Altersations in cerebral dynamics at high altitude following partial acclimatization in humans: wakefulness and sleep

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Ainslie PN, Burgess K, Subedi P, Burgess KR. Altersations in cerebral dynamics at high altitude following partial acclimatization in humans: wakefulness and sleep. J Appl Physiol 102: 658–664, 2007. Firstpublished October 19, 2006; doi:10.1152/japplphysiol.00911.2006.—We tested the hypothesis that, following exposure to high altitude, cerebrovascular reactivity to CO2 and cerebral autoregulation would be attenuated. Such alterations may predispose to central sleep apnea at high altitude by promoting changes in brain PCO2 and thus breathing stability. We measured middle cerebral artery blood flow velocity (MCAv; transcranial Doppler ultrasound) and arterial blood pressure during wakefulness and polysomnographic-monitored sleep, dynamics cerebral autoregulation and MCAv during steady-state changes in MCAv in relation to changes in blood pressure were evaluated using transfer function analysis. High altitude was associated with an increase in central sleep apnea index (0.2 ± 0.4 to 20.7 ± 23.2 per hour) and an increase in mean blood pressure and cerebrovascular resistance during wakefulness and sleep. MCAv was unchanged during wakefulness, whereas there was a greater decrease during sleep at high altitude compared with low altitude (–9.1 ± 1.7 vs. –4.8 ± 0.7 cm/s; P < 0.05). At high altitude, compared with low altitude, the cerebrovascular reactivity to CO2 in the hypocapnic range was unchanged (5.5 ± 0.7 vs. 5.3 ± 0.7%/mmHg; P = 0.06), while it was lowered in the hypocapnic range (3.1 ± 0.7 vs. 1.9 ± 0.6%/mmHg; P < 0.05). Dynamic cerebral autoregulation was further reduced during sleep (P < 0.05 vs. low altitude). Lowered cerebrovascular reactivity to CO2 and reduction in both dynamic cerebral autoregulation and MCAv during sleep at high altitude may be factors in the pathogenesis of breathing instability.

autoregulation; polysomnography; sleep-disordered breathing

THE PATHOGENESIS OF CENTRAL sleep apnea, also referred to as Cheyne-Stokes respiration, at high altitude remains incompletely understood. Central sleep apnea is an abnormal periodic breathing pattern in which central apneas and hypopneas alternate with periods of hyperventilation that have a waxing-waning pattern of tidal volume that classically has been associated with severe decompensated heart failure (6). A leading hypothesis relates central sleep apnea to be caused by a sleep-related apnea threshold triggered by hypocapnia (11). Although they have not been investigated extensively, especially following ascent to high altitude where central sleep apnea commonly develops in otherwise healthy humans, breathing pattern and brain blood flow are closely linked by partial pressure of arterial CO2 (Paco2) (35, 39). The effects of CO2 on cerebral blood flow (CBF) provide an important counterregulatory mechanism, which serves to minimize changes in brain [H+](where brackets denote concentration), thereby stabilizing the breathing pattern in face of perturbations in Paco2 (39). For example, hypocapnia normally causes marked cerebral vasoconstriction and reduces CBF, which attenuates the fall in brain Pco2 relative to that of the arterial blood (11). Accordingly, ventilatory inhibition in response to reduced Paco2 will be lessened because of the attenuated decrease in central chemoreceptor [H+]. A reduction in CO2 vascular reactivity of the brain during wakefulness has been identified in patients with congestive heart failure and central sleep apnea; this reduction may affect stability of the breathing pattern (39). Changes in CBF may, therefore, play an important role in etiology of central sleep apnea at high altitude.

CBF is typically reduced during stable non-rapid eye movement sleep (14, 20, 22, 36). This reduction is believed to be mainly linked to a decrease in the metabolic demand of brain tissue in non-rapid eye movement sleep (22). It is not known if CBF regulation is impaired during non-rapid eye movement sleep at high altitude, but such impairment could hypothetically promote breathing instability. Recent studies have indicated that cerebral autoregulation is impaired during wakefulness in newcomers at high altitude (17) and is associated with the pathogenesis of acute mountain sickness (38). Normally, cerebral autoregulation maintains CBF over a wide range of systemic blood pressures (30), thereby protecting the brain against the dangers of hypoxia at low perfusion pressures and against the risk of brain edema at high arterial pressures. Such impairment in autoregulation may predispose to central sleep apnea at high altitude by allowing CBF to oscillate with arterial blood pressure, thereby promoting changes in central chemoreceptor stimulation and thus the apneic threshold. To the best of the authors’ knowledge, there are no available data concerning the combined alterations in CBF reactivity and autoregulation during wakefulness and sleep at high altitude. Accordingly, the main objective of this project was to test the hypotheses that CBF reactivity is reduced during wakefulness following partial acclimatization to high altitude. Given that alterations in autoregulation are important in maintaining CBF over a wide range of systemic blood pressures, a reduction during sleep may promote, in part, breathing instability and thus central sleep apnea. Thus the second objective of the
project was to test the hypothesis that CBF autoregulation would be lowered during sleep at high altitude.

MATERIALS AND METHODS

Subjects

Five healthy subjects [32 ± 12 (SD) yr; 3 men; body mass index 23 ± 2 kg/m²] participated in this study. All subjects were given both verbal and written instructions outlining the experimental procedure, and written, informed consent was obtained. Participants were not taking any medication, all were nonsmokers, and none had any history of cardiovascular, cerebrovascular, or respiratory disease. The research study was approved by the Conjoint Health Research Ethics Board at the University of Calgary, the Human Research Ethics Committee of Northern Sydney Health, and the Nepalese Research Council.

Experimental Design

Subjects were instructed to refrain from exercise and alcohol for 12 h before the investigation and to refrain from caffeine 4 h before experimental testing. Studies were carried out in Kathmandu (1,400 m) and in Khunde (3,840 m) following a 9-day ascent to altitudes >5,000 m. Following a 10-min rest, blood flow velocity in the middle cerebral artery (MCAv) and arterial blood pressure were collected continuously at rest for 15 min during the day (wakefulness). Data were collected in the afternoon (1:00–4:00 PM) on all occasions. In a randomized order at both sea level and at high altitude, the measurements were then collected again for 60–120 min during simultaneous polysomnographic monitored sleep. Arterial blood gases and neurological symptoms typically associated with acute mountain sickness were also collected. These measurements are described below.

Measurements of MCAv and arterial blood pressure. MCAv was estimated by the continuous measurement of backscattered Doppler signals from the right middle cerebral artery using a 2-MHz pulsed Doppler ultrasound system (Power M-Mode Doppler 100, Spencer Technologies). Following previously described search techniques (2, 3), the Doppler probe was secured with a headband device (Spencer Technologies, Nicolet Instruments, Madison, WI) to maintain optimal insonation position and angle throughout the protocol. Arterial blood pressure and heart rate were measured continuously using finger photoplethysmography (Portapress, TPD Biomedical Instrumentation). Great care was taken to ensure that identical settings of Doppler and photoplethysmography (Portapress, TPD Biomedical Instrumentation). Great care was taken to ensure that identical settings of Doppler ultrasound system were used each time. This procedure was made very reproducible due to the combination of M-mode and Doppler spectral analysis techniques (26). Cerebrovascular resistance was calculated from mean arterial blood pressure/MCAv. The blood pressure and the transcranial Doppler waveforms were sampled continuously at 200 Hz using an analog-to-digital converter (Powerlab/16SP ML795; ADInstruments, Colorado Springs, CO) and stored on a personal computer for off-line computations.

CO₂ reactivity testing. All experiments were conducted in the awake sitting position and at similar times of the day in an attempt to standardize the effect of the diurnal variability of cerebral vasomotor reactivity. Subjects wore eyeshades and headphones playing relaxing music of their choice to minimize distraction during the ventilatory response testing. Subjects were instructed to hyperventilate slowly down to an end-tidal PCO₂ (PetCO₂) of ~17 Torr for 5 min. They then rebreathed a mixture of 7% CO₂ in 93% oxygen from an 8-liter reservoir. Ventilation was measured by a turbine system, and PetCO₂ was measured by a portable high-speed infrared CO₂ analyzer (Jaeger Oxycon mobile system). Two runs of both the hyper-hypocapnic tests were completed upon each occasion, and the results were averaged. Each run was separated by at least 10 min of room air breathing to allow the circulatory and ventilatory variables to return to baseline levels. The slope of MCAv/PetCO₂ was determined by the least squares linear regression analysis for each subject in the hyper- and hypocapnic range, as well as for each group (low altitude vs. high altitude). The relationship between MCAv/PetCO₂ was only considered acceptable when linearity ($r > 0.7$) was demonstrated.

Blood gases. Arterial blood gases from the radial artery were obtained at rest using a 25-gauge needle into a preheparinized syringe with the subject in the seated position after 10 min of rest. Following standardized calibration, all blood samples were analyzed using a battery powered arterial blood-gas analyzing system (i-STAT system; i-STAT, East Windsor, NJ).

Sleep studies. All sleep studies were carried out with a Compumedics portable system (PS2; Melbourne, Australia). The portable sleep system allowed the collection of 13 channels of data, very similar in scope to that available in the sleep laboratory: one channel of ECG, two channels of EEG, two channels of electrooculogram, one channel of submental electromyogram, one channel of leg movement, one channel of body position, two channels of respiratory displacement (thoracic and abdominal displacement by inductance plethysmography), one channel of snoring, one channel of nasal flow signal via nasal cannula, and one channel of saturation by digital pulse oximetry (saturation accuracy ±2% between 70 and 100% with finger probe). The subjects were set up for the polysomnogram by experienced polysomnography technologists, according to standard format, as described in depth elsewhere (8, 9). All studies were scored by the same certified polysomnography technologist, who was blinded as to the nature of the study, using standard definitions (5, 31). In brief, apneas were defined as the absence of airflow of at least 10-s duration associated with either a ≥4% desaturation or an arousal. Hypopneas were defined as a reduction in airflow to <50% baseline, lasting at least 10 s and associated with either a ≥4% desaturation or an arousal. Central apneas were defined as an apnea with a corresponding absence of effort evident in the effort bands. A central hypopnea was defined as an hypopnea, where there was a simultaneous and parallel reduction in effort evident in the effort bands. Obstructive apneas and hypopneas were defined as apneas or hypopneas where there was a persisting or increased effort evident in the effort bands (7).

Acute mountain sickness. Neurological symptoms typically ascribed at high altitude were examined using the Lake Louise Questionnaire (33). Acute mountain sickness was defined if a subject presented with a total Lake Louise score (self assessment + clinical scores) of ≥4 points.

Transfer function analysis. The beat-to-beat mean arterial blood pressure and MCAv were obtained by integrating analog signals within each cardiac cycle, linearly interpolated and resampled at 2 Hz for spectral analysis (41). For transfer function analysis, the cross-spectrum between the change in mean arterial blood pressure and MCAv was estimated and then divided by the autospectrum of mean arterial blood pressure. During wakefulness and sleep, transfer gain and phase were calculated. Additionally, the coherence function was calculated to estimate the fraction of output (MCAv) that can be linearly related to input power (mean arterial blood pressure) at each frequency. This coherence function, like a correlation coefficient, varies between 0 and 1. For these calculations, 3 min of steady-state mean arterial blood pressure and MCAv were used during wakefulness during the day, wakefulness immediately before sleep, and during non-rapid eye movement (stage 2) sleep. During stage 2 sleep, data were visually inspected to ensure that sampling was not made during apneic events. Such apneic events (cessation of breathing >10 s) caused surges in both the mean arterial blood pressure and MCAv. A minimum of four periods of 3 min of steady-state mean arterial blood pressure and MCAv were collected during non-rapid eye movement sleep (stage 2) from each individual, and these periods were subsequently averaged. Blood pressure fluctuations in the low-frequency range (0.07–0.02 Hz) are independent of the respiratory frequency and are known to reflect cerebral autoregulatory mechanisms (12, 28, 41). Thus we used the low-frequency spectral power of the mean value of transfer gain, phase, and coherence function to identify dynamic cerebral autoregulation during wakefulness and sleep. Cere-
bral autoregulation decreases the transmission effect of pressure on flow; therefore, an increased transfer function gain or decreased transfer function phase between pressure and flow can be interpreted as an increased effect of transmission, which suggests that dynamic cerebral autoregulation is impaired.

Statistical Analysis

All data were analyzed using the SPSS social statistics package (version 9, Surrey, UK). A Shapiro-Wilks test was applied to each dependent variable to mathematically assess distribution normality. Parametric and nonparametric equivalents of a two-factor trial (low altitude vs. high altitude and exposure time: wakefulness vs. sleep, repeated-measures ANOVA) and two-way mixed ANOVA with one between- (state: low altitude vs. high altitude) and one within-factor (exposure time) were incorporated to examine the effects of trial, time, and state on selected variables. Relationships between selected variables were identified using Pearson product-moment correlation or Spearman’s rank correlation coefficient. Significance for all two-tailed tests was established at an α-level of P < 0.05, and data are expressed as means ± SD.

RESULTS

Subjects

All of the five subjects completed all of the experimental testing during wakefulness and sleep at high altitude following the 9-day ascent to altitudes >5,000 m. Due to technological problems, sleep data were not obtained on one subject in Kathmandu. To account for this missing data, a sleep study conducted at 1,200 m under identical experimental procedures using the same equipment was subsequently included in the analysis. This study was conducted 6 mo following the descent from altitude to ensure that there were no carry-over effects from the altitude acclimatization. All subjects were free from symptoms of acute mountain sickness during each experimental testing time, as indicted by a Lake Louise Questionnaire score of <2 points.

Changes in Wakefulness Variables

As shown in Table 1, the expected changes in arterial blood gases were evident, i.e., respiratory alkalosis with concomitant hypocapnia. At high altitude, there was an elevation in both heart rate and mean arterial blood pressure (P < 0.05 vs. low altitude; Table 1). While MCAv was unchanged at high altitude, there was an increase in cerebral vascular resistance (P < 0.05; Table 1). At high altitude during wakefulness, compared with low altitude, the cerebrovascular reactivity to CO2 in the hypercapnic range was unchanged (Fig. 1A), while it was lowered in the hypocapnic range (P < 0.05; Fig. 1B).

Changes in Sleep-Related Variables

The relevant summary results from the sleep studies are shown in Table 1. At both altitudes, compared with the baseline period immediately before sleep, there was a decrease in mean arterial blood pressure and MCAv. At high altitude, however, MCAv decreased more during non-rapid eye movement sleep compared with low altitude (P < 0.05; Fig. 2A), while the decrease in mean arterial blood pressure was comparable between low altitude and high altitude (Fig. 2B). During sleep at high altitude, there was an increase in transfer function gain and a decreased transfer function phase (Fig. 2, C and D), indicating impairment in dynamic cerebral autoregulation. A further indication of impairment in cerebral autoregulation at high altitude was highlighted in a strong correlation between the decrease in MCAv and mean arterial blood pressure from wakefulness to sleep (r = 0.82; P < 0.05). Such relationships were not evident from wakefulness to sleep at low altitude (r = 0.21; P > 0.05). Finally, at high altitude only, the severity of the central sleep apnea index was correlated with the decrease in MCAv from wakefulness to sleep (r = 0.84; P < 0.05; Fig. 3).

DISCUSSION

The major novel findings of this study are that 1) hypocapnic CO2 vascular reactivity of the brain is reduced during wakefulness at high altitude relative to low altitude; 2) cerebral autoregulation was impaired during non-rapid eye movement sleep at high altitude; and 3) at high altitude, mean arterial blood pressure was elevated during wakefulness and sleep, while MCAv was unchanged during wakefulness. During sleep, however, a greater decrease in MCAv was observed at high altitude compared with low altitude (despite similar decreases in mean arterial blood pressure during sleep at both altitudes). Collectively, the lowered cerebrovascular reactivity to CO2, and the reduced dynamic cerebral autoregulation and MCAv during sleep (which was correlated to the severity of central sleep apnea) at high altitude may further promote the pathogenesis of breathing instability.

Influence of Altitude on Wakefulness Responses

As shown in the present study, following a 9-day ascent to high altitude, there was a significant elevation in mean arterial blood pressure during both wakefulness and sleep. Previous studies have also documented that sojourns at high altitude are

Table 1. Alterations in arterial blood gases and cardiovascular and cerebrovascular function following ascent to high altitude during wakefulness

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Low Altitude (1,400 m)</th>
<th>High Altitude (3,840 m)</th>
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<tbody>
<tr>
<td>Arterial blood gases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.425 ±0.042</td>
<td>7.449 ±0.009</td>
</tr>
<tr>
<td>PaCO2, Torr</td>
<td>35.9 ±2.4</td>
<td>23.7 ±4.6*</td>
</tr>
<tr>
<td>PaO2, Torr</td>
<td>74.4 ±3.4</td>
<td>54.4 ±3.1*</td>
</tr>
<tr>
<td>HCO3-, mmol/l</td>
<td>23.4 ±1.8</td>
<td>19.0 ±0.9*</td>
</tr>
<tr>
<td>SaO2, %</td>
<td>95.4 ±0.9</td>
<td>90.2 ±1.8*</td>
</tr>
<tr>
<td>Cardiovascular function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>59.2 ±9.6</td>
<td>65.0 ±10.3*</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>81.8 ±5.7</td>
<td>88.3 ±6.4*</td>
</tr>
<tr>
<td>Cerebrovascular function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCAv, cm/s</td>
<td>53.7 ±4.6</td>
<td>52.6 ±6.0</td>
</tr>
<tr>
<td>CVR, mmHg·cm⁻¹·s</td>
<td>1.53 ±0.12</td>
<td>1.69 ±0.15*</td>
</tr>
<tr>
<td>Hypercapnic cerebrovascular reactivity to CO2, %/mmHg</td>
<td>5.46 ±0.69</td>
<td>5.25 ±0.65</td>
</tr>
<tr>
<td>Hypocapnic cerebrovascular reactivity to CO2, %/mmHg</td>
<td>3.06 ±0.72</td>
<td>1.92 ±0.62*</td>
</tr>
<tr>
<td>LF phase, rad</td>
<td>0.52 ±0.04</td>
<td>0.50 ±0.03</td>
</tr>
<tr>
<td>LF gain, cm·s⁻¹·mmHg⁻¹</td>
<td>0.81 ±0.06</td>
<td>0.90 ±0.08*</td>
</tr>
<tr>
<td>LF coherence, units</td>
<td>0.76 ±0.07</td>
<td>0.73 ±0.08</td>
</tr>
</tbody>
</table>

Values are means ± SD. PaCO2, arterial PCO2; PaO2, arterial PO2; HCO3-, bicarbonate; SaO2, arterial O2 saturation; HR, heart rate; MAP, mean arterial blood pressure; MCAv, middle cerebral artery blood flow velocity; CVR, cerebral vascular resistance; LF, low frequency. *P<0.05; difference compared with low altitude.
accompanied by increases in mean arterial blood pressure (10, 15, 18) that are possibly mediated by augmented sympathetic activity. The effect of an augmented sympathetic activity on the human cerebral circulation is less clear. Work in experimental animals (23) and recent findings in humans indicate that the importance of sympathetically mediated vasoconstriction in the cerebral circulation may be to protect the blood-brain barrier when limits of autoregulation are exceeded (3, 21, 28, 42).

Influence of High Altitude on Sleep

The development of central sleep apnea at high altitude has been well described. The putative mechanism for this effect has been suggested to be a sleep-related apneic threshold triggered by hypocapnia and increased gain of the ventilatory response (11, 35). Typically, however, the effects of CO₂ on CBF provide an important counterregulatory mechanism, which serves to minimize changes in brain [H⁺], thereby stabilizing the breathing pattern (11). In the present study, if the changes in MCAv reflect the changes in the posterior circulation supplying the medulla, then the lowered MCAv and impairment in cerebral autoregulation during sleep at high altitude may cause changes in central chemoreceptor stimulation and thus the apneic threshold, which potentially could promote the observed breathing instability at high altitude. In support of this notion was the correlation between the severity of central sleep apnea and the change in MCAv. In other words, at high altitude, those with the largest decrease in MCAv had the highest number of central events per hour (Fig. 3), suggesting a link between central chemoreceptor stimulation and CBF. The impairment in the dynamic cerebral autoregulatory mechanisms was also reflected in the strong negative relationship between the decreases in mean arterial blood pressure and MCAv during sleep at high altitude. Normally, effective cerebral autoregulation acts to hold CBF constant when blood pressure varies over a wide range (60–150 mmHg) and, hence, acts to reduce any correlation between these quantities (30). Pragmatically, impairment in normal cerebral autoregulatory mechanisms may make the brain more susceptible to the dangers of hypoxia at low perfusion pressures and to the risk of brain edema at high arterial pressures.

Fig. 1. Individual middle cerebral artery blood flow velocity (MCAv) responses to CO₂ during wakefulness at both low and high altitude. Separate slopes are shown for hypercapnic (A) and hypocapnic (B) MCAv responses to CO₂. Each point represents the averaged data for each participant from two trials. *P < 0.05: difference compared with high altitude.

Fig. 2. Awake-sleep (stage 2) changes in MCAv (A), mean arterial blood pressure (MAP; B), and low-frequency (LF) gain (C), phase (D), and coherence (E) at low and high altitude. A minimal of four periods of 3 min of steady-state MAP and MCAv were collected and averaged during non-rapid eye movement sleep (stage 2). *P < 0.05: difference compared with high altitude.
Alterations in Cerebral CO₂ Reactivity

In healthy subjects, hypercapnia leads to vasodilatation of cerebral arterioles in the downstream bed and a subsequent increase in CBF, whereas hypocapnia leads to vasoconstriction and a subsequent decrease in CBF. The reduction in cerebrovascular reactivity to hypercapnia at high altitude is consistent with the findings in patients with central sleep apnea who also have a diminished cerebrovascular response to CO₂, especially to hypocapnia (39). The mechanism(s) by which central sleep apnea and/or prolonged exposure to hypoxia may compromise cerebrovascular reactivity to CO₂ remains to be established. Regardless of the underlying mechanisms, previous research has shown that there is a fall of ~70% in cerebrovascular reactivity to CO₂ during stage 3-4 non-rapid eye movement sleep in otherwise healthy individuals at sea level (24). If the reported reduction in wakefulness cerebrovascular CO₂ reactivity can be extrapolated to a differential sleep-related CO₂ reactivity at high altitude, this could conceivably affect stability of the breathing pattern by causing ventilatory overshooting during hypercapnia and undershooting during hypocapnia (39). Importantly, recent reports in animals (27) and humans (40) indicate that peripheral chemosensitivity may be of importance in the initiation of central sleep apnea. For example, hypoxia may enhance central sleep apnea through a combination of its stimulating effect on the peripheral chemoreceptor and its suppressive effect on central respiratory drive (40). Since there are major changes in ventilatory control following ascent to high altitude (i.e., an increase in the ventilatory response to hypoxia and a leftward shift in the ventilatory response to CO₂), the relative contribution of peripheral-central chemosensitivity in the initiation of central sleep apnea following acclimatization to high altitude remains unknown.

Potential Limitations

First, we used Doppler ultrasound to measure flow velocity, rather than blood flow, in the middle cerebral artery. Nevertheless, the majority of research suggests that MCAv is a reliable index of CBF (13, 19, 34, 37). Second, we used photoplethysmography to measure arterial pressure at rest and during sleep. Although photoplethysmographic measurements correlate well with intra-arterial measurements during experimental manipulations of arterial pressure (29), the absolute values can sometimes be inaccurate. Nevertheless, our reported change in arterial blood pressure following ascent to high altitude is comparable to previous studies (10, 15, 18), and we used both the absolute and relative change in mean arterial blood pressure as the dependent measure during sleep. Third, we acknowledge that our small sample size may inflate the magnitude of the correlations, and our findings warrant further confirmation with a larger sample size. Finally, due to subject comfort, we only studied the first 1–2 h of sleep each night. Although this period allowed a relatively stable period of stage 2 sleep to make our measurements, it is known that CBF decreases during non-rapid eye movement sleep throughout the night and is at its lowest level in the early morning (14). It is unfortunate that our findings were not extended throughout the full sleep cycle. Since previous work has shown a major reduction in cerebrovascular reactivity to CO₂ during stage 3-4 non-rapid eye movement sleep (24), such information may have provided further insight into the evolution of cerebral hemodynamics and breathing instability throughout the full sleep cycle. Since relative hypercapnia is known to impair normal cerebral autoregulation under wakefulness conditions (1, 4, 38), it is unfortunate that we were not able to monitor PetCO₂ during sleep. Hypoventilation during sleep typically results in an elevation of PaCO₂ of ~3–8 Torr. Whether modest increases in PaCO₂ during sleep also impair normal cerebral autoregulation is unknown; however, the unchanged cerebral autoregulation during sleep at low altitude provides preliminary evidence that sleep-related hypercapnia has little effect on cerebral autoregulation.

Implications

If the changes in MCAv reflect the changes in the posterior circulation supplying the medulla, then the changes in CBF during sleep onsets may cause changes in central chemoreceptor stimulation. Alterations in central chemoreceptor stimulation, with a potential modulation from peripheral chemoreceptors (40), may promote the observed breathing instability at high altitude. Such alterations in central chemoreceptor could potentially be mediated by impairment in dynamic cerebral autoregulation, i.e., nonconstant brain.
blood flow. Similarly, impairment in cerebral autoregulation, in addition to reduction in CO₂ reactivity of the brain (24, 39), may be an additional important mechanism that may promote central sleep apnea in patients with congestive heart failure. The apparent greater decrease in MCAv at high altitude during sleep may further place the brain at risk of hypoxic damage. We speculate that lower tissue oxygen delivery to the brain caused by a lower MCAv and lower arterial O₂ saturation during sleep could potentially underlie the well-reported, long-term impairment in neurological function following ascent to high altitude (16, 32).

In conclusion, exposure to high altitude is associated with altered cerebrovascular CO₂ reactivity to hypocapnia and a reduction in MCAv and dynamic cerebral autoregulation during sleep. This observation offers rationale for further studies on the role of abnormal regulation of cerebral hemodynamics during wakefulness and sleep in the adaptation to high altitude.

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