causative factor determining AMS susceptibility.

Chemosensitivity to CO2. The Duffin CO2 rebreathe method
was used to estimate peripheral and central chemosensitivity using both hyperoxic and hypoxic rebreathing tests.

Hyperoxic VRT. The hyperoxic VRT decreased in all of our
subjects following 6 h of HH and NH. Both intermittent hypoxia (15) and field studies (1, 7) have reported a similar
lowering of the VRT. A significant but modest correlation was
observed between LLS and hyperoxic VRT (r = 0.37; P <
0.05) in NH, yet no association was observed in HH (r = 0.09;
P = 0.36); more validation is needed to confirm the accuracy of
this finding. The most conservative explanation for this
finding would be the possibility of a type I error.

Hypoxic VRT. As with the hyperoxic VRT, 6 h of hypoxia
lowered the hypoxic VRT with no difference between HH and
NH. This finding corresponds with previous studies (15, 20, 21,
40). This change in peripheral VRT could be regarded as an
early protective mechanism, similar to the increased HVR often seen after acute hypoxic exposures as a result of increased
peripheral chemosensitivity (12, 15, 36).

Hyperoxic S1. The increase in hyperoxic S1 after NH exposure
and the trend for increased S1 after HH (P = 0.084) suggest that our hypoxic exposure was of sufficient duration to
increase central chemosensitivity. Studies have shown similar
findings using end-tidal forcing (instead of rebreathing) (2) and
after a 2- to 4-day sojourn to 5,050 m (7).

Hypoxic S1. Our results showed an increase in hypoxic S1
following exposure to HH and NH. Our findings are consistent
with the previous literature examining chemosensitivity in a
terrestrial hypobaric hypoxia model where lowering of the
VRT is a typical response (1), and increases in slope sensitivity
are seen in hypoxic rebreathing (1) as well as in hyperoxic
rebreathing (7). Lowering of the S1 following NH exposure
was unexpected. This finding needs to be reproduced in future

**Fig. 4. Mean LLS of AMS susceptible subjects (AMS+) and AMS-resistant subjects (AMS−) at hour 6 across all four environmental conditions. Filled
bars, AMS+ subjects (n = 5); open bars, AMS− subjects (n = 6). **Signif-
icant difference from AMS− subjects (P < 0.0001).
studies to confirm its validity. Hypoxia tolerance, as manifested by the presence or absence of AMS, appears unrelated to CO₂ chemosensitivity at this time.

**HVR.** The HVR did not change after either HH (P = 0.41) or NH (P = 0.098). We expected increased HVR after the hypoxic exposures, since this has previously been described by others using field or intermittent hypoxia exposures (12, 15, 36). These changes were reported after exposure to multiple intermittent hypoxia bouts or after several days at altitude where factors such as ventilatory acclimatization to hypoxia (chemosensitivity changes) or long-term plasticity (changes in respiratory motor neuron activity) may come into effect (31). Therefore, it is possible that our hypoxic stimulus was insufficient to induce changes in the HVR. Furthermore, our HVR tests were conducted following completion of the Duffin re-breathing test, where subjects experience bouts of hyperventilation, hypocapnia, hypercapnia, and hypoxia; it is possible these perturbations influenced the HVR measures. During the basal breathing phase of the HVR test, our subjects resting PETCO₂ was 35.3 ± 1.53 Torr. Finally, the HVR test has significant inter- and intra-individual variability. Although our coefficient of variability was in the middle of the range of those previously reported (5, 13), it may have been large enough to mask any small changes in HVR postexposure. Furthermore, similar to previous studies (10, 24), we did not find a strong correlation between HVR and AMS susceptibility, under either hypoxic condition.

**Cardiorespiratory parameters.** The most striking finding was the absence of differences in ventilatory measures between HH and NH, which contradicts previous experiments (6, 16, 39, 41). The LLS correlated positively to ḟB (greater LLS in those with higher ḟB) at 5-h mean in AMS+ subjects in both the HH and NH condition. Subject discomfort (headache, nausea) potentially favored this shallow rapid breathing pattern. However, the higher ḟB in AMS+ subjects did not yield differences in V̇E or SpO₂ between AMS+ and AMS− subjects. No correlations were found between SpO₂ measured acutely (5 min) or subacutely (30 min) and AMS susceptibility, making early saturation status a poor indicator of AMS susceptibility in this study. Of interest was the chronological ventilatory response to hypoxia. Both HH and NH caused an abrupt increase in V̇E, followed by a depression lasting ~1 h, followed by a progressive rise. Accordingly, SpO₂ followed suit and was lowest at the 30-min time point before gradually rising to a new steady state. HR increased significantly throughout the exposure in all conditions. Although the subjects were well familiarized with the chamber before the commencement of the study, it was still an unusual environment with restrictive quarters, loud noise, and a rigorous testing schedule, which increased overall stress. Additionally, the gradual increase in HR could be due to cardiac drift caused by dehydration, since a few subjects reported minimizing their water intake to avoid urinating inside the chamber. In summary, cardiorespiratory parameters did not differ between HH and NH nor were they linked to AMS susceptibility. Individual resting cardiorespiratory variables are, according to this study, poor predictors of AMS.

**AMS.** In contrast to previous studies, the LLS did not differ between HH and NH (17, 34, 41), as seen in Fig. 4. We demonstrated very similar LLS, with NH having a trend of slightly higher scores than HH in both the overall group and the AMS+ group; however, this was not significant. The LLS was predominantly weighted by the presence of a headache, which is the key and reoccurring symptom. This study differed from previous studies that reported higher LLS in HH than in NH in that our exposure duration was slightly shorter (6 h vs. 9 h), and our hypoxic dose was more severe (PIO₂ of 75 Torr vs. 80 Torr) than that of Roach et al. (34) and Loeppky et al. (16). Additionally, ventilation in Loeppky et al.’s (16) study was nearly identical at 6 h and 9 h (10.6 vs. 10.3 l/min), and no significant difference was reported for V̇T or ḟB from 6 h to 10 h. Therefore, we expect no major differences in results had we done a longer exposure. A key reason for the difference between the present study and prior studies relates to our study design (32). We used a repeated-measures, blinded, pseudorandomized design, and our hypoxic exposures were separated by at least 2 wk and the normoxic exposures by at least 1 wk. Our hypoxic dose calculations were based on inspired gases (i.e., PIO₂) as opposed to room air, as seen in Table 1. Failure to include water vapor in hypoxic dose calculations would lead to discordant hypoxic doses, making comparisons of little value (3, 14). We strived to maintain the chamber ṖCO₂ at 1 Torr throughout the 12 exposure days. To our knowledge, of the multi-hour studies comparing HH and NH, only Loeppky et al.’s study reported ambient room CO₂ (ṖCO₂ was maintained below 3.7 Torr) (16). Studies comparing minor changes in Ve should report ambient ṖCO₂, since accumulations of CO₂ could confound V̇E measurements. Regardless, since ambient ṖCO₂ was similar in all exposure days, we are confident this factor did not influence our measured parameters. Finally, it is worthwhile to mention that past reports comparing HH to NH examined subjects already living at altitude. In Loeppky et al.’s study (16, 17), subjects living at 1,524 m were used, whereas Roach et al.’s (34) study used subjects living between 1,500 and 1,600 m. By using sea-level subjects, we eliminated this potential confounding factor. As such, there are a series of potential reasons that may explain why we did not see many of the purported differences between NH and HH that have been previously reported.

**Limitations**

Our sample size (n = 11), established from power calculations based on a study with similar outcomes (16), provided a detectable effect size of 0.8 with power set at 0.8. Based on this power calculation and the measured standard deviation of this study, a 2.65 l/min difference in V̇E would have been needed to detect a significant difference between HH and NH. Although the possibility of type II error is present, small sample sizes, and consequently less study power, remain a tradeoff of small but intensive physiological studies. Our ventilation values in normoxia (NN and NH) were higher than typical resting values (~15 vs. ~5–8 l/min). The slightly elevated ventilation might have resulted from the respiratory apparatus (22), having subjects sitting as opposed to supine, and being in the chamber might have induced some minor anxiety/stress. Due to the high baseline ventilation in normoxia, small differences between NH and HH might be overlooked and overwhelmed by the nonspecific stimulus of face masks and other stimuli of the testing environment. Nonetheless, we minimized confounds by comparing values within subjects and by using identical protocols and equipment across exposures.
In conclusion, previous studies examining HH and NH have shown a trend for greater severity of AMS in HH coupled with lower ventilatory rates. We found that, in a controlled laboratory model, AMS has similar incidence and severity in HH or NH, whereas physiological parameters were comparable between HH and NH. We demonstrated a lowering of the central and peripheral VRT to CO₂ following 6 h of hypoxia, increased central sensitivity after NH, and increased peripheral responses to NH and HH may not be as significant as previously shown. Hypobaria differs at the lung and brain; however, small discrepancies at either site may not be clinically relevant. Based on these findings, we conclude that the differences between responses to NH and HH may not be as significant as previously observed.

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AUTHOR CONTRIBUTIONS
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