Effects of Hypobaric Hypoxia on Cerebral Autoregulation

Andrew W. Subudhi, PhD; Ronney B. Panerai, PhD; Robert C. Roach, PhD

Background and Purpose—Acute hypoxia is associated with impairment of cerebral autoregulation (CA), but it is unclear if altered CA during prolonged hypoxia is pivotal to the development of cerebral pathology, such as that seen in acute mountain sickness (AMS). This investigation evaluated relationship between CA and AMS over 9 hours of hypobaric hypoxia.

Methods—Fifty-five subjects (41 males, 14 females) were studied in normoxia (PaO₂=625 mm Hg) and after 4 and 9 hours of hypobaric hypoxia (PaO₂=425 mm Hg; approximately 4,875 m). Resting, beat-by-beat changes in arterial blood pressure, and middle cerebral artery blood flow velocity were recorded at each time point while breathing room air. Transfer function analyses were used to estimate autoregulation indices (ARI). In 29 subjects, ARI during isocapnic hyperoxia and cerebral vasomotor reactivity during modified rebreathing were also determined to isolate effects of hypoxia and CO₂ reactivity on CA.

Results—Self-reported Lake Louise AMS Questionnaire scores ≥3 with headache were used to differentiate between AMS-positive (n=27) and AMS-negative (n=28) subjects (P<0.01). ARI decreased and CO₂ reactivity increased in both groups at 4 hours (P<0.01) and did not progress at 9 hours, despite increased incidence and severity of AMS (P<0.01). Impairments in ARI were alleviated with isocapnic hyperoxia at 4 and 9 hours (P<0.01) and were not related to CO₂ reactivity.

Conclusions—These results indicate that hypoxia directly impairs CA but that impaired CA does not play a pivotal role in the development of AMS. (Stroke. 2010;41:641-646.)

Key Words: acute mountain sickness • altitude • cerebral blood flow • transcranial Doppler • vascular reactivity

In healthy individuals, cerebral autoregulation (CA) effectively buffers changes in perfusion pressure to maintain consistent blood flow. CA is impaired in diseases in which hypoxia occurs secondary to ischemia (eg, stroke, carotid artery stenosis, and traumatic brain injury); however, whether hypoxic impairment of CA contributes to the progression of such diseases has not been established. Whereas we and others have recently shown that acute hypoxia (≈10 minutes) impairs CA, it is unknown if such impairment persists during prolonged periods of hypoxia (eg, hours) and leads to the development of cerebral pathology. Acute mountain sickness (AMS) offers a unique clinical model to address this question because the illness can be induced and reversed in controlled laboratory settings.

It has been hypothesized that elevated cerebral blood flow and impaired CA during acute hypoxia may disrupt the blood–brain barrier, causing vasogenic edema. Ensuing meningeal stress or increased intracranial pressure, if cerebral compliance is limited, could be responsible for headache, dizziness, and nausea that define AMS. This hypothesis appears to be supported by a few studies showing that CA is impaired after AMS has developed (6–48 hours) and that the degree of CA impairment is moderately correlated with AMS symptomology (r²=0.20–0.50); however, no studies have reported serial measurements of CA as AMS develops to establish a definitive link between impairment of CA and onset of AMS. Additionally, because CA remains impaired after successful acclimatization to high altitude and persists in life-long residents of high altitude, a relationship between CA and AMS remains questionable. We report the first (to our knowledge) sequential measurements of CA during 9 hours of hypobaric hypoxia to test the hypothesis that changes in CA would be directly related to the development of AMS.

Materials and Methods

Recruitment and Screening

After institutional ethics approval, potential subjects were screened to identify those with no histories of head injuries, migraines, smoking, or medical conditions affected by hypoxia, such as anemia, pregnancy, or hypertension. Additionally, a brief altitude history was obtained to exclude those with recent (<1 month) exposure to altitudes >2,500 m. After obtaining written consent, volunteers were physically examined and excluded if results revealed previously undisclosed medical conditions, or if they were not able to achieve at

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least 200 W of effort during an incremental cycle ergometer test. Of 66 consenting subjects, 55 (41 males, 14 females) meeting the inclusion criteria completed the following protocol.

**Protocol**

This study represents the placebo arm of a large, multiyear study investigating cerebral pathophysiology resulting from hypoxia. All subjects received placebo medications 24 hours before baseline (BL) measurements (P<sub>H</sub> 625–630 mm Hg; relative humidity, 12%–28%; 19°C–23°C) and throughout a 10-hour period in a hypobaric chamber (P<sub>H</sub> 425 mm Hg; relative humidity, 13%–29%; 19°C–22°C) the next day. Inside the chamber, subjects performed 4 30-minute sets of submaximal cycling (50% altitude specific V<sub>O2max</sub>), with 15 minutes of rest between sets, to increase the incidence of AMS. Subjects then rested for the remaining 7 hours of hypoxia. Measures of CA and AMS were evaluated at BL, 4 hours, and 9 hours, as described.

In one cohort, 26 subjects (16 males, 10 females) rested in a supine position for 15 minutes while being instrumented to monitor beat-by-beat changes in arterial blood pressure (ABP) via a tonometer placed over the right radial artery (Colin 7000; Colin Medical Instruments) and middle cerebral artery blood flow velocity (CBFv) insonated through the ipsilateral temporal window at depths of ~50 mm (Model Multi Dop T2; DWL Electronic Systems). Doppler probes were secured to a custom headset to preserve insonation angle and traced with indelible ink to guide subsequent replacements. Data were then recorded for 6 to 10 minutes for transfer function analysis of CA while breathing room air (PIO<sub>2</sub>=250 mm Hg). Isocapnia was achieved by manually adjusting the flow of hyperoxic gas using the sequential gas delivery method. Additionally, cerebral vasomotor reactivity to CO<sub>2</sub> (CVMR) during a modified rebreathing protocol (6-L reservoir filled with gas to produce a P<sub>CO<sub>2</sub></sub> of 250 and P<sub>CO<sub>2</sub></sub> of 50 mm Hg at each period) was evaluated to determine the relative influence of CO<sub>2</sub> reactivity on CA.

In all experiments, expired gases and volumes were analyzed using fast response analyzers (Ametek 3-3A and CD-3A; AEI Technologies; or O<sub>2</sub>cap; Oxigra) and a heated pneumotach (Hans Rudolph). Blood oxygen saturation was monitored by finger-pulse oximetry (N-595; Nellcor) and ECG via standard 3-lead configuration (Bioamp; ADInstruments). Analog signals from each instrument were integrated with a data acquisition system (Powerlab 16SP; ADInstruments), which sampled at 200 Hz throughout the experimental periods.

Self-reported sections (headache, gastrointestinal distress, dizziness, fatigue) of the Lake Louise AMS Questionnaire were used to evaluate AMS symptoms at BL, 4 hours and 9 hours. Subjects with Lake Louise AMS Questionnaire score ≥ 3 with headache at 9 hours were defined as AMS-positive (AMS+); those with Lake Louise AMS Questionnaire score ≤ 2 or without headache were defined as AMS-negative (AMS−).

**Table 1. Effects of Hypobaric Hypoxia in AMS− (n=28) and AMS+ (n=27) Subjects**

<table>
<thead>
<tr>
<th>Variable</th>
<th>BL</th>
<th>4 Hours</th>
<th>9 Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>LLQ</td>
<td>0.43±0.74</td>
<td>0.44±0.64</td>
<td>1.54±1.34</td>
</tr>
<tr>
<td>V&lt;sub&gt;La&lt;/sub&gt;, L/min</td>
<td>9.58±2.12</td>
<td>8.89±1.76</td>
<td>11.83±4.08†</td>
</tr>
<tr>
<td>Pet&lt;sub&gt;O&lt;sub&gt;2&lt;/sub&gt;&lt;/sub&gt;, mm Hg</td>
<td>79.3±5.5</td>
<td>79.2±5.0</td>
<td>43.1±2.7†</td>
</tr>
<tr>
<td>PetCO&lt;sub&gt;2&lt;/sub&gt;, mm Hg</td>
<td>36.1±3.2</td>
<td>36.3±3.3</td>
<td>31.6±3.2†</td>
</tr>
<tr>
<td>SpO&lt;sub&gt;2&lt;/sub&gt;, %</td>
<td>96.0±1.5</td>
<td>96.1±1.7</td>
<td>79.5±5.4†</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>63.2±11.7</td>
<td>60.1±8.0</td>
<td>90.3±13.2†</td>
</tr>
<tr>
<td>Mean ABP, mm Hg</td>
<td>91.5±13.9</td>
<td>86.6±10.8</td>
<td>81.9±13.7†</td>
</tr>
<tr>
<td>Mean CBFv, cm/sec</td>
<td>58.6±8.9</td>
<td>57.1±12.5</td>
<td>57.3±11.7</td>
</tr>
<tr>
<td>CVRi, mm Hg/cm/sec</td>
<td>1.60±0.35</td>
<td>1.60±0.44</td>
<td>1.48±0.40</td>
</tr>
<tr>
<td>ABP PSD, mm Hg&lt;sup&gt;2&lt;/sup&gt;/Hz</td>
<td>9.41±4.44</td>
<td>7.01±4.97</td>
<td>12.48±12.05</td>
</tr>
<tr>
<td>CBFv PSD, cm&lt;sup&gt;2&lt;/sup&gt;/sec&lt;sup&gt;2&lt;/sup&gt;/Hz</td>
<td>7.85±5.15</td>
<td>7.55±6.27</td>
<td>14.81±12.53†</td>
</tr>
<tr>
<td>Coherence</td>
<td>0.52±0.11</td>
<td>0.47±0.14</td>
<td>0.61±0.12†</td>
</tr>
<tr>
<td>Gain, %/%</td>
<td>0.63±0.20</td>
<td>0.71±0.28</td>
<td>0.84±0.24†</td>
</tr>
<tr>
<td>Phase, rad</td>
<td>0.54±0.31</td>
<td>0.55±0.35</td>
<td>0.34±0.15</td>
</tr>
<tr>
<td>Step response</td>
<td>4.70±1.10</td>
<td>4.11±1.53</td>
<td>3.30±1.11†</td>
</tr>
<tr>
<td>%CBFv recovery</td>
<td>66.13±7.3</td>
<td>57.6±25.0</td>
<td>42.4±17.9†</td>
</tr>
</tbody>
</table>

Transfer function analysis results from low-frequency range (<0.10 Hz). Different from *AMS−, †BL, and ‡4 hours at P<0.01. CVRi indicates cerebrovascular resistance index; HR, heart rate; LLQ, Lake Louise AMS Questionnaire; PSD, power spectral density; SpO<sub>2</sub>, blood oxygen saturation; SpO<sub>2</sub>, blood oxygen saturation.

CA was determined using transfer function analysis and subsequent step response, as previously described, to quantitatively describe the effects of spontaneous changes in blood pressure on cerebral blood flow velocity. Briefly, resting ABP and CBFv tracings were cleaned for removal of random signal noise and smoothed using median (5 points) and Butterworth filters in succession. Beat-by-beat data were extracted and resampled at 5 Hz. Fast-Fourier transformations using the Welch algorithm with 512-point windows and 40% overlap were performed to obtain power spectral densities of ABP and CBFv. The average power spectral densities, coherence, gain, and phase shift were evaluated in the low-frequency range of autoregulation (<0.10
Hz), associated with cycle lengths >10 sec. An inverse fast-Fourier transformation was then performed using both gain and phase shift to yield an impulse response in the time domain. Integration of the impulse yielded a step response that was fit to one of Tiecks et al.'s autoregulation index models (ARI) and used to determine percent CBFv recovery 4 sec after the peak impulse, in which higher scores are reflective of better CA (ARI range, 0–9; percent recovery after peak impulse range, 0%–100%).

CVMR was defined as the slope of the linear fit between percent resting CBFv and PetCO2 during modified rebreathing. Additionally, the cerebrovascular conductance index, which corrected CVMR for changes in ABP, was calculated from the slope of the linear fit between percent resting CBFv/ABP and PetCO2.

Statistics
Preliminary analyses indicated no differences between the 2 cohorts in cardiorespiratory, cerebrovascular, or transfer function analysis results, so data were pooled for further analysis. CA and CVMR measurements were analyzed using mixed factor ANOVA, with AMS status (AMS+ vs AMS−) analyzed over time (BL, 4 hours, and 9 hours) for room air and hyperoxic conditions. Criteria for significance were set at $P<0.01$ for main and interaction effects; $t$ tests were used for post hoc analyses of differences across time and FIO2 (paired) and between AMS status (independent) using more stringent criteria ($P<0.01$) to control for type I error. Pearson product moment correlations were calculated between CA, CO2 reactivity, and AMS scores at 4 and 9 hours ($P<0.05$). Data are presented as means±SD.

Results
Subjects completing the protocol were 29±7 years old, 178.2±9.9 cm tall, and weighed 74.4±12.5 kg. Hypoxia decreased blood oxygen saturation, PetO2, and PetCO2, and increased VE and heart rate at 4 and 9 hours ($P<0.05$). Mean ABP was lower at 4 hours compared to that at BL and 9 hours ($P<0.01$). None of these effects was different between AMS+ (n=27) and AMS− (n=28) subjects (Table 1). Composite Lake Louise AMS Questionnaire and headache severity scores increased from 4 to 9 hours in the AMS+ group only (Table 1). No individuals who met the criteria for AMS at 4 hours were AMS− at 9 hours.

Cerebral Autoregulation
Table 1 displays the results of the transfer function analysis and step responses while breathing room air (FIO2=0.21) at each time point. Fast-Fourier transformations of time series data from both cohorts revealed that hypobaric hypoxia resulted in pronounced low-frequency oscillations (>10 sec/cycle) in power spectral densities of CBFv ($P<0.01$), but not ABP. Transfer function analysis showed stronger relationships (coherence), greater transmittal of signal amplitudes (gain), and smaller phase shifts between ABP and CBFv, suggesting impairment of CA at 4 and 9 hours of hypoxia ($P<0.01$). These findings were confirmed by ARI (Figure 1) and percent recovery after peak impulse scores derived from the step response ($P<0.01$). No differences were detected between AMS− and AMS+ groups at any time point, even when groups were stratified by the highest (50%) vs lowest (50%) AMS scores or blood oxygen saturation values. Correlations between ARI and Lake Louise AMS Questionnaire scores (composite and headache subscale) were not significant at either 4 ($r=−0.13; P=0.37$; Figure 2) or 9 hours ($r=−0.05; P=0.72$; Figure 2).
Effect of Isocapnic Hyperoxia

The manual sequential gas delivery method enabled us to rapidly adjust $P_{O_2}$ to $\approx 250$ mm Hg while maintaining $P_{CO_2}$ (Table 2). Isocapnic hyperoxia increased blood oxygen saturation, ABP, and cerebrovascular resistance (cerebrovascular resistance index = ABP/CBFv) at all time points ($P<0.01$) and decreased CBFv at 4 and 9 hours ($P<0.01$). Impairments in CA at 4 and 9 hours of hypoxia were completely alleviated during isocapnic hyperoxia (Figure 3), as indicated by reductions in coherence and gain coupled with increases in phase shift, ARI, and percent recovery after peak impulse ($P<0.01$).

Reactivity to Carbon Dioxide

CVMR increased continually over 9 hours of hypoxia, with AMS$^+$ ($n=11$) showing greater reactivity than AMS$^-$ ($n=18$) at 9 hours ($P<0.01$) in the second cohort; however, when corrected for changes in blood pressure (ie, cerebrovascular conductance index), differences between groups were not significant (Table 3). Lake Louise AMS Questionnaire scores were moderately correlated with CVMR at 9 hours ($r=0.55; P<0.01$), but not with cerebrovascular conductance index ($r=0.19; P=0.34$).

Discussion

Results from this study refute the prevalent hypothesis that impairment of CA is a pivotal element in development of AMS. We tested the hypothesis that CA would become more impaired as AMS developed in subjects during 9 hours of hypobaric hypoxia; however, our data demonstrate evidence to the contrary. Whereas hypoxia did impair CA, changes were similar in those in whom AMS developed and in those to the contrary. Whereas hypoxia did impair CA, changes were similar in those in whom AMS developed and in those who remained healthy. Additionally, we found no evidence to suggest that the degree of CA impairment was related to the progression of AMS over 9 hours of hypoxia. These results indicate that hypoxia directly impairs CA, but that impaired CA does not explain the development of AMS.

Our data differ from previous studies$^{11–13}$ that have reported moderate associations between CA and AMS scores. Variations in methodology and interpretation may explain the different conclusions. First, in 2 of the aforementioned studies,$^{11,12}$ correlations between transfer function analysis gain scores and AMS symptomology were used to suggest modest links between CA and AMS ($r^2\approx0.20–0.50$). We also found a small but significant correlation between gain and Lake Louise AMS Questionnaire scores; yet, as we have...
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known to alter CA26 and is affected by changes in ventilatory

been demonstrated in healthy individuals after 1 to 2,11 5 to

remaining healthy. Because similar impairment in CA has

demonstrate that this effect is consistent at 4 and 9 hours, with

changes in CO2 reactivity to the integrated CA response27

vasodilatory responses to maintain cerebral blood flow and

mined is why. It is conceivable that during severe hypoxia,

impairing CA. Additionally, potential contributions from

could effectively restrict blood flow (eg, reduced PaCO2) i na

oxygenation may override or counteract CA mechanisms that

were evaluated using modified CO2 rebreathing at each time

segments in CA were completely reversed by isocapnic hyper-

hypoxia per se is the driving factor suppressing CA during

hydropic hypoxia.

In seeking to explain the mechanism by which hypoxia

affects CA, our attention was drawn to patterns seen in mean

CBFv tracings, in which slow, cyclic variations (≤0.10 Hz;

>10 sec/cycle) were visibly amplified during hypoxia and

attenuated during hyperoxia. Because intact CA should effec-
tively dampen changes in CBFv, the mechanisms allowing or

generating these large oscillations during hypoxia are of

particular interest. We speculate that hypoxia may be ampli-

fying fluctuations in CBFv either by the augmented ABP to

CBFv gain or by stimulation of rhythmic brain stem activity

purported to control cerebral vessel tone and intracranial

pressure.28–30 Such brain stem-derived effects may supere

des or mask mechanisms responsible for CA in normoxia and

may explain why hypoxia amplified slow oscillations in

CBFv in the brain, but not in ABP measured in the radial

artery. This hypothesis could be tested by short-term blocking

of specific neurotransmitter activity during acute hypoxic

exposure, because hypoxic effects on CA can be detected

within 10 minutes5,6 and readily reversed with supplemental

oxygen. Thus, hypoxia offers a promising model for isolating

mechanisms contributing to the integrated CA response and

may lead to new methods of clinical treatment for those in

whom impaired CA secondary to hypoxia increases the risk

for cerebrovascular complications.

Summary

Hypoxia alone appears to directly impair CA; however,

impaired CA does not explain the onset or development of

AMS. Hypoxia offers a unique model for investigating the

mechanisms responsible for impaired CA as assessed by

transfer function analysis because it can be studied in con-
trolled laboratory settings with minimal risk to subjects.

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Disclosure

None.
References


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