HIGHLIGHTED TOPIC | Hypoxia

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

Normand A. Richard,1 Inderjeet S. Sahota,4 Nadia Widmer,2 Sherri Ferguson,3,4 A. William Scheel,1 and Michael S. Koehle1,4,5

1School of Kinesiology, University of British Columbia, Vancouver, British Columbia, Canada; 2Department of Medicine, University of British Columbia, Vancouver, British Columbia, Canada; 3Environmental Medicine and Physiology Unit, Faculty of Science, Simon Fraser University, Burnaby, British Columbia, Canada; 4Department of Biomedical Physiology and Kinesiology, Simon Fraser University, Burnaby, British Columbia, Canada; and 5Division of Sport Medicine, Department of Family Practice, Vancouver, British Columbia, Canada

Submitted 15 March 2013; accepted in final form 27 June 2013

Richard NA, Sahota IS, Widmer N, Ferguson S, Scheel AW, Koehle MS. Acute mountain sickness, chemosensitivity, and cardiorespiratory responses in humans exposed to hypobaric and normobaric hypoxia. J Appl Physiol 116: 945–952, 2014. First published July 3, 2013; doi:10.1152/japplphysiol.00319.2013.—We examined the control of breathing, cardiorespiratory effects, and the incidence of acute mountain sickness (AMS) in humans exposed to hypobaric hypoxia (HH) and normobaric hypoxia (NH), and under two control conditions [hypobaric normoxia (HN) and normobaric normoxia (NN)]. Exposures were 6 h in duration, and separated by 2 wk between hypoxic exposures and 1 wk between normoxic exposures. Before and after exposures, subjects (n = 11) underwent hyperoxic and hypoxic Duffin CO2 rebreathing tests and a hypoxic ventilatory response test (HVR). Inside the environmental chamber, minute ventilation (VE), tidal volume (VT), frequency of breathing (fB), blood oxygenation, heart rate, and blood pressure were measured at 5 and 30 min and hourly until exit. Symptoms of AMS were evaluated using the Lake Louise score (LLS). Both the hypoxic and hyperoxic CO2 thresholds were lower after HH and NH, whereas CO2 sensitivity was increased after HH and NH in the hypoxic test and after NH in the hypoxic test. Values for HVR were similar across the four exposures. No major differences were observed for VE or any other cardiorespiratory variables between NH and HH. The LLS was greater in AMS-susceptible than in AMS-resistant subjects; however, LLS was alike between HH and NH. In AMS-susceptible subjects, fB correlated positively and VT negatively with the LLS. We conclude that 6 h of hypoxic exposure is sufficient to lower the peripheral and central CO2 threshold but does not induce differences in cardiorespiratory variables or AMS incidence between HH and NH.

CO2 control of breathing; Lake Louise score; simulated altitude

HYPOBARIC HYPOXIA (HH) lowers the PO2 by reduction of barometric pressure (Pb). Normobaric hypoxia (NH) lowers the PO2 by reducing the fraction of inspired oxygen (FIO2) through addition of exogenous nitrogen (N2) without altering Pb. Acute mountain sickness (AMS) is a self-limiting illness experienced by some when exposed to hypoxia for a period of ~6–10 h; however, in some, symptoms develop as soon as 1 h after hypoxia exposure (9). 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 (9). 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). Some have hypothesized that microembolism in the alveolar capillaries, as a result of lowered Pb, may hinder pulmonary gas exchange in hypobaria (8, 41) and that lowering Pb induces greater dead-space ventilation in HH (39). Other reported differences include higher minute ventilation (VE), tidal volume (VT), and end-tidal O2 and CO2 in NH and a lower frequency of breathing (fB) and blood oxygenation in HH (6, 16, 18, 38, 39, 41). To maintain adequate arterial blood oxygenation, VE rapidly increases following hypoxia exposure; yet the magnitude of this response, interpreted as the peripheral chemosensory input, is not homogeneous. Accordingly, it has been hypothesized that those with a blunted hypoxic ventilatory response (HVR) might be more susceptible to AMS than those with a brisk HVR. For example, compared with their AMS-resistant (AMS−) counterparts, AMS-susceptible (AMS+) subjects have a lower HVR (28, 30). This does not appear to be a universal finding (10, 23, 24). Changes in central chemosensitivity test parameters, such as decreased ventilatory response threshold to hypercarbia, are seen post-hypoxia exposure (15, 20). Furthermore, central chemosensitivity, as measured using a progressive CO2 rebreathing method, recently has been demonstrated to differ between AMS+ and AMS− subjects (30). Thus the magnitude of one’s response to a CO2 rebreathing test in response to hypoxic exposure might be associated with AMS susceptibility and has yet to be compared between HH and NH. Despite considerable advancements in hypoxia research, studies have yet to compare the control of breathing along with AMS severity and cardiorespiratory responses between HH and NH, and a consensus on the differences between HH and NH does not exist. The synergistic effect between hypobaria and hypoxia along with the “specific response to hypobaric hypoxia” 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.

Environmental chamber. The chamber (Perry Baromedical, Florida) was equipped with CO2, O2, P50, humidity, and temperature sensors (Analox 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/721 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 NN, the main lock was pressurized to 427 Torr without modifying the FiO2.

Table 1. Gas partial pressures and simulated altitudes

<table>
<thead>
<tr>
<th>Altitude, m</th>
<th>HH</th>
<th>NH</th>
<th>HH</th>
<th>NN</th>
</tr>
</thead>
<tbody>
<tr>
<td>4500</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>750</td>
<td>19.8</td>
<td>10.5</td>
<td>20.93</td>
<td></td>
</tr>
<tr>
<td>85</td>
<td>80</td>
<td>166</td>
<td>160</td>
<td></td>
</tr>
<tr>
<td>75</td>
<td>75</td>
<td>150</td>
<td>150</td>
<td></td>
</tr>
</tbody>
</table>

HH, hypobaric hypoxia; NH, normobaric hypoxia; HN, hypobaric normoxia; NN, normobaric normoxia; P50, barometric pressure; P2O2, inspired O2 fraction; P2O2, inspired CO2 fraction; PIO2, inspired PO2.

Sampling. Subjects underwent the control of breathing tests 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 (3813 Athletic series, Hans Rudolph, Shawnee, KS) measuring flow upon which f50 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 (P2O2) 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 P2O2 (P2CO2) 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, P2CO2 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 P2CO2 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 P2CO2, 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 HCV method is 17.9% (range 8.3–26.3%) (35), whereas for the Duffin test it is 18–32% for CO2 sensitivity and 3–8% for the CO2 threshold (11).

Use of a minor amount of CO2 accumulation in the chamber where ambient P2CO2 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 f50 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 (P2O2) 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 P2O2 (P2CO2) 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.

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.

Environmental chamber. The chamber (Perry Baromedical, Florida) was equipped with CO2, O2, P50, humidity, and temperature sensors (Analox 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/721 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 NN, the main lock was pressurized to 427 Torr without modifying the FiO2. In 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 pressurized to 427 Torr without modifying the FiO2.

In hypobaric hypoxia (HH), the main lock was decompressed to 427 Torr without modifying the FiO2. In hypobaric hypoxia (HH), the main lock was decompressed to 427 Torr without modifying the FiO2. In hypobaric hypoxia (HH), the main lock was decompressed to 427 Torr without modifying the FiO2.

HVR. The HVR was measured on the familiarization day, before and after exposures with procedures based on methods from our research group (13, 15). Suprine 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 P2CO2 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).
Ventura, CA) connected to the mouthpiece by sample lines. Data were converted to digital signals (PowerLab 16/30 ADInstruments, Colorado Springs, CO) and viewed in real time using commercially available software (LabChart, ADInstruments, Colorado Springs, CO). A pulse oximeter (Avant 9600, Nonin Medical, Plymouth, MN) was attached to the index finger, and the test terminated once blood oxygen saturation ($SpO_2$) reached 75%. From the acquired data, $Ve$ was plotted against $SpO_2$, and a linear slope was fit where the magnitude of this slope was considered the HVR (13).

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 $SpO_2$ were measured using right earlobe pulse oximetry (CANL-425SV-A, Med Associates, St. Albans, VT) and ventilation by means of 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 $SpO_2$ 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 $\pm$ SD) were calculated for cardiorespiratory parameters, AMS scores, and control of breathing measures. Values for all data were expressed as $mean \pm SD$; ventilatory parameters were expressed as $liters/min$. Data were also examined for normality using a Kolmogorov-Smirnov test. Friedman’s test was completed followed by a post hoc Wilcoxon test for the previously mentioned time points and for each of the four conditions (HH, NH, HN, NN). Bonferroni’s test was undertaken for cardiorespiratory variables, AMS, and control of breathing measures for the previously mentioned time points and for the coefficient of variation was 0.056 for the VRT and 0.28 within-subject coefficient of variation for the VRT and S1 in the hypoxic 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.

Hydrostatic VRT. The hydrostatic 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 ($\Delta$VRT) were determined. The $\Delta$VRT was larger in NH than in NN and $P < 0.01$), but no difference was seen between HH and the other conditions (Fig. 1). Finally, the post-chamber hydrostatic VRT correlated negatively to LLS (i.e., lower VRT in AMS + 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

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age, yr</th>
<th>Height, cm</th>
<th>Weight, kg</th>
<th>BMI, kg/m²</th>
<th>FVC, liters</th>
<th>FEV₁, liters</th>
<th>FEV₁/FVC, %</th>
<th>Systolic BP, mmHg</th>
<th>Diastolic BP, mmHg</th>
<th>HR, beats/min</th>
<th>AMS+ / AMS−</th>
</tr>
</thead>
<tbody>
<tr>
<td>s005</td>
<td>18</td>
<td>181</td>
<td>74.6</td>
<td>22.7</td>
<td>4.31</td>
<td>4.05</td>
<td>94</td>
<td>125</td>
<td>76</td>
<td>82</td>
<td>AMS+</td>
</tr>
<tr>
<td>s006</td>
<td>20</td>
<td>185.5</td>
<td>76</td>
<td>22.1</td>
<td>7.66</td>
<td>6.17</td>
<td>80.5</td>
<td>118</td>
<td>78</td>
<td>69</td>
<td>AMS+</td>
</tr>
<tr>
<td>s007</td>
<td>19</td>
<td>172</td>
<td>61.6</td>
<td>20.1</td>
<td>5.08</td>
<td>4.09</td>
<td>80.4</td>
<td>104</td>
<td>69</td>
<td>77</td>
<td>AMS+</td>
</tr>
<tr>
<td>s009</td>
<td>20</td>
<td>175</td>
<td>72.5</td>
<td>24.2</td>
<td>6.23</td>
<td>5.22</td>
<td>83.8</td>
<td>107</td>
<td>73</td>
<td>80</td>
<td>AMS+</td>
</tr>
<tr>
<td>s010</td>
<td>19</td>
<td>168.5</td>
<td>60</td>
<td>21.1</td>
<td>4.74</td>
<td>3.84</td>
<td>81</td>
<td>119</td>
<td>71</td>
<td>60</td>
<td>AMS−</td>
</tr>
<tr>
<td>s013</td>
<td>21</td>
<td>185</td>
<td>77</td>
<td>22.4</td>
<td>5.54</td>
<td>4.41</td>
<td>80.9</td>
<td>120</td>
<td>71</td>
<td>74</td>
<td>AMS−</td>
</tr>
<tr>
<td>s014</td>
<td>23</td>
<td>183</td>
<td>74</td>
<td>22.1</td>
<td>5.55</td>
<td>4.55</td>
<td>82.7</td>
<td>125</td>
<td>70</td>
<td>68</td>
<td>AMS−</td>
</tr>
<tr>
<td>s016</td>
<td>23</td>
<td>190</td>
<td>90</td>
<td>24.9</td>
<td>8.8</td>
<td>7.22</td>
<td>82</td>
<td>111</td>
<td>58</td>
<td>60</td>
<td>AMS−</td>
</tr>
<tr>
<td>s017</td>
<td>32</td>
<td>178</td>
<td>73</td>
<td>23.1</td>
<td>6.34</td>
<td>5.2</td>
<td>82</td>
<td>112</td>
<td>79</td>
<td>54</td>
<td>AMS+</td>
</tr>
<tr>
<td>s018</td>
<td>34</td>
<td>183</td>
<td>112</td>
<td>33.5</td>
<td>5.56</td>
<td>4.54</td>
<td>81.7</td>
<td>115</td>
<td>76</td>
<td>100</td>
<td>AMS+</td>
</tr>
</tbody>
</table>

AMS. Mean $\pm$ SD

AMS− Mean $\pm$ SD

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.

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 $V_E$, HR, and $SpO_2$ at their representative time points. The 5-min $V_E$ during HH and NH was significantly higher than during the two normoxic conditions ($P < 0.05$). The 5-h mean $V_E$ in NH was higher than HN ($P < 0.05$) and NN ($P < 0.01$). The $V_E$ in HH ($P < 0.05$) 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 $V_E$ and LLS. No differences from the above-mentioned were seen when $V_E$ was normalized for body surface area (BSA). No differences were demonstrated for $f_b$ in all conditions at all time points. A correlation was observed between $f_b$ 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 ($r = 0.43; P < 0.05$). $V_T$ was higher in NH than in HN 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 $V_T$. The AMS+ subjects had a lower 5-h mean $V_T$ 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 hy-
poxic conditions as opposed to the normoxic conditions at all time points (P < 0.0001). In HH, SpO₂ was lower at 30 min than at 5 min (P < 0.05). In NH, SpO₂ was lower at 30 min than at 5 min and 5-h mean (P < 0.01). Both hypoxic conditions elicited greater HR than the normoxic conditions at all time points (P < 0.05) (Table 3). HR increased significantly in all conditions from 5 min to 5-h mean. The HR data in both normoxic conditions (NN and HN) did not differ from control data taken during the familiarization (Table 3). One subject was removed from the BP analysis since erroneous measures were experienced in his blood pressure measurement. No significance was observed for systolic and diastolic blood pressure between and within condition at all time points or between AMS+ and AMS− subjects.

AMS. The LLS recorded from the last questionnaire completed inside the chamber identified subjects as AMS+ or AMS−. Subjects s007 and s009 exited at 5 h in HH, and s007 exited at 4 h in NH as they met AMS severity criteria for removal. The mean LLS were greater in the two hypoxic conditions (P < 0.05) than in the two normoxic conditions. The LLS for the group as a whole did not differ between HH (2.27 ± 3.29) and NH (2.54 ± 3.14) (P > 0.05). In hypoxia, the AMS+ group had significantly elevated LLS scores (P < 0.0001) (Fig. 4).

**DISCUSSION**

**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 P_b along 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 exposure 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 rebreathing 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 hypoxic rebreathing (7). Lowering of the S1 following NH exposure was unexpected. This finding needs to be reproduced in future

---

**Table 3. Statistics for experimental conditions**

<table>
<thead>
<tr>
<th>Condition</th>
<th>V̇_E, l/min</th>
<th>VT, liters</th>
<th>SpO₂, %</th>
<th>f_a, breaths/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HH</td>
<td>18.9 ± 6.7</td>
<td>18.5 ± 4.7</td>
<td>14.8 ± 3.7</td>
<td>14.8 ± 3.3</td>
</tr>
<tr>
<td>NH</td>
<td>16.4 ± 4.9</td>
<td>16.5 ± 5.2</td>
<td>12.7 ± 3.2</td>
<td>13.6 ± 2.8</td>
</tr>
<tr>
<td>30 min</td>
<td>16.5 ± 3.6**</td>
<td>17.6 ± 2.9*</td>
<td>14.8 ± 2.9</td>
<td>14.4 ± 2.6</td>
</tr>
<tr>
<td>5-h mean</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HH</td>
<td>11.1 ± 0.5†</td>
<td>1.2 ± 0.5</td>
<td>0.98 ± 0.4</td>
<td>1 ± 0.4</td>
</tr>
<tr>
<td>NH</td>
<td>1.03 ± 0.4#</td>
<td>1.1 ± 0.6</td>
<td>0.9 ± 0.4</td>
<td>1.02 ± 0.5</td>
</tr>
<tr>
<td>5-h mean</td>
<td>1.05 ± 0.3**</td>
<td>1.2 ± 0.4</td>
<td>0.9 ± 0.3</td>
<td>0.99 ± 0.3</td>
</tr>
<tr>
<td>HN</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 min</td>
<td>19.6 ± 7.3</td>
<td>17.9 ± 5.8</td>
<td>17.3 ± 5.9</td>
<td>17.5 ± 6.7</td>
</tr>
<tr>
<td>30 min</td>
<td>18.7 ± 6.9</td>
<td>17.6 ± 6.2</td>
<td>16.6 ± 6.3</td>
<td>15.8 ± 6.8</td>
</tr>
<tr>
<td>5-h mean</td>
<td>18 ± 5.6</td>
<td>17.8 ± 5.4</td>
<td>16.5 ± 4.9</td>
<td>17 ± 6.6</td>
</tr>
<tr>
<td>SpO₂, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 min</td>
<td>86.4 ± 5.9</td>
<td>85.6 ± 5.3</td>
<td>100 ± 0</td>
<td>100 ± 0</td>
</tr>
<tr>
<td>30 min</td>
<td>80.5 ± 6.6†</td>
<td>80.5 ± 6.6*</td>
<td>100 ± 0</td>
<td>100 ± 0</td>
</tr>
<tr>
<td>5-h mean</td>
<td>82 ± 5.8</td>
<td>80.6 ± 5.3</td>
<td>100 ± 0</td>
<td>100 ± 0</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 min</td>
<td>86.5 ± 19.8</td>
<td>87.8 ± 10.9</td>
<td>72.3 ± 12.1</td>
<td>71.5 ± 13.9</td>
</tr>
<tr>
<td>30 min</td>
<td>90.2 ± 15.4</td>
<td>90.1 ± 15.9</td>
<td>75.9 ± 11.7</td>
<td>74.9 ± 13.9</td>
</tr>
<tr>
<td>5-h mean</td>
<td>96.6 ± 12.6*</td>
<td>95.2 ± 14.1*</td>
<td>80.4 ± 11.5*</td>
<td>76.3 ± 10.1*</td>
</tr>
</tbody>
</table>

Values are means ± SD. V̇_E, minute ventilation; VT, tidal volume; f_a, frequency of breathing; SpO₂, blood O₂ saturation. *Significantly higher than NN and HN; **significantly higher than NN; †significantly higher than HN; ††significantly lower than the 5-min time point; ‡significantly lower than the 5-min and 5-h mean time point; #significantly higher than the 5-min time point.
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 rebreathing test, where subjects experience bouts of hyperventilation, hypcapnia, hypercapnia, and hypoxia; it is possible these perturbations influenced the HVR measures. During the basal breathing phase of the HVR test, our subjects resting $P_{\text{ETCO}_2}$ was $35.3 \pm 1.53$ 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 $f_B$ (greater LLS in those with higher $f_B$) 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 $f_B$ in AMS+ subjects did not yield differences in $V_E$ or $S_{PO_2}$ between AMS+ and AMS− subjects. No correlations were found between $S_{PO_2}$ 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 $V_E$, followed by a depression lasting ~1 h, followed by a progressive rise. Accordingly, $S_{PO_2}$ 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 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. 9h), and our hypoxic dose was more severe ($P_{O_2}$ 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 $V_T$ or $f_B$ 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., $P_{O_2}$) 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 $P_{CO_2}$ 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 ($P_{CO_2}$ was maintained below 3.7 Torr) (16). Studies comparing minor changes in $V_E$ should report ambient $P_{CO_2}$, since accumulations of CO₂ could confound $V_E$ measurements. Regardless, since ambient $P_{CO_2}$ 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 $V_E$ 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 sensitivity after exposure to HH and NH. There was no significant effect of hypobaria alone. The HVR was unaffected by 6 h of hypoxia induced either by PaO₂ 427 Torr or by FiO₂ of 10.5%. It is plausible that hypobaric hypoxia and normobaric hypoxia differ 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.

ACKNOWLEDGMENTS

We thank all of our subjects for participation, the physicians, Drs. Valerie Athaide and Paul Hertz who volunteered their time, M. J. MacInnis for reviewing the manuscript, and James Mayall for technical operation of the hypobaric chamber.

GRANTS

This study was supported by the Natural Sciences and Engineering Research Council of Canada (NSERC). N. A. Richard was supported by the B.C. Sports Medicine Research Foundation.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: N.A.R., S.F., A.W.S., and M.S.K. conception and design of research; N.A.R., I.S.S., N.W., S.F., A.W.S., and M.S.K. performed experiments; N.A.R. and N.W. analyzed data; N.A.R. and M.S.K. interpreted results of experiments; N.A.R. prepared figures; N.A.R. and M.S.K. drafted manuscript; N.A.R., S.F., A.W.S., and M.S.K. edited and revised manuscript; N.A.R., I.S.S., N.W., S.F., A.W.S., and M.S.K. approved final version of manuscript.

REFERENCES

13. Koehle MS, Foster GE, McKenzie DC, Sheel AW. Increased central sensitivity after exposure to HH and NH. There was no significant effect of hypobaria alone. The HVR was unaffected by 6 h of hypoxia induced either by PaO₂ 427 Torr or by FiO₂ of 10.5%. It is plausible that hypobaric hypoxia and normobaric hypoxia differ 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.

ACKNOWLEDGMENTS

We thank all of our subjects for participation, the physicians, Drs. Valerie Athaide and Paul Hertz who volunteered their time, M. J. MacInnis for reviewing the manuscript, and James Mayall for technical operation of the hypobaric chamber.

GRANTS

This study was supported by the Natural Sciences and Engineering Research Council of Canada (NSERC). N. A. Richard was supported by the B.C. Sports Medicine Research Foundation.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: N.A.R., S.F., A.W.S., and M.S.K. conception and design of research; N.A.R., I.S.S., N.W., and S.F. performed experiments; N.A.R. and N.W. analyzed data; N.A.R. and M.S.K. interpreted results of experiments; N.A.R. prepared figures; N.A.R. and M.S.K. drafted manuscript; N.A.R., S.F., A.W.S., and M.S.K. edited and revised manuscript; N.A.R., I.S.S., N.W., S.F., A.W.S., and M.S.K. approved final version of manuscript.

REFERENCES

13. Koehle MS, Foster GE, McKenzie DC, Sheel AW. Increased central sensitivity after exposure to HH and NH. There was no significant effect of hypobaria alone. The HVR was unaffected by 6 h of hypoxia induced either by PaO₂ 427 Torr or by FiO₂ of 10.5%. It is plausible that hypobaric hypoxia and normobaric hypoxia differ 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.


