Worsening of central sleep apnea at high altitude—a role for cerebrovascular function

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Burgess KR, Lucas SJ, Shepherd K, Dawson A, Swart M, Thomas KN, Lucas RA, Donnelly J, Peebles KC, Basnyat R, Ainslie PN. Worsening of central sleep apnea at high altitude—a role for cerebrovascular function. J Appl Physiol 114: 1021–1028, 2013. First published February 21, 2012; doi:10.1152/japplphysiol.01462.2012.—Although periodic breathing during sleep at high altitude occurs almost universally, the likely mechanisms and independent effects of altitude and acclimatization have not been clearly reported. Data from 2005 demonstrated a significant relationship between decline in cerebral blood flow (CBF) at sleep onset and subsequent severity of central sleep apnea that night. We suspected that CBF would decline during partial acclimatization. We hypothesized therefore that reductions in CBF and its reactivity would worsen periodic breathing during sleep following partial acclimatization. Repeated measures of awake ventilatory and CBF responsiveness, arterial blood gases during wakefulness, and overnight polysomnography at sea level, upon arrival (days 2–4), and following partial acclimatization (days 12–15) to 5,050 m were made on 12 subjects. The apnea-hypopnea index (AHI) increased from to 77 ± 49 on days 2–4 to 116 ± 21 on days 12–15 (P = 0.01). The AHI upon initial arrival was associated with marked elevations in CBF (+28%, 68 ± 11 to 87 ± 17 cm/s; P < 0.05) and its reactivity to changes in PaCO2 (>90%, 2.0 ± 0.6 to 3.8 ± 1.5 cm·s−1·mmHg−1 hypercapnia and 1.9 ± 0.4 to 4.1 ± 0.9 cm·s−1·mmHg−1 for hypocapnia (P < 0.05)). Over 10 days, the increases resolved and AHI worsened. During sleep at high altitude large oscillations in mean CBF velocity (CBFv) occurred, which were 35% higher initially (peak CBFv = 96 cm/s vs. peak CBFv = 71 cm/s) than at days 12–15. Our novel findings suggest that elevations in CBF and its reactivity to CO2 upon initial ascent to high altitude may provide a protective effect on the development of periodic breathing during sleep (likely via moderating changes in central PCO2).

Although central sleep apnea (CSA) is not as common as obstructive sleep apnea, it remains a very significant and increasing clinical problem. The causes of CSA at sea level have been extensively explored in the context of patients with congestive heart failure (17). However, independent of heart failure, CSA also occurs almost universally at high altitude but the mechanisms are less completely understood (37, 47). The development of hypoxic-induced periodic breathing during sleep has been attributed to the marked increase in ventilatory responses to hypoxia and hypercapnia (controller gain), with consequent narrowing of the difference between eupneic PCO2 and apneic threshold (17, 18). The common trigger to both CSA in heart failure and high-altitude exposure is transient arterial hypocapnia (i.e., a decrease in PaCO2)(17) during light (stages 1 and 2 non-rapid eye movement) sleep.

Changes in PaCO2 may also influence breathing pattern via its influence on cerebral blood flow (CBF). For example, PaCO2-induced changes in CBF (22, 39, 44) provide an important protective mechanism that serves to minimize changes in brain [H+] levels, thereby stabilizing breathing (22, 39, 44). For example, during sleep, pharmacological blunting of CBF and its reactivity to CO2 leads to elevations in controller gain, reduced CO2 reserve, and subsequently increases the susceptibility to apneas and breathing instability during sleep (43).

It is known that CBF (38) and its reactivity to changes in CO2 (29) are elevated upon initial exposure to high altitude and return almost to baseline values within approximately 1 wk during acclimatization. In addition, acute drug-induced elevations in CBF velocity and reactivity to PaCO2, are related to improvements in breathing stability at high altitude during wakefulness (21). Thus CBF and its related reactivity to PaCO2, via its influence on central chemosensitivity, may provide an important mechanism in the pathophysiology of CSA (45).

Since the relative contributions of the likely mechanisms (e.g., chemosensitivity, CBF, pH) to CSA are largely unknown, we used natural exposure to high altitude as a cheap and reproducible means for experimental investigation of CSA that might also be applicable to patients with heart failure. Although two previous studies [that did not include arterial blood gases samples, CBF, or polysomnography (PSG) monitoring] have described nocturnal breathing patterns during acclimatization at high altitude (10, 37), by making additional simultaneous physiological measurements we aimed to gain further insight into the mechanisms of the severity of CSA during early and partial acclimatization to high altitude. We hypothesized that reductions in CBF and its vascular reactivity would be reflected in worsening of periodic breathing during sleep following partial acclimatization.

Materials and Methods

Twelve normal healthy adults (eight men and four women) with a mean age of 30 ± 10 yr (mean ± SD) and body mass index of 23 ± 2 kg/m2 volunteered for this study, which was approved by the Lower South Regional Ethics Committee of Otago and the Nepal Health...
Medical Research Council and conformed to the standards set by the Declaration of Helsinki. Written informed consent was obtained.

**Experimental Design and Ascent Protocol**

Following full familiarization with the experimental procedures (visit one), the participants underwent three experimental trials: one at sea level (Dunedin, New Zealand; barometric pressure 755 ± 7 mmHg) and two repeated trials while living at high altitude (5,050 m; the Ev-K2-CNR Pyramid Laboratory, Khumbu Valley, Nepal; barometric pressure 413 ± 1 mmHg). The high altitude trials were completed upon initial arrival (2–4 days) and then at *days 12–15*. Sea level testing was completed 2 wk before arriving in Nepal. This study was part of a larger research expedition, and consequently participants took part in a number of studies conducted during the 2 wk at the Pyramid Laboratory (reported elsewhere, e.g., 5a, 20, 29). Although some of the awake data presented in Fan et al. 2010 and Lucas et al. 2011 form part of these current data (e.g., awake CBFv), the a priori and primary questions addressed in the current paper (how sleep apnea severity is influenced by altered CBF and reactivity at high altitude during acclimatization) are novel and are exclusively dealt with here. Participants did not undergo testing associated with another study for at least 48 h prior to any testing session for the current study.

**Ascent profile.** Participants spent 7 days at Kathmandu (~1,400 m) before flying to Lukla (2,860 m). They then trekked to the Ev-K2-CNR Pyramid Laboratory over an 8-day period, which included rest days at Namche Bazar (3,450 m) and Pheriche (4,252 m). During the first 7 days of trekking, all participants used small dose (125 mg twice daily) of acetazolamide during the trek to help speed acclimatization and limit altitude illness (8). However, medication was ceased 48 h before reaching 5,050 m altitude and is therefore an unlikely confounder to our experiment design, since the reported half-life for acetazolamide is ~10 h (36) and this low-dose quantity is reported to be 90–100% excreted within 24 h after administration (35). Five subjects were treated upon arrival at 5,050 m for moderate acute mountain sickness (AMS) with dexamethasone (8 mg i.m. then 4 mg orally twice over 16 h). Treated subjects were excluded from testing for 48 h after treatment. We have been unable to find any evidence to suggest that such a brief period of treatment with dexamethasone could affect ventilatory control, respiratory muscle function, or CBF.

**Experimental Procedures**

Each experimental trial included an arterial blood gas sample, ventilatory response testing, and a night of full polysomnographic monitored sleep with cerebral blood flow also measured during the first 2–4 h of sleep (Fig. 1). Following the blood gas sample, participants were instrumented and completed a 5-min baseline data collection period. Participants then completed a modified hyperoxic rebreathing and an isocapnic hypoxia ventilatory control test. The protocol and related analysis of the ventilatory response tests used in this study have been previously described in detail elsewhere (16, 20); see below for brief details. In a smaller sample size than the current study, we previously showed high test-retest reproducibility in the ventilatory and cerebrovascular responses to changes in CO₂ and O₂ at high altitude (3).

The order of each respiratory testing was randomized, and full recovery was permitted between each trial. All testing was completed in the afternoon, and participants were instructed to avoid caffeine, alcohol, and exercise within 12 h prior to the experimental testing.

Cerebrovascular hemodynamics and respiratory variables were measured continuously at 200 Hz using an analog-to-digital converter (Powerlab 16/30 ML880, Powerlab 8/30 ML870, ML240; ADInstruments) interfaced with a computer and were subsequently analyzed using commercially available software (Chart v7, ADInstruments).

**Modified hyperoxic rebreathing method.** Participants wore a nose clip and breathed through a mouthpiece connected to a Y-valve, which allowed switching from room air to a 6-liter rebreathing bag filled with 7% CO₂ and 93% O₂. Following >2 min of baseline room-air breathing, participants were instructed to hyperventilate for 5 min to lower and then maintain a partial pressure of CO₂ (PETCO₂) at 22 ± 2 mmHg (sea level) and 17 ± 2 mmHg (5,050 m). Participants were then switched to the rebreathing bag following an expiration and instructed to take three deep breaths to ensure rapid equalization of PCO₂ in the rebreathing circuit. The modified rebreathing tests were terminated when either 1) PETCO₂ reached 60 mmHg; 2) partial pressure of end-tidal O₂ (PETO₂) could no longer be maintained above 160 mmHg; 3) VE exceeded 100 l/min, or 4) the participant reached the end of his/her tolerance.

These rebreathing data were analyzed on a breath-by-breath basis using a specially designed program (Full Fit Rebreathing program, Version 3.1, Toronto, Canada). In brief, the initial three-breath equilibration, sighs, swallows, and aberrant breaths were excluded from analysis. Next, the breath-by-breath PETCO₂ values were plotted against time and fitted with a least squares regression line to minimize inter-breath variability (19, 31). Subsequently, VE and MCAv were plotted against the predicted PETCO₂ by the regression analysis.

The VE plot was fitted with a model made up of two segments separated by one breakpoint (19). The first segment was taken to be resting VE. Thereafter, VE increased in conjunction with the predicted PETCO₂. Since hyperoxia (PETO₂ ≥ 150 mmHg) is reported to diminish the peripheral chemoreceptors (15, 24), the observed breakpoint was taken as the ventilatory recruitment threshold of the central chemoreflex, whereas the second segment was assumed to be the ventilatory CO₂ sensitivity attributed to the central chemoreflex alone (19, 31).

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**Fig. 1.** Schematic of the experimental protocol. Following instrumentation of transcranial Doppler ultrasound, ECG, and blood pressure (approximately 15–20 min), an arterial blood gas sample was collected. Following an >10-min period of rest and a 5-min resting baseline, measurements of hyperoxic rebreathing (hypocapnic and hypercapnia responsiveness) and isocapnic hypoxic sensitivity were made in a randomized order. Thereafter, participants were setup for full overnight polysomnography (PSG). Cerebral blood flow velocity (CBFv) was measured during the first 2–4 h of sleep.
Linear regression was also applied to the MCAv changes during the modified hyperoxic rebreathing. Unlike the V̇E response, there were no differential breakpoints observed in the MCAv measurements, thus a single line was fitted. Modeling was based on the sum of least squares for nonlinear regression using LabVIEW software (Levenberg-Marquardt algorithm, LabVIEW 7.1, National Instruments).

Isocapnic hypoxia. Participants wore a nose clip and breathed through a mouthpiece connected to a Y-valve allowing switching from room air to a circuit consisting of a 6-liter rebreathing bag and a soda lime reservoir. The protocol began with baseline room-air breathing, before participants were switched to the rebreathing circuit. Participants filled the rebreathing bag with room air drawn in through their nose and expired into the bag. Once the bag was full (ensuring that this was at the end of an expiration) the nose clip was attached and rebreathing began. The isocapnic hypoxia was terminated when either 1) the PetO₂ reached 45 mmHg at sea level and 30 mmHg at 5,050 m; 2) the V̇E exceeded 100 l/min; or 3) the participant reached the end of his/her tolerance. These breath-by-breath V̇E data were plotted against PetO₂, and an inverse first-order polynomial function was used to obtain the hypoxic ventilatory response curve (16).

SLEEP STUDIES. Following the ventilatory response tests, participants were set up for the polysomnogram (Somnet PSG: Melbourne, Australia) by experienced polysomnography technologists, according to standard format (12, 13). All studies were scored by the same certified polysomnography technologist, who was blinded as to the nature of the study, using standard definitions (2, 34).

CEREBRAL BLOOD FLOW VELOCITY. Blood flow velocity in the right middle cerebral artery (MCAv) was measured while subjects were awake during the ventilatory response tests and for the first 2–4 h of sleep using a 2-MHz pulsed Doppler ultrasound system (DWL, Compumedics) using search and fixation techniques described elsewhere (1, 40).

BLOOD GASES. Before each ventilatory response test, blood from the radial artery was obtained after 10-min supine rest using a 25-gauge needle into a preheparinized syringe and analyzed using a calibrated arterial blood-gas machine (NPT 7 series, Radiometer, Copenhagen, Denmark).

Data analysis and statistical approach. BASELINE AND CEREBRAL VASCULAR/VENTILATORY RESPONSE DATA. There were complete data sets (n = 12) at sea level for all variables; however, some MCAv and ventilatory response test data at high altitude were incomplete, because either the test failed or the result was more than two standard deviations from the mean. These were uncommon events, however, with only five missing data points from 72 measurements of hypoxic and hypercapnic ventilatory responses and one missing MCAv-CO₂ data point during high-altitude testing.

PSG and cerebral hemodynamic data during sleep. There were complete data sets for all PSG measures. Polysomnogram and cerebral hemodynamic data were synchronized at the time of collection (start of PSG recording marked on chart) and confirmed during analysis with time-of-day matching between the acquisition software. Technical problems during high-altitude testing resulted in three hemodynamic data files being lost during night recording (one at days 2–4 and two at days 12–15). Overall, cerebral hemodynamic data during sleep were obtained from 10 participants at sea level, 9 participants at days 2–4, and 8 at days 12–15 at high altitude, respectively. Waking and stage 2 sleep MCAv data were averaged over more than 3–5 min, and peak and nadir of MCAv oscillations averaged over >20 cycles.

Time course of change for sleep, hemodynamic, and ventilatory measures was examined using linear mixed modeling (SPSS v19, SPSS), which can be employed for unbalanced and mixed (between and within-subjects factors) repeated measures design (14). Changes in the profile of MCAv oscillations at the two high-altitude time points were analyzed by paired t-test. Finally, the relationship between dependent variables of interest and the development of CSA was tested using linear regression.

RESULTS

Sleep Architecture

Total sleep time was on average longer at high altitude than sea level (370 vs. 390 and 403 min; Table 1). There was an increase in the proportion of time spent in the lighter sleep stages (NREM stages 1 and 2) at high altitude, whereas the proportion of total sleep time spent in slow wave sleep (SWS; stages 3 and 4) was reduced at high altitude but rapid eye movement sleep (REM) was preserved (Table 1). The total duration of exposure to 5,050 m was 15 days. The mean initial apnea-hypopnea index (AHI) increased from 76.9 ± 48.9 on days 2–4 to 115.9 ± 21.2 on days 12–15 (P = 0.01; Fig. 2). The arousal index was not significantly different (27.1 ± 14.1 vs. 32 ± 12.5; Table 2).

Awake MCAv, Cerebrovascular Reactivity, Arterial Blood Gases, and Chemoreflexes

Upon initial arrival to high altitude, MCAv was elevated (up 31 ± 31%, P < 0.01) compared with sea level, but had re-

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Table 1. Sleep architecture at sea level and across the initial 2 wk after ascent to high altitude (5,050 m)

<table>
<thead>
<tr>
<th></th>
<th>Total Sleep Time, min</th>
<th>Stage 1 NREM %</th>
<th>Stage 2 NREM %</th>
<th>SWS %</th>
<th>REM Sleep %</th>
<th>Sleep Efficiency %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sea level</td>
<td>370 ± 73</td>
<td>3 ± 1</td>
<td>57 ± 10</td>
<td>26 ± 6</td>
<td>15 ± 7</td>
<td>81 ± 8</td>
</tr>
<tr>
<td>High altitude</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 2–4 days</td>
<td>390 ± 53</td>
<td>5 ± 3</td>
<td>62 ± 7</td>
<td>17 ± 5</td>
<td>16 ± 8</td>
<td>73 ± 8</td>
</tr>
<tr>
<td>At 12–15 days</td>
<td>403 ± 53</td>
<td>3 ± 1</td>
<td>61 ± 6</td>
<td>18 ± 5</td>
<td>18 ± 6</td>
<td>79 ± 9</td>
</tr>
</tbody>
</table>

Values are mean ± SD (n = 12). NREM, non-rapid eye movement sleep; REM, rapid eye movement sleep. *P < 0.05 compared with sea level.
was elevated (after 2 wk. Likewise, cerebrovascular reactivity to hypocapnia respectively). HCVR (hypocapnia over time at high altitude was related to elevation in level to 3.8 (3.5 of a greater magnitude at altitude, from 1,029 (HVR; described by “Parameter A”) increased after 2 wk at high altitude compared with sea level (P < 0.05 vs. sea level; ‡). There was also a trend toward a significant relationship between worsening CSA and the change in the HCVR from initial arrival to days 12–15 (R² = 0.42; P = 0.057).

DISCUSSION

We have provided a detailed description of the independent effects of altitude and of acclimatization on periodic breathing during sleep. Our novel findings illustrate that elevations in CBF and its reactivity to CO₂ upon initial arrival to high altitude appear to modulate the severity of periodic breathing during sleep. As CBF returned toward normal sea level values over time, this effect wore off and CSA severity increased. This was most likely mediated initially by reduced stimulation of central chemoreceptors by P₉₉₂. Later, ventilatory responses increased, while simultaneous removal of central P₉₂ became less. As a result, periodic breathing during sleep was less on initial arrival compared with that after 12–14 days at the same altitude. We acknowledge that our results do not prove a protective effect of increased cerebral blood flow on CSA; however, the following discussion outlines the evidence and methodological considerations supporting these conclusions.

Sleep at High Altitude

While the occurrence of periodic breathing at high altitude, along with changes in sleep architecture and arterial oxygen saturation have been described (10, 12, 37), considerations of mechanisms and their relative contributions that may underlie the development of this nocturnal breathing pattern have not been reported. At a lower altitude (3,840 m) to the present study, following 9 days deacclimatization from higher altitudes, we previously concluded that impaired CBF responsiveness contributes to CSA (4). However, in that study, we believe that the descent from the higher altitude (5,400 m) may have reduced CBF reactivity initially, which would have then risen

Table 2. MCAv and arterial blood gases at sea level and across the initial 2 wk after ascent to high altitude (5,050 m)

<table>
<thead>
<tr>
<th>Cerebrovascular (20, 29)</th>
<th>Sea Level</th>
<th>High Days 2–4</th>
<th>Altitude Days 12–15</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCAv, cm/s</td>
<td>68 ± 11</td>
<td>87 ± 17†</td>
<td>69 ± 10‡</td>
</tr>
<tr>
<td>Hypercapnia reactivity, cm⁻¹/mmHg</td>
<td>2.0 ± 0.6</td>
<td>3.8 ± 1.5†</td>
<td>2.8 ± 1.5</td>
</tr>
<tr>
<td>Hypocapnia reactivity, cm⁻¹/mmHg</td>
<td>1.9 ± 0.4</td>
<td>4.1 ± 0.9†</td>
<td>3.5 ± 1.1‡</td>
</tr>
<tr>
<td>Arterial blood gases (6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaO₂, mmHg</td>
<td>100 ± 8</td>
<td>43 ± 3†</td>
<td>48 ± 3½</td>
</tr>
<tr>
<td>PaCO₂, mmHg</td>
<td>42 ± 4</td>
<td>29 ± 3†</td>
<td>26 ± 2½</td>
</tr>
<tr>
<td>pH</td>
<td>7.44 ± 0.02</td>
<td>7.47 ± 0.03†</td>
<td>7.44 ± 0.03‡</td>
</tr>
<tr>
<td>BE</td>
<td>4.3 ± 2.9</td>
<td>-1.7 ± 2.9†</td>
<td>-6.1 ± 2.5‡</td>
</tr>
<tr>
<td>Arousal index, events/h</td>
<td>10.7 ± 3.6</td>
<td>27.1 ± 14.1‡</td>
<td>32 ± 12.5</td>
</tr>
<tr>
<td>Central AHI, events/h</td>
<td>0</td>
<td>76.9 ± 48.9‡</td>
<td>115.9 ± 21.2‡</td>
</tr>
<tr>
<td>HCVR, l·min⁻¹·mmHg⁻¹</td>
<td>3.7 ± 2.6</td>
<td>4.7 ± 1.6</td>
<td>8.3 ± 5.7‡</td>
</tr>
<tr>
<td>HVR (Parameter A)</td>
<td>1.286 ± 797</td>
<td>1.029 ± 609</td>
<td>2.046 ± 879‡</td>
</tr>
</tbody>
</table>

Values are mean ± SD (n = 12). All data tested by mixed model analysis (see methods). *P < 0.05 vs. days 2–4 (paired post hoc comparisons by Wilcoxon sign rank test). †P < 0.01 vs. sea level; ‡P < 0.001 vs. days 2–4; MCAv, mean cerebral blood flow velocity; BE, calculated base excess; HCVR, hypercapnic ventilatory response; HVR, hypoxic ventilatory response.
back toward baseline (i.e., the opposite to the observations of the present study examining the effect of ascent to higher altitude). Therefore, the lowered reactivity we previously observed (4) may represent changes that occur during descent and that relate to potentially decreasing severity of CSA at altitude, which is supported by the lower AHI we observed in that study compared with the current after similar time spent at altitude (i.e., ~2 wk; 21 ± 23 vs. 116 ± 21 events/h).

Bloch et al. (10) have described the nocturnal breathing pattern during acclimatization to 7,546 m; however, PSG sleep variables were not obtained and potential mechanisms related to the development of CSA were not considered, apart from speculation of a possible increase in loop gain. In a more recent study (33), this group investigated the influence of acute exposure to 4,559 m on sleep using PSG during the first and third night at this elevation. They reported that AHI was increased to 59 events/h on the first night and that this altitude-induced hypoxemia was associated with a reduction in total sleep time, slow-wave sleep, and REM sleep and an increased number of arousals. Three days of acclimatization resulted in partial improvements of oxygen saturation and of alterations in sleep architecture despite a further increase in AHI (to 91/h). Thus, these findings indicate that periodic breathing was not the predominant cause of sleep disturbances at altitude. The findings of our study contrast somewhat from their initial observations regarding changes in sleep architecture with acute exposure to high altitude (Table 1). However, because of our slow ascent profile, higher elevation and first PSG collection occurring during days 2–4, it is perhaps not surprising that we observe differences between sleep patterns from those induced by an immediate exposure to 4,559 m.

How May CBFV Reactivity Affect the CSA Severity Following Partial Acclimation?

The supportive evidence of a putative role of CBF and reactivity on breathing stability is now clear. First, pharmacological blunting of CBF and its reactivity to CO2 leads to elevations in controller gain, reduced CO2 reserve, and subsequent increased susceptibility to apneas and breathing instability during sleep (43). These changes are also evident during wakefulness (22). Moreover, in a parallel study to this, we have illustrated that acute (via intravenous acetazolamide) elevations in CBF velocity and reactivity to PaCO2 are related to improvements in breathing stability at high altitude during wakefulness (23). Thus, CBF and its related reactivity to PaCO2, via its influence on central chemosensitivity, provide an important mechanism in the pathophysiology of CSA. We speculate that these protective effects on CSA during initial exposure to high altitude are via effective buffering of changes in central PaCO2 and hence reductions in controller gain (i.e., chemosensitivity). Moreover, after partial acclimatization, CBF and its reactivity decline, resulting in a further increase in HCVR and universally severe CSA (see individual lines Fig. 2), changes ultimately mediated via elevations in controller gain (6) and reduced CO2 reserve.

Cerebral Blood Flow During Sleep

This is the first study to report on the cerebral hemodynamics during sleep over a period of partial acclimatization at high altitude. In the absence of the wakefulness drive to breathe, marked oscillations in CBF occurred as a consequence of the periodic breathing, similar in nature to that reported in patients with sleep at sea level (25, 28). Consistent with our previous
study (4), we observed a relation between the decline in CBF from awake to NREM sleep, albeit being only a modest predictor of CSA. Interestingly, the relation was stronger at 2 wk when absolute perfusion was lower (both awake and during sleep), thus further supporting the idea that reduced $[H^+]$ washout within the brain enhances chemoreceptor activation (see above). Moreover, given the link between breathing pattern and CBF (39, 44), these oscillations in CBF are likely to be important in the pathophysiology of periodic breathing. Indeed, regardless of the causation of the first apnea, i.e., whether alterations in basal CBF (38), cerebral, or arterial $PCO_2$ (20, 26, 30) (or a combination of these and others factors) start the apnea cycle, the large swings in CBF that ensue seem likely to exacerbate the under- and overshooting of ventilatory drive that characterizes the central sleep apnea disorder (18).

**Interaction Between Central and Peripheral Chemoreceptors**

Animal experiments have been conducted in awake dogs in which both sets of chemoreceptors could be perfused separately with fluids containing different $PCO_2$ levels, during which time chemoreflex testing was conducted (9). Those studies showed a significant interaction between both sites of receptors. Carotid body stimulation or inhibition was shown to raise or lower the central HCVR.

In a decerebrate rat preparation, Day and Wilson (16) reported that central (brain stem) hypocapnia ($PCO_2 = 20$ mmHg, similar to the levels our subjects experienced at $5,050$ m) caused increased sensitivity of the carotid body to changes in both $PO_2$ and $PCO_2$. Although the above experiments were performed in animal models, similar interactions may well have occurred in our subjects. However, the VR testing techniques that we used have captured any changes in HVR and HCVR resulting from such interactions. We acknowledge, however, that with these methods we are unable to provide insight into any chemoreflex interactions and the extent to which these interactions may be influenced by changes in acid-base status.

**Teleological Limits on CSA**

The average duration of AHI in this study was about 22 s (Table 3), consistent with many other reports (10, 33). Therefore, the maximum CSA index (i.e., when cycling is continuous throughout sleep) is, on average, 3,600/22, or about 160/ min. Since the development of CSA is almost exclusive to non-REM sleep (especially during stages 1 and 2 light sleep), the maximum overall CSA index possible is $160/ \times$ non-REM time/total sleep time. Table 1 shows that non-REM occupied, on average, ~80% of sleep time. Thus the maximum overall CSA index would be, on average, 136/h. Naturally this limit would vary depending on individual difference in cycle duration and percent of time in REM sleep. Figure 3 shows the progression of AHI to this maximal limit within 10–12 days acclimatization to $5,050$ m. After this point, the AHI cycling is continuous and has therefore reached the maximal theoretical value. These calculations are important as they indicate that the development of AHI becomes independent of key factors affecting its stability (e.g., controller gain, apneic threshold, and cerebrovascular influences).

Figure 2 demonstrates a good deal of scatter in the AHI values of the subjects at days 2–4, presumably due in large part to variability in intrinsic ventilatory responsiveness and CBF reactivity. With partial acclimatization all subjects approached the maximum CSA index discussed above, so the scatter became much less.

**Role of Arousal from Sleep**

Arousal from sleep is a very common feature of CSA, typically occurring during the hyperpnic phase of the cyclic breathing. It has been felt that the hyperpnea of CSA caused arousal and that the arousal was crucial in perpetuating the instability of breathing that typifies CSA (46). In earlier studies at similar altitudes the arousal index has tracked fairly closely the increase in AHI with increasing altitude (25) at least up to 3,840 m; thereafter it appears to have plateaued around 30/min. An exception being the Anholm et al. (7) paper, in which arousals at a comparable simulated altitude were 86/h. However, their subjects wore face masks during sleep, which likely caused increased arousals. Although there are some data from United Kingdom groups suggesting benzodiazepines can reduce CSA by reducing arousals (32), these current data suggest that this role has been overemphasized (see Table 2). One is drawn to conclude that the cyclical changes in CBF may be more important than repeated arousal from sleep in perpetuating CSA at high altitude because of the plateauing of arousals. It should also be noted that arousals without a clear temporal relationship to periodic breathing cycles during sleep have also been reported (7, 22, 27). From this and earlier papers, it now seems likely that periodic breathing does not always cause arousal. Conversely, just as is the case at sea level, there are many other causes of arousal, which often cannot be identified by PSG.

**Methodological Considerations**

A limitation of this study is that the measured acclimatization was limited to ~10 days. However, our data are consistent with recent data from others (10, 37) and expands on a recent comparison of PSG monitored sleep during the first and third night of acute exposure to 4,559 m (33). Moreover, as discussed above, even after 10 days our data indicate that CSA was close to the maximal limit (assuming only minor change in cycle length). These limits are completely consistent with these findings from Bloch and coworkers (10) at comparable altitudes (5,300 m; AHI = 114 events/h, range 81–130) measured within 2–3 days of arrival and at higher elevations (6,850 m, AHI = 132 events/h, range 103–157). Collectively, our findings reveal that irrespective of altitude or time spent at altitude, it seems likely that CSA reaches a maximal capacity within 1 wk of being >4,000 m.

The use of CBF velocity as an index of absolute CBF should be done cautiously. For example, transcranial Doppler ultrasound (TCD) assumes constant diameter of the isolated intracranial arteries to estimate changes in flow; recent data indicate that acute (<3 h) changes in hypoxia ($SaO_2 <80\%$) may result in dilation of the MCA and hence a misrepresentation of flow at these levels (41, 42). However, in the context and support of the current study it was also reported that the diameter of the MCA was unchanged <5,300 m at high altitude(42). Nevertheless the usefulness of TCD in measuring changes associated with stimulus response protocols (reactivity testing or changes during sleep), as well as regional differences by analyzing delta baseline changes in both absolute and
relative terms, makes it a powerful cerebral imaging tool (especially for field and sleep-based research) with high temporal and spatial resolution (5).

These results may be unique to these subjects under the specific conditions described. They may not be able to be generalized to other situations at high altitude because of the asperent profile and the prior use of acetazolamide and in some cases dexamethasone, although the asperent profile is one that is commonly used and the expected effect of prior use of oral acetazolamide is only to advance acclimatization (8) and limit AMS. We are unaware of any effects from the brief treatment with dexamethasone on ventilatory control or CBF.

We acknowledge that our findings do not establish causation between the potentially protective influences of CBF regulation in CSA at high altitude. Nevertheless, these findings are consistent with the critical role of cerebrovascular function in mediating changes in central PCO2, controller gain, and therefore breathing stability during both wakefulness and sleep at sea level. We feel our findings are fully consistent with these reports and underscore the importance of cerebrovascular function as an important mechanism in the pathophysiology of CSA at high altitude.

Conclusions

Our novel findings indicate that elevations in CBF and its reactivity to CO2 upon initial ascent to high altitude provide a protective effect on the development of periodic breathing during sleep (likely via moderating changes in central PCO2). Because the arousals index did not increase in parallel with the increase in AHI, we feel our findings are fully consistent with these reports and underscore the importance of cerebrovascular function as an important mechanism in the pathophysiology of CSA at high altitude.

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Disclosures

No conflicts of interest, financial or otherwise, are declared by the authors. Intravenous acetazolamide use was off label.

Author Contributions


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