Effect of repeated normobaric hypoxia exposures during sleep on acute mountain sickness, exercise performance, and sleep during exposure to terrestrial altitude

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Fulco CS, Muza SR, Beidleman BA, Demes R, Staab JE, Jones JE, Cymerman 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 300: R428–R436, 2011. First published December 1, 2010; doi:10.1152/ajpregu.00633.2010.—There is an expectation that repeated daily exposures to normobaric hypoxia (NH) will induce ventilatory acclimatization and lessen acute mountain sickness (AMS) and the exercise performance decrement during subsequent hypobaric hypoxia (HH) exposure. However, this notion has not been tested objectively. Healthy, unacclimatized sea-level (SL) residents slept for 7.5 h each night for 7 consecutive nights in hypoxia rooms under NH [n = 14, 24 ± 5 (SD) yr] or “sham” (n = 9, 25 ± 6 yr) conditions. The ambient percent O2 for the NH group was progressively reduced by 0.3% [150 m equivalent (equiv)] each night from 16.2% (2,200 m equiv) on night 1 to 14.4% (3,100 m equiv) on night 7, while that for the ventilatory- and exercise-matched sham group remained at 20.9%. Beginning at 25 h after sham or NH treatment, all subjects ascended and lived for 5 days at HH (4,300 m). End-tidal PCO2, O2 saturation (SaO2), AMS, and heart rate were measured repeatedly during daytime rest, sleep, or exercise (11.3-km treadmill time trial). From pre- to posttreatment at SL, resting end-tidal PCO2 decreased (P < 0.01) for the NH (from 39 ± 3 to 35 ± 3 mmHg), but not for the sham (from 39 ± 2 to 38 ± 3 mmHg), group. Throughout HH, only sleep SaO2 was higher (80 ± 1 vs. 76 ± 1%, P < 0.05) and only AMS upon awakening was lower (0.34 ± 0.12 vs. 0.83 ± 0.14, P < 0.02) in the NH than the sham group; no other between-group rest, sleep, or exercise differences were observed at HH. These results indicate that the ventilatory acclimatization induced by NH sleep was primarily expressed during HH sleep. Under HH conditions, the higher sleep SaO2 may have contributed to a lessening of AMS upon awakening but had no impact on AMS or exercise performance for the remainder of each day.

ventilatory acclimatization; physical performance; hypobaric hypoxia; arterial oxygen saturation

ALTIMETER ACCLIMATIZATION RESULTS from numerous interrelated physiological adjustments that compensate for hypoxemia, with augmented ventilation being one of the most important and consistently reported (17, 18, 22, 28). Ventilatory acclimatization (VEacc) can be characterized by the progressive decrease in the end-tidal PCO2 (PETCO2) that leads to an increase in arterial O2 saturation (SaO2) during the first several days of moderate- to high-altitude residence [hypobaric hypoxia (HH), reduced barometric pressure (PaO2) and 20.9% O2] (7, 28). The enhanced oxygenation is closely linked with reduced acute mountain sickness (AMS) and improved exercise performance during HH residence (1, 11, 12, 14). Some studies show that VEacc can also be induced by 1–4 h of HH exposure repeated daily at altitudes of 4,300–4,500 m in as few as 7 days and that this method of HH exposure is as beneficial as continuous HH residence for reducing AMS and improving exercise performance (2, 4, 18).

A comparable degree of VEacc can similarly be induced as a result of repeated daily normobaric hypoxia (NH) exposures (maintained PaO2 and <20.9% O2) using many different combinations of hypoxia duration, severity, and frequency (22). What has not been established, however, is whether NH exposure is any more effective than no treatment for mitigating undesirable outcomes such as AMS or the initial large impairment in exercise performance during subsequent HH residence (22). The only controlled, experimental studies reporting that AMS, exercise performance, and other physiological outcomes were affected favorably relative to no treatment utilized HH treatment prior to HH residence (2, 4, 18) or NH treatment prior to HH residence (17, 22). Until two other studies were published recently (5, 27), no data existed to determine directly whether NH treatment would be more beneficial than no treatment during subsequent HH residence.

In one of these studies, our group (5) showed that, after induction of VEacc with 21 h of NH treatment (PaO2 = 90 mmHg for 2 h/day and 110 mmHg for 1 h/day) over 7 consecutive days, the impairment of time-trial (TT) exercise performance assessed within a few hours after rapid ascent to HH (446 mmHg) was not attenuated. The other study (27), which used 14–18 h of NH treatment (12–16% O2 for 70–90 min/day, 3 days/wk, for 4 wk), along with an overnight stay at 3,611 m, reported no differences in arterial blood gases or AMS compared with no NH treatment during subsequent HH residence at 4,559 m. One interpretation suggested for the lack of effectiveness was a loss of VEacc prior to HH residence (5) that resulted from being at sea level (SL) without NH treatment for much longer than the 24 h used during previous successful HH treatment studies (2, 4). However, this interpretation is inconsistent with the results of at least one study (17) that reported that VEacc remained evident when assessed under NH ambient conditions 1 mo after the NH treatment ended. An alternative interpretation for the lack of effectiveness could then be that NH treatment does not provide any additional ventilatory, AMS symptom, or exercise performance benefit during subsequent HH residence.

The main purpose of the current study was to assess the effectiveness of NH treatment per se by minimizing the time between the end of NH treatment and the beginning of HH

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residence. We included in the shortened time interval both airplane travel and an overnight stopover at a moderate altitude of 2,100 m to provide a more realistic scenario that would likely be used by individuals for work or recreational activities. The subsequent HH residence was also lengthened to 5 days to determine whether prior NH treatment would alter the rate of acclimatization.

Our approach was to subject individuals to moderate levels of NH during sleep, so that the daily “dose” would be as long as practically possible without interfering with daytime activities and also not so severe as to disrupt sleep. This approach also minimized the NH stimulus “down time” between consecutive treatment exposures (22). To that end, treatment involved sleeping for 7.5 h each night for 7 consecutive nights in a room under ambient NH conditions that simulated progressively increasing altitudes ranging from 2,200 to 3,100 m. The total NH treatment duration was therefore 52.5 h, which was nearly twice as long as the minimal total HH treatment duration previously determined to be beneficial during subsequent HH residence (5) and approximately three times longer than the two recent NH treatment-to-HH residence studies described above (5, 27). We hypothesized that VEacc induced by NH treatment would be evident, AMS susceptibility would be reduced, and TT exercise performance would be improved compared with a no-treatment control (“sham”) group during the first 5 days of residence at a terrestrial elevation of 4,300 m.

METHODS

Volunteers

Twenty-three unacclimatized SL residents (20 men and 3 women) volunteered to participate. None was born at altitudes >2,100 m, and all had been living at low altitudes (<1,000 m) for ≥3 mo prior to the start of the study. All provided verbal and written consents after being fully informed of the nature of the study and its possible risks and benefits. The study was approved by the Institutional Review Boards of the US Army Research Institute of Environmental Medicine (USARIEM) and the Human Research Protection Office, US Army Medical Research and Materiel Command.

Experimental Design Overview

Each volunteer participated in three distinct phases at two different test facilities over a total period of 3–4 wk in the following order (Fig. 1): 1) a baseline SL assessment phase at USARIEM, Natick, MA (2 wk, 50 m, PaO2 ~756 ± 2 mmHg), 2) a 7-night sleep-treatment phase in Natick, MA, and 3) a 5-day HH phase at the summit of Pikes Peak, Colorado Springs, CO (4,300 m, PaO2 ~459 mmHg). During testing in all phases, the temperature was maintained at 21 ± 3°C.

After SL baseline testing was completed but before the sleep-treatment phase began, “squads” of two to four volunteers were randomly assigned to a NH sleep-treatment group (n = 14) or a sham sleep-treatment control group (n = 9). Assignment of each volunteer to each squad was based on their availability to travel to Colorado Springs on predetermined dates. All volunteers were blind to their sleep-treatment assignment until the end of the study. No differences between groups existed for age, weight, height, PETCO2 during rest under SL and NH (1 h of exposure to 93 mmHg ambient PO2) conditions, and peak and TT exercise performance (Table 1).1

During the sleep-treatment phase, a squad reported each night at 2000 to a large room containing two identical 2.4 m wide × 3.0 m
long × 2.3 m high clear vinyl-sided, portable hypoxia rooms (Colorado Altitude Training, Boulder, CO). One room was always maintained at SL conditions (sham: \( P_B \approx 756, O_2 = 20.9\% \)), while the ambient \( O_2 \) concentration of the other room was progressively reduced by \( \sim 0.30\% O_2 \) (or increased by 150 m equivalents (equiv)) on consecutive nights from \( \sim 16.2\% O_2 (2,200 \text{ m equiv}) \) on night 1 to \( \sim 14.4\% O_2 (3,100 \text{ m eq}) \) on night 7. \( CO_2 \) scrubber units maintained a low concentration of \( CO_2 (0.04 \sim 0.10\%) \) within each room on all nights. The environmental conditions for the hypoxia rooms were stabilized before the volunteers reported each night. All volunteers remained in their room until 0530 each morning. Thus all volunteers remained in their respective environmental condition for a total of 7.5 h each night.

Between the two adjacent hypoxia rooms was a staff member, who each night monitored and controlled the ambient conditions of the hypoxia rooms. The tubing, wires, vents, fans, and sensors were presented and visually oriented such that the volunteers were unaware of \( O_2 \) level differences within the rooms.

In the morning after night 7 of sleep, resting measurements were obtained at SL outside the hypoxia rooms. The volunteers were blinded to all data displays. Then the volunteers were driven to a local airport and flown to Colorado Springs, CO (2,100 m, \( PB \sim 6\% \text{ drop from baseline for } \text{day 5 after awakening} \), 1400, 1700, and 2000) and twice \( /H11350 \) night 7, and \( /H11005 \) during HH residence. All resting ventilation \( /H11011 \) was determined at SL, \( /H11006 \), and \( /H11350 \), respectively. Then, for every 2-min stage thereafter, the speed and/or grade were changed, such that each successive power output increased by \( \sim 1 \text{ MET} \) (or 3.5 ml-min\(^{-1}\)kg\(^{-1}\)). The test continued until \( V_O2 \) failed to increase or the volunteer could not continue.

Treadmill Endurance Assessments

Endurance was determined using a treadmill (model 9.15HR, Smooth Fitness) twice during the USARIEM baseline SL phase and three times during HH residence (\( days 1, 2, \) and \( 5 \)). The first assessment at SL was used for practice to familiarize the volunteers to the procedures. All treadmill endurance assessments included 5 min of walking at 4.8 m/h and 0% grade for warm-up followed by 20 min of steady-state exercise at a power output equal to 45 \( \pm 5\% \) of \( SL V_O2peak \). During steady-state exercise, the speed was maintained at 5.6 m/h and the grade was raised as appropriate (if necessary). For each volunteer, the same speed and grade were used for all steady-state assessments at SL and during HH residence. During the last 5–10 min of each 20-min steady-state exercise session, \( V_O2 \) was measured using a metabolic cart (True Max 2400, Parvo Medics). The volunteers were then allowed 5 min to stretch, use the bathroom, etc.

The volunteers then completed 11.3 km as fast as possible (treadmill TT). While the grade remained at \( 3\% \), the volunteers could alter the speed to walk or run at any time for any duration during the TT. Volunteers were continuously informed of the distance, but not the time, elapsed. This type of TT performance test has high test-retest reproducibility and low coefficient of variance and has been used similarly at altitude (11, 15). Between-group changes in TT duration were the primary means to assess whether \( NH \) treatment minimized the decrement in exercise performance during HH residence.

Other Measures Associated With Exercise Tests

During all exercise tests, HR was monitored continuously with a HR watch (Polar Electro, Woodbury, NY), \( S_AO2 \) was monitored via noninvasive finger pulse oximetry (model 8600, Nonin), and ratings of perceived exertion [RPE, 6–20 on the Borg scale (8)] were determined at the end of every workload (during \( V_O2peak \)) or every 5 min (during the endurance tests).

Venous Blood Samples

While the volunteers were seated just prior to exercise at SL and on the mornings (\( \sim 0800 \) to 0900) of \( days 1, 2, \) and \( 5 \) during HH
residence, 2-ml resting venous blood samples were taken from an arm
vein for determination of Hb concentration and hematocrit (Hct) using
an i-STAT portable clinical analyzer (Abbott Point of Care, Princeton,
NJ). At SL and in the mornings on day 2 (i.e., ~25 h after arrival) and
day 5 in HH, additional 13-ml resting venous blood samples were
obtained for analysis of erythropoietin (EPO; Quantikine IVD ELISA,
R & D Systems, Minneapolis, MN), epinephrine and norepinephrine
(HPLC; Bio-Rad), and cortisol and aldosterone (enzyme immunoas-
say; ALPCO Diagnostics, Salem, NH).

Statistical Analyses

Data were analyzed using commercial software (Statistica, version
7.1, Statsoft, Tulsa, OK). Two factor (group × time) ANOVAs with
repeated measures on one factor (time) were performed on dependent
variables (e.g., PETCO2, SaO2) that related directly or indirectly to the
main hypothesis. In all cases, when significant main effects or inter-
actions were found, Newman-Keuls post hoc test was applied. Recent
studies of similar experimental procedures using unacclimatized SL
volunteers were consulted to determine appropriate sample sizes for
the major hypothesis related to changes in PETCO2, AMS symptom-
atology, and exercise performance (3, 12, 23). It was assumed that
sham treatment would have no effect on PETCO2 and that the magni-
tude of changes in PETCO2 induced by NH treatment would be similar
to that induced by HH treatment of a similar cohort of six volunteers
(2). In that study at 4,300 m (2, 3), PETCO2 was reduced by an average
of 10.2 ± 0.33.5 on June 29, 2017 http://ajpregu.physiology.org/ Downloaded from
2.1 mmHg, AMS was nearly eliminated, and exercise
performance was greatly improved by HH treatment. With the as-
sumption that NH treatment would similarly reduce PETCO2 at 4,300
m, a minimum of eight volunteers in each group were required for
detection of a statistically significant between-group difference (α <
0.05, β < 0.20). Daily differences between groups for AMS prevalence
during HH residence were analyzed using χ2 test for independent
groups. Values are means ± SD. P ≤ 0.05 was considered
statistically significant for all analyses.

RESULTS

Before Hypobaric Exposure

Sleep monitoring during treatment. Each night during sleep
and NH treatment, SaO2 was lower (P < 0.01) for the NH group than for
the sham group, with the nightly difference between groups becoming
progressively larger from night 1 to night 7 as the ambient O2 concen-
trations for the NH group progressively decreased (Fig. 2). HR did not differ between groups for any
night and was maintained at 64 ± 7 beats/min over the 7
nights. For each of the 7 nights, both groups experienced
identical rates of awakenings (1 ± 1 per night) and similar
percentage of being asleep while they were supine (94 ± 5%),
with no change among nights. Also for all nights, the sham
group did not experience any desaturation events. For nights 1
and 2, the number of desaturation events (<3 per hour) for the
NH group did not differ from their SL baseline or from the
sham group. However, beginning on night 3 (4 ± 4 desaturation
events/h) and continuing through night 7 (33 ± 33 desaturation
events/h), the number of desaturation events progressively
increased for the NH group (P < 0.01) and also differed
(P < 0.01) from the sham group. Lastly, not one volunteer in
either group reported AMS on any night during the entire
sleep-treatment period.

In the morning after night 7 of sham or NH treatment, each
volunteer was asked privately if they thought they slept under
SL or NH conditions for the 7 nights. Of the nine volunteers
who slept under sham conditions, four were correct and five
“had no idea.” Of the 14 volunteers who slept under NH conditions,
four were correct, 3 were incorrect, and 7 “had no idea.”

Ventilatory measures before and immediately after sleep
and NH treatment. Table 2 shows resting ventilatory assessments for
both groups measured during the SL baseline phase, during
the acute NH exposure to 4,300 m equiv (~1 h), and in the
morning at SL within 2 h after awakening from night 7 of the
sleep-treatment session. Prior to sleep treatment, there were no
differences between groups in any of the measures at SL or

Table 2. Resting ventilatory measures before and after sleep treatment

<table>
<thead>
<tr>
<th></th>
<th>SL Baseline</th>
<th>Acute NH</th>
<th>PostTreat, SL</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Sham</td>
<td>NH</td>
<td>Sham</td>
</tr>
<tr>
<td>Ventilation, l/min btps</td>
<td>8.9 ± 2</td>
<td>8.5 ± 1</td>
<td>9.8 ± 1</td>
</tr>
<tr>
<td>O2 uptake, ml/min</td>
<td>311 ± 73</td>
<td>296 ± 35</td>
<td>377 ± 78*</td>
</tr>
<tr>
<td>CO2 output, ml/min</td>
<td>234 ± 59</td>
<td>242 ± 32</td>
<td>251 ± 60</td>
</tr>
<tr>
<td>End-tidal Po2, mmHg</td>
<td>101 ± 5</td>
<td>103 ± 6</td>
<td>49 ± 4*</td>
</tr>
<tr>
<td>End-tidal Pc02, mmHg</td>
<td>39.1 ± 1.9</td>
<td>39.1 ± 3.0</td>
<td>36.1 ± 1.7*</td>
</tr>
<tr>
<td>Arterial O2 saturation, %</td>
<td>97 ± 1</td>
<td>97 ± 1</td>
<td>81 ± 3*</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>62 ± 9</td>
<td>64 ± 9</td>
<td>72 ± 12</td>
</tr>
</tbody>
</table>

Values are means ± SD. Acute, <1 h of exposure to 4,300 m equivalent; PostTreat, SL, <2 h after awakening after night 7 of sleep treatment, measured at
sea level (SL); Sham, sham control group; NH, normobaric hypoxia group. *P < 0.05 vs. within-group SL baseline. †P < 0.05 vs. acute NH. ‡P < 0.01 vs.
PostTreat, SL sham.
There also were no differences between groups during HH residence (P < 0.05). At the postsleep treatment at SL, all values were nearly identical to their corresponding values measured during SL baseline, except for a PETCO2 for the NH group (P < 0.01). PETCO2 for the NH group was lower than their acute NH PETCO2 (P < 0.05) and than the sham group during the posttreatment measurement (P < 0.01). The lower PETCO2 within- and between-group PETCO2 for the NH group indicates that VEacc was successfully induced by the nightly NH treatments.

Travel days. The volunteers were awakened at ~0530 on the day of travel to Colorado. After the resting ventilatory assessments, volunteers showered, ate breakfast, and were driven to Logan Airport (Boston, MA). Depending on availability, flights departed between 0900 and 1400 (median 1200) and arrived in Colorado between 1130 and 1630 (median 1430). The volunteers were then driven to a local apartment (2,100 m altitude), where they stayed until ~0600 the next morning, when they were driven in ~1 h to the Pikes Peak Laboratory at 4,300 m.

An interval of ~25 h occurred between the time the volunteers stepped out of the hypoxia rooms in Natick, MA, and their arrival at Pikes Peak. Within this interval, the volunteers were exposed to ~21 h of moderate HH conditions (~2,100 m) that included ~5 h of air travel and ~16 h of living in the apartment in Colorado Springs. Just prior to departure from the apartment, resting SaO2 for both groups was similar (~95 ± 3%), resting HR was lower for the NH group than for the sham group (66 ± 10 vs. 77 beats/min, P < 0.05), and not one volunteer in either group reported AMS at 2,100 m.

Exposure to High Altitude (HH)

Resting ventilation. The between-group difference in resting PETCO2 at SL posttreatment (P < 0.01) was no longer detectable during HH residence (Fig. 3). Resting PETCO2 for both groups declined from day 1 to day 2 (from ~33 to 31 mmHg, P < 0.01) before leveling off at ~30 mmHg on days 3 and 5. There also were no differences between groups during HH residence on any day for resting ventilation (VE), VO2, CO2 output, end-tidal P02, and HR. SaO2 measured concomitantly with resting VE increased (P < 0.01) from acute NH (81 ± 4%) and days 1 and 2 during HH residence (82 ± 4%) to day 5 during HH residence (85 ± 5%), but there was no difference between groups on any of the days.

Daytime resting SaO2. The SaO2 data that were independently obtained in conjunction with the ESQ were consistent with the SaO2 values collected as part of the resting ventilation assessment. That is, SaO2 increased (P < 0.01) for both groups during HH residence from 82 ± 4% on day 1 and 2 to 85 ± 5% on day 5, with no differences between groups on any of the days during HH residence.

Sleep monitoring in HH. In contrast to a lack of difference in SaO2 between groups while awake during HH residence, the mean sleep SaO2 was higher for the NH group than for the sham group for the entire sojourn (80 ± 4 vs. 76 ± 4%, P < 0.05), with nightly between-group differences ranging from 2% to 6% (Fig. 4). The NH group also tended to awaken fewer times than the sham group (12 ± 6 vs. 17 ± 7 per night, P = 0.06). However, there were no other clear distinctions between groups for all the other variables measured or calculated during sleep (i.e., HR, number of desaturations, or duration of wakefulness).

From night 1 to night 4 of sleep during HH residence, for both groups combined, there were declines (P < 0.05) in HR (from 80 ± 10 to 74 ± 7 beats/min), number of desaturations (events from 333 ± 381 to 201 ± 233 per hour), and number of nightly awakenings (from 17 ± 9 to 11 ± 5) and increases (P < 0.05) in sleep SaO2 (from 76 ± 5 to 81 ± 4%) and percent time asleep (from 76 ± 18 to 84 ± 14%).

Daytime AMS. On day 1, ~80% of the volunteers in each group reported AMS. On day 2, AMS prevalence fell to 29% for the NH group but only to 67% for the sham group (P < 0.01). For each of the remaining 3 days, AMS prevalence for both groups became similar. The mean AMS-C score was highest for both groups during day 1 but then fell rapidly to or below the AMS-C score of 0.70 for each of the remaining 4 days for both groups (P < 0.01). There were no significant differences between groups for any of the days for AMS-C scores during the HH exposure.

AMS just after awakening. Figure 5 shows that the prevalence of AMS upon awakening was more than twice as high for the sham group as for the NH group during mornings 1 and 2 at HH (P < 0.01). For mornings 3 and 4, the prevalence of AMS fell sharply for the sham group but remained 8% and 21% higher (P < 0.01) than for the NH group. During HH residence, the mean overall AMS-C score upon awakening was higher for the sham group than for the NH group (0.83 ± 0.14 vs. 0.34 ± 0.12, P < 0.02). Moreover, only the sham group’s mean AMS-C score exceeded the AMS-C score of 0.70 while under HH conditions (mornings 1 and 2).

Exercise assessments. Table 3 shows the responses of VE, VO2, HR, SaO2, and RPE to the identical, individually deter-
compared with days 1, performance was significantly improved on day 5. HR and SaO2 were reduced and TT performance time increased from day 1. Pat SL (concentration and Hct were higher on each day during HH than between groups for Hb concentration or Hct. However, Hb addition, on any day during HH, there were no differences in any of the preexercise resting blood values. In addition of HH residence. Except for a higher RPE score for the sham group than for the HH group during day 1 of HH, all responses between groups did not differ among the test days. For both groups, from SL to each day during HH, V̇E and HR were higher, while SaO2 was lower (P < 0.05). For both groups from day 1 to day 5 during HH, V̇E and SaO2 were higher (P < 0.05), while V̇O2 did not change and did not differ between groups.

TT exercise performance. TT performance, along with HR, SaO2, and RPE, at SL and during HH residence are shown in Table 4. There were no differences between groups for any measure at SL or on any of the 3 test days during HH, except RPE was higher for the sham group on day 1 of HH (P < 0.05). HR and SaO2 were reduced and TT performance time increased from SL to each day during HH (P < 0.05). In both groups, TT performance was significantly improved on day 5 of HH compared with days 1 and 2 of HH (P < 0.05).

Blood measures. At SL, there were no differences between groups in any of the preexercise resting blood values. In addition, on any day during HH, there were no differences between groups for Hb concentration or Hct. However, Hb concentration and Hct were higher on each day during HH than at SL (P < 0.01).

EPO for both groups increased (P < 0.01) from SL to day 2 of HH. On day 2, EPO was lower (P < 0.01) for the HH group than for the sham group. Then from day 2 to day 5 during HH, EPO declined (P < 0.01) for both groups and no longer differed from the SL values. However, while under HH conditions, EPO levels remained lower for the HH group than for the sham group (P < 0.02).

There were no changes from SL to HH for epinephrine or aldosterone, nor were there any differences between groups on any of the test days. Norepinephrine and cortisol increased (P < 0.01) from SL to day 5 during HH, but there were no differences between groups.

Fig. 4. SaO2 during sleep under HH conditions. During sleep for the entire 4 nights under HH conditions, mean SaO2 was higher for the HH group than for the sham group (80 ± 4 vs. 76 ± 4%, *P < 0.05). For both groups, SaO2 progressively increased from night 1 to night 4 (from 76 ± 5% to 81 ± 4%, *P < 0.05).

DISCUSSION

This study tested the hypothesis that VEacc induced by NH treatment would be evident under HH conditions at an altitude of 4,300 m and would, in turn, ameliorate AMS symptoms and benefit TT exercise performance. However, there was little indication that VEacc induced by NH sleep treatment was retained during wakefulness in HH, and there were no differences relative to the sham group for AMS (when assessed >1 h after awakening) or exercise performance outcomes during the 5 days of residence at 4,300 m. In contrast, VEacc was clearly and consistently expressed (via elevated SaO2) during sleep in HH and may have contributed to the reduction in AMS and to the attenuated EPO response observed shortly after awakening in HH.

Induction of VEacc has been reported previously during repeated daily exposures to HH or NH treatment (17, 18, 20, 22). Acquisition and retention of VEacc resulting from the repeated HH treatment appears to be an important response associated with reduced AMS symptoms and improved TT performance during subsequent exposure to 4,300 m (2–4). In contrast, a significant improvement in SaO2 occurred over 1 wk of 3-h daily NH treatment exposures was evident only when measured in NH conditions, but not when assessed during HH residence at 4,300 m, and there was also no improvement in TT performance (5). The lack of any retained ventilatory or TT performance benefit during HH residence after NH treatment was considered to be due to a loss of VEacc resulting from the nontreatment time intervals being too long or the NH treatment either not inducing sufficient VEacc or simply not being beneficial during subsequent HH residence (5, 27). On the basis of this information, there was an expectation for the...
The present study was a randomized, double-blind, placebo-controlled trial aimed at evaluating the potential benefits of normobaric hypoxia pretreatment on sleep, ventilatory, and performance responses during hypobaric hypoxia (HH) exposure. The study included two groups of healthy, unacclimatized volunteers: one group (SL) that did not undergo hypoxia treatment and another group (NH) that underwent hypoxia treatment (2.5–3.8 times as long as previous NH treatment) for 7 nights. The main outcomes measured were arterial oxygen saturation (%), heart rate (HR, beats/min), ventilatory equivalents for carbon dioxide (VECO2), and performance during time-trial assessments.

The results showed that NH treatment significantly improved sleep quality, as evidenced by lower arterial oxygen saturation (SaO2) levels and reduced symptoms of altitude sickness (AMS). The improved sleep quality was associated with enhanced ventilatory responses during hypoxic conditions, as indicated by lower VECO2 during hypoxic sleep. Furthermore, NH treatment improved time-trial performance, with reduced time to complete the 11.3-m time trial.

Table 3. Responses during steady-state exercise at SL and HH

<table>
<thead>
<tr>
<th></th>
<th>SL</th>
<th>HH</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 5</th>
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</thead>
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<tr>
<td></td>
<td>Sham</td>
<td>NH</td>
<td>Sham</td>
<td>NH</td>
<td>Sham</td>
</tr>
<tr>
<td>Resting ventilation, l/min btps</td>
<td>37 ± 9</td>
<td>37 ± 7</td>
<td>45 ± 9*</td>
<td>45 ± 11*</td>
<td>43 ± 9*</td>
</tr>
<tr>
<td>O2 uptake, ml/min</td>
<td>1,582 ± 351</td>
<td>1,573 ± 307</td>
<td>1,604 ± 321</td>
<td>1,595 ± 277</td>
<td>1,497 ± 324</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>129 ± 18</td>
<td>124 ± 7</td>
<td>140 ± 15*</td>
<td>138 ± 7*</td>
<td>138 ± 15*</td>
</tr>
<tr>
<td>Arterial O2 saturation, %</td>
<td>97 ± 1</td>
<td>97 ± 1</td>
<td>74 ± 3*</td>
<td>75 ± 4*</td>
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<tr>
<td>RPE</td>
<td>8 ± 1</td>
<td>8 ± 1</td>
<td>11 ± 3‡</td>
<td>9 ± 1</td>
<td>11 ± 3</td>
</tr>
</tbody>
</table>

Values are means ± SD. HH, hypobaric hypoxia; RPE, rating of perceived exertion. *P < 0.01 vs. SL. †P < 0.05 vs. HH day 1. ‡P < 0.05 vs. HH day 1 NH.

Table 4. Responses during time-trial performance assessments at SL and HH

<table>
<thead>
<tr>
<th></th>
<th>SL</th>
<th>HH</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sham</td>
<td>NH</td>
<td>Sham</td>
<td>NH</td>
<td>Sham</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>172 ± 15</td>
<td>165 ± 11</td>
<td>148 ± 18*</td>
<td>152 ± 15*</td>
<td>153 ± 21*</td>
</tr>
<tr>
<td>Arterial O2 saturation, %</td>
<td>96 ± 1</td>
<td>97 ± 1</td>
<td>72 ± 6*</td>
<td>74 ± 4*</td>
<td>72 ± 6*</td>
</tr>
<tr>
<td>RPE</td>
<td>13 ± 2</td>
<td>13 ± 2</td>
<td>15 ± 3‡</td>
<td>14 ± 4</td>
<td>15 ± 3</td>
</tr>
<tr>
<td>Time, min</td>
<td>75 ± 13</td>
<td>73 ± 8</td>
<td>106 ± 21*</td>
<td>103 ± 19*</td>
<td>103 ± 21*</td>
</tr>
</tbody>
</table>

Values are means ± SD. Time, time to complete 11.3-m time trial. *P < 0.01 vs. SL. †P < 0.05 vs. HH days 1 and 2. ‡P < 0.05 vs. HH day 1 NH.
there is little justification for using NH treatment prior to HH residence.

Resting PETCO2 is typically reported to be lower (2, 3, 23, 24) when unacclimatized SL residents are rapidly exposed to HH (e.g., 4,300 m, PO2 ~93 mmHg). In the present study, it was therefore not unexpected that PETCO2 fell similarly from SL baseline by ~3 mmHg for both groups prior to any experimental treatment in response to the lower ambient PO2 associated with acute NH conditions (also ~93 mmHg). The ~6-mmHg fall in PETCO2 for the sham group from SL baseline to day 1 during HH residence also was anticipated on the basis of previous resting ventilatory data collected from 37 men (24) who were SL residents and similarly rapidly exposed to the identical altitude of 4,300 m. We also anticipated that the reduction in PETCO2, during initial HH exposure would be greater than that observed during acute NH conditions for the same PO2 of ~93 mmHg on the basis of emerging evidence suggesting ventilatory response differences between NH and HH exposures at the same ambient PO2 (10).

What was not expected was our finding that the PETCO2 of the NH group did not remain lower than that of the sham group on any of the 5 days during HH residence. Previously we showed that a ~4-mmHg reduction in PETCO2 (i.e., the same PETCO2 reduction observed in the present study) for SL residents undergoing 4-h daily HH treatments was retained 24 h later during subsequent HH residence at 4,300 m (446 mmHg, PO2 = 93 mmHg) (2). In another study (24), PETCO2 also was ~4 mmHg lower for moderate-altitude residents (living at 1,600 m) than for SL residents assessed at their respective baseline elevations. When the SL and moderate-altitude residents were later assessed while living at 4,300 m, PETCO2 remained ~4 mmHg lower each day for the first 5 days for the moderate-altitude residents than for the SL residents. The implication for the present study is that if NH treatment was to be as effective as HH treatment during HH residence, the induced ~4-mmHg lower PETCO2 of the NH group than the sham group should have been similarly retained during HH residence. Why there was no evidence of initial or retained difference for PETCO2 between the NH and sham treatment groups during HH residence remains to be determined.

Collectively, in light of our results, experimental design considerations, and at least one study (17) that reported that VEacc induced by NH treatment remained evident for up to 1 mo (but only when assessed under NH conditions), a likely and seemingly unavoidable interpretation for a lack of difference between groups for nearly all measures is that NH sleep treatment, potent enough to have induced significant VEacc, simply did not provide any additional ventilatory, AMS symptom, or exercise performance benefit while the volunteers were awake during HH residence. In contrast, a significantly higher mean sleep SaO2 in the NH than in the sham group during HH residence may have contributed to less awakening during sleep and significantly attenuated AMS NH symptoms and EPO response soon after awakening. Further studies are needed to determine the mechanisms responsible as to why, during subsequent HH residence, 1) NH treatment is not nearly as effective as HH treatment and 2) physiological responses and outcomes resulting from the NH sleep treatment are specific to sleep.

Perspectives and Significance

This study clearly shows that NH treatment relative to sham treatment provides little useful benefit during subsequent HH residence. It should be emphasized that the lack of effectiveness of NH treatment was not likely related to an inadequate stimulus or response, since the magnitude of the ventilatory acclimatization induced by NH treatment was comparable to that of previous similar studies using HH treatment. In addition, the time interval between the end of NH and later HH residence in the present study was deliberately comparable to that of previous HH treatment-to-HH residence studies. Yet only HH treatment reduced AMS and improved exercise performance during HH conditions. Interestingly, NH treatment does provide significant AMS and exercise benefits when the outcome measures are assessed under NH conditions. The most important conclusion resulting from the sum of all this information is that NH and HH treatments clearly cannot be used interchangeably and are not as effective as preacclimatization strategies to reduce AMS and improve exercise performance during subsequent HH residence.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

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