Morning attenuation in cerebrovascular CO₂ reactivity in healthy humans is associated with a lowered cerebral oxygenation and an augmented ventilatory response to CO₂

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Cummings KJ, Swart M, Ainslie PN. Morning attenuation in cerebrovascular CO₂ reactivity in healthy humans is associated with a lowered cerebral oxygenation and an augmented ventilatory response to CO₂. J Appl Physiol 102: 1891–1898, 2007. First published February 22, 2007; doi:10.1152/japplphysiol.01437.2006.—We hypothesized that, in healthy subjects without pharmacological intervention, an overnight reduction in cerebrovascular CO₂ reactivity would be associated with an elevated hypercapnic ventilatory [ventilation (Ve)] responsiveness and a reduction in cerebral oxygenation. In 20 healthy male individuals with no sleep-related disorders, continuous recordings of blood velocity in the middle cerebral artery, arterial blood pressure, Ve, end-tidal gases, and frontal cortical oxygenation using near infrared spectroscopy were monitored during hypercapnia (inspired CO₂, 5%), hypoxia [arterial O₂ saturation (SaO₂) ~84%], and during a 20-s breath hold to investigate the related responses to hypercapnia, hypoxia, and apnea, respectively. Measurements were conducted in the evening (6–8 PM) and in the early morning (6–8 AM). From evening to morning, the cerebrovascular reactivity to hypercapnia was reduced (5.3 ± 0.6 vs. 4.6 ± 1.1%/Torr; P < 0.05) and was associated with a reduced increase in cerebral oxygenation (r = 0.39; P < 0.05) and an elevated morning hypercapnic Ve response (r = 0.54; P < 0.05). While there were no overnight changes in cerebrovascular reactivity or Ve response to hypoxia, there was greater cerebral desaturation for a given SaO₂ in the morning (AM, −0.45 ± 0.14 vs. PM, −0.35 ± 0.14%/SaO₂; P < 0.05). Following the 20-s breath hold, in the morning, there was a smaller surge middle cerebral artery velocity and cerebral oxygenation (P < 0.05 vs. PM). These data indicate that normal diurnal changes in the cerebrovascular response to CO₂ influence the hypercapnic ventilatory response as well as the level of cerebral oxygenation during changes in arterial PCO₂: this may be a contributing factor for diurnal changes in breathing stability and the high incidence of stroke in the morning.

Morning cerebral CO₂ vascular reactivity might directly increase the susceptibility for periodic breathing by increasing the central chemoreceptors’ contribution to loop gain. In support of this hypothesis are recent data indicating that an indomethacin-induced alteration in the cerebrovascular response to CO₂ is sufficient to change the ventilatory response to CO₂ (45). Thus normal diurnal changes in the cerebrovascular response to CO₂ might increase the susceptibility for periodic breathing in the morning, even during wakefulness.

Accordingly, we tested two hypotheses: first, that a morning reduction in cerebrovascular CO₂ reactivity would be reflected in an elevation in the ventilatory response to CO₂; second, due to a morning reduction in cerebrovascular CO₂ reactivity, that the relative level of cerebral oxygenation with elevated inspired CO₂, mild hypoxia, or during a breath hold is reduced in the morning compared with evening. To test these hypotheses, we combined transcranial Doppler to assess middle cerebral artery blood velocity (MCAV) and near infrared spectroscopy (NIRS) for the monitoring of local cerebral oxygenation. Transcranial Doppler provides a direct measure of blood flow velocity, whereas NIRS provides activation-dependent information; therefore, the combination of both NIRS and MCAV provides complementary information for the evaluation of cerebral hemodynamics. Although there are some reports using combined measurements of NIRS and MCAV during vasomotor reactivity tests (4, 40), no studies have examined the overnight changes in the simultaneous assessment of cerebrovascular reactivity using NIRS and transcranial Doppler measurements of MCAV.

MATERIALS AND METHODS

Subjects

Twenty healthy male individuals [aged 25 ± 4 (mean ± SD), body mass index 24 ± 4 kg/m²] volunteered for this study, which was approved by the Lower South Regional Ethics committee and conformed to the standards set by the Declaration of Helsinki. Subjects were informed of the experimental procedures and possible risks involved in the study, and written, informed consent was obtained. Subjects were not taking any medication, all were nonsmokers, and none had any history of cardiovascular, cerebrovascular, or respiratory disease.

Experimental Design

Subjects were instructed to abstain from exercise and alcohol 24 h before and not to eat a heavy meal or consume caffeine 4 h before
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experimental testing. Each subject then visited the laboratory on three occasions. The first visit served to fully familiarize each subject with all of the experimental procedures (between 6 and 8 PM) and to enable a comparison with the main testing session at the same time of day (~2 days apart). During this initial visit, all of the main tests, with the exceptions of the overnight polysomnography sleep study, were performed on each participant. On the second and third visit, experimental testing was carried out in the evening (between 6 and 8 PM) and the following morning (between 6 and 8 AM), respectively. Following the evening tests of the second visit only, subjects underwent an overnight domiciliary sleep study to ensure adequate sleep quality and exclude obstructive sleep apnea or other sleep pathology. Subjects were awakened at 5:30 AM, and morning experiments were conducted 30 min after awakening at ~6 AM. All subjects resided close to the university (within a 10-min drive) and were transported via car the short distance to the laboratory. Following a 30-min period of rest, the combined cardiorespiratory and cerebrovascular responses to hypercapnia, hypoxia, and apnea were determined, as detailed below. Recovery was allowed in between each test to ensure that baseline cardiorespiratory and cerebrovascular responses were obtained (i.e., baseline in the last 5 min of rest before any intervention). All variables were recorded continuously into a computer for off-line analysis.

Measurements of cerebral blood flow velocity, arterial blood pressure, and cortical oxygenation. Cerebral blood flow (CBF) MCAV was measured using a 2-MHz pulsed Doppler ultrasound system (DWL Doppler, Sterling, VA) using search techniques described elsewhere (1). Beat-to-beat arterial blood pressure (BP) was monitored using finger photoplethysmography (Finometer, TPD Biomedical Instrumentation). Although photoplethysmographic measurements correlate well with intra-arterial measurements during experimental manipulations of arterial pressure (26), the absolute values can sometimes be inaccurate; therefore, all BP data are normalized to the 5-min baseline preceding any intervention and expressed as percent change from this baseline. Likewise, as used in other studies, MCAV was also expressed at the percent change from this baseline to enable the same relative comparison to the changes in BP and to reduce interindividual variability that is unrelated to the experimental manipulation (2, 3, 27). Frontal cortical oxyhemoglobin (oxy-Hb) concentrations were monitored noninvasively using NIRS (NIRO-200; Hamamatsu Photonics KK, Hamamatsu, Japan). A probe holder containing an emission probe and detection probe was attached at the right side of forehead with a distance of 5 cm between the probes. The methodology of this system has been described previously (24). NIRO-200 measures the concentration changes of oxy-Hb, deoxyhemoglobin (deoxy-Hb), and total hemoglobin (t-Hb) using a modified Beer-Lambert law (5). It gives an absolute unit (micromoles per liter) for the changes in oxy- and deoxy-Hb by incorporating an optical path length. In the brain, t-Hb, oxy-Hb, and deoxy-Hb were measured simultaneously every 1 s throughout the experiment and expressed as the magnitude of the change from the initial value. Total oxygenation index (TOI% = oxyHb/t-Hb × 100) was calculated by the NIRS system from the light attenuation slope along the distance from the emitting point as detected by the sensors in the receiving optode. All data, including measurements of respiratory gas exchange, were acquired continuously at 200 Hz using an analog-to-digital converter (Powerlab/16SP ML795; ADInstruments, Colorado Springs, CO) interfaced with a computer. Data were sampled at 200 Hz and stored for subsequent analysis using commercially available software (Chart version 5.02, ADInstruments).

Measurements of respiratory gas exchange. Subjects breathed through a leak-free respiratory mask (Hans-Rudolph 8980, Kansas City, MO) attached to a one-way non-rebreathing valve (Hans-Rudolph 2700). Expiratory flow was measured using a heated pneumotach (Hans-Rudolph HR800). Arterial O2 saturation (SaO2) was measured using pulse oximetry at the finger (model ML3200). End-tidal PCO2 (PETCO2) and PO2 (PETO2) were sampled from a leak-free mask and measured by a gas analyzer (model CD-3A, AEI Technologies, Pittsburgh, PA). Ventilatory and gas values (flow, tidal volume, frequency) were displayed in real time during testing (PowerLab, ADInstruments, Colorado Springs, CO). Expiratory volume was calculated using the integrated flow signal and the frequency of breathing.

Hypercapnic challenge. Following an 8-min baseline, 5% CO2 with 21% O2 and a balance of nitrogen were added to the breathing circuit for 3 min. The last minute of the exposure was used for data analysis. The cerebrovascular reactivity to hypercapnia was characterized as the slope of the linear regression fitted to the percent change in MCAV from baseline per Torr increase in PETCO2. Likewise, for the NIRS recordings, hypercapnic reactivity was considered as the relative change from baseline in the values of oxy-Hb, deoxy-Hb, t-Hb, and cerebral TOI per Torr increase in PETCO2. The slope of the ventilatory and mean arterial BP (MAP) response to hypercapnia was characterized in the same way, i.e., the change in ventilation (VE) or MAP per Torr increase in PETCO2.

Poikilocapnic hypoxic challenge. Following an 8-min baseline, hypoxemia (average SaO2 82–86%) was induced with 12% O2 and a balance of nitrogen, added to the breathing circuit for 3 min. This level of inspired O2 was chosen to induce a mild desaturation, in the range of that observed with Cheyne-Stokes breathing in patients with congestive heart failure (6). Exposure to acute poikilocapnic hypoxia was selected to examine the interactive effects of hypocapnia and hypoxia on CBF. The last minute of the exposure was used for data analysis. The hypocapnic cerebrovascular reactivity was characterized as the slope of the linear regression between the percent changes in MCAV from baseline with SaO2. For the NIRS recordings, hypoxic reactivity was considered as the relative change from baseline in the values of oxy-Hb, deoxy-Hb, t-Hb, and cerebral TOI per percent decrease in SaO2. The slope of the ventilatory and MAP response to hypoxia was characterized in the same way, i.e., the change in VE or MAP per percent decrease in SaO2.

Breath hold. Starting at functional residual capacity, subjects refrained from breathing for 20 s, followed by exhaling for the determination of PETCO2. Three to four breath-hold trials were repeated in each individual. The changes in MAP, CBF velocity, and cerebral oxygenation, as well as to the subsequent nadir of SaO2 after the breath hold, were compared with the baseline.

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 for a microphone to record 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 and manually scored according to standard format (29).

Statistical analysis. All data were analyzed using the SPSS social statistics package (Version 9, Surrey, UK). A Shapiro-Wilk’s test was applied to each dependent variable to mathematically assess distribution normality. Statistical comparisons between evening and morning measurement were performed using a Student’s paired sample t-test. Correlational analyses were used to determine the reproducibility of the dependent variables between repeat trials by comparing the two data sets, which were both collected between 6 and 8 PM using correlational analyses. Significance for all two-tailed tests were established at an α-level of P < 0.05, and data are expressed as means ± SD.
RESULTS

Subjects and Sleep-Related Variables

All subjects were observed to have normal sleep architecture, good sleep efficiency (81 ± 5%), did not snore, and had no sleep-disordered breathing. The mean values for steady-state cerebrovascular and cardiorespiratory variables in the evening and morning are shown in Table 1. There were no significant differences in any of the cerebrovascular or cardiorespiratory variables.

Cerebral Reactivity, Oxygenation, and Ventilatory Responsiveness to Hypercapnia

From evening to morning, there was a significant decrease in both hypercapnic cerebrovascular reactivity (PM, 5.1 ± 1.1 vs. AM, 4.6 ± 1.1%/Torr PETCO2; P < 0.05; Fig. 1) and cerebral oxygenation (PM, 1.5 ± 0.7 vs. AM, 1.1 ± 0.5%/Torr PETCO2; P < 0.05; Fig. 1), while the hypercapnic ventilatory response was elevated (PM, 1.24 ± 0.91 vs. AM, 1.59 ± 1.0 l·min⁻¹·Torr⁻¹ PETCO2; P < 0.05; Fig. 1). The reduced cerebrovascular reactivity to hypercapnia in the morning was associated with the increased hypercapnic ventilatory response (r = 0.54; P < 0.05; Fig. 2A) and to the smaller increase in cerebral oxygenation (r = 0.39; P < 0.05; Fig. 2B), compared with the evening measurements. The relative decrease in cerebral oxygenation during hypercapnia in the morning was attributable mainly to a smaller increase in oxy-Hb (PM, 4.1 ± 0.7 vs. AM, 3.81 ± 0.5 μmol·l⁻¹·Torr⁻¹ PETCO2; P < 0.05). There were no overnight differences in the hypercapnic response of either t-Hb (PM, −0.9 ± 0.3 vs. AM, −1.0 ± 0.5 μmol·l⁻¹·Torr⁻¹ PETCO2; P > 0.05) or MAP (PM, 0.35 ± 0.21 vs. AM, 0.38 ± 0.25 mmHg/Torr PETCO2; P > 0.05).

Cerebral Oxygenation During Mild Hypoxia

In the last minute of hypoxia, the mild decrease in MCAV was not significantly different from the baseline value in either the evening or morning (sensitivity: PM, 0.71 ± 0.42%/SaO2; AM, 0.60 ± 0.56%/SaO2; Fig. 3). There were no overnight differences in the level of hypoxemia between morning and evening (SaO2: PM, 84.4 ± 1.9%; AM, 84.0 ± 2.1%) or hypocapnia (PETCO2: PM, −2.9 ± 1.3 Torr; AM, −2.7 ± 1.9 Torr).

Table 1. Steady-state cerebrovascular and cardiorespiratory variables monitored in the evening and early morning

<table>
<thead>
<tr>
<th>Variable</th>
<th>Time</th>
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<tbody>
<tr>
<td></td>
<td>Evening (PM)</td>
</tr>
<tr>
<td>Cerebrovascular</td>
<td></td>
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<tr>
<td>MCAV, cm/s</td>
<td>62.2±11.2</td>
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<tr>
<td>CVR, mmHg·cm⁻¹·s⁻¹</td>
<td>1.29±0.21</td>
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<tr>
<td>TOI, %</td>
<td>71.0±3.5</td>
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<tr>
<td>Cardiovascular</td>
<td></td>
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<tr>
<td>MAP, mmHg</td>
<td>83.4±9.2</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>52.6±7.1</td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
</tr>
<tr>
<td>Ventilation, l/min</td>
<td>8.1±1.1</td>
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<tr>
<td>PETCO2, Torr</td>
<td>106.12±4.2</td>
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<td>PETCO2, Torr</td>
<td>41.9±2.0</td>
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<tr>
<td>SaO2, %</td>
<td>98.0±0.9</td>
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</table>

Values are means ± SD based on 5 min of steady-state averaged data (n = 20). MCAV, middle cerebral artery flow velocity; CVR, cerebrovascular resistance; TOI, total cerebral oxygenation index; MAP, mean arterial pressure; HR, heart rate; PETCO2, and PETCO2, end-tidal PO2 and Pco2, respectively; SaO2, arterial oxygen saturation. Evening measurement is based on the evening of the full study before the overnight domiciliary sleep study and the repeat early morning tests. No differences existed between the two evening measurements (data not shown).
Despite this same stimulus, during the last minute, there was a greater cerebral desaturation during hypoxia in the morning compared with evening (PM, 0.45 ± 0.14% of baseline, \( P < 0.05 \) vs. AM, 0.35 ± 0.14% of baseline, \( P < 0.05 \); Fig. 3), owing to a greater decrease in oxy-Hb (PM, 2.1 ± 0.7 vs. AM, 2.9 ± 0.5 μmol/l; \( P < 0.05 \)), with no changes in t-Hb (PM, −0.4 ± 0.4 vs. AM, −0.6 ± 0.5 μmol/l; \( P < 0.05 \)). There were no overnight differences in the response of MAP to changing \( \text{SaO}_2 \) (PM: 0.18 ± 0.12 vs. 0.16 ± 0.09 mmHg/\( \text{SaO}_2 \); \( P > 0.05 \)).

**Breath Hold**

As illustrated in Fig. 4, after a 20-s breath hold, there was a smaller surge in both MCAV (AM, 29 ± 5 vs. PM, 35 ± 7% of baseline, \( P < 0.05 \)) and in cerebral oxygenation (AM, 5.6 ± 2.7 vs. PM, 7.2 ± 2.3% of baseline, \( P < 0.05 \)) in the early morning compared with the early evening. Similar to the cerebral oxygenation changes during hypercapnia, the reduction in cerebral oxygenation during the breath hold was predominantly due to a reduction in oxy-Hb, since t-Hb was unchanged between the evening and morning testing sessions. There were no overnight differences in \( \text{SaO}_2 \), BP, or \( \text{PETCO}_2 \) during or following the 20-s breath hold.

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**Fig. 2.** Relationship between overnight reduction in slope of the MCAV/CO₂ response to the elevated \( \text{Ve/CO}_2 \) (A) and to a reduction in cerebral oxygenation [total oxygenation index (TOI); B] in each individual (\( n = 20 \)). These data indicate that a morning reduction in MCAV/CO₂ reactivity is strongly associated with changes in the ventilatory responsiveness to elevations in CO₂ and also to a reduction in cerebral oxygenation. B: there seemed to be two visual outliers; however, upon closer examination, these data points are within 3 SD of the sample mean and, therefore, not classed as statistical outliers. Furthermore, these two data points do not reflect any noncompliance or technical error, and all other data (i.e., heart rate, MCAV, blood pressure, end-tidal \( \text{PCO}_2 \)) were normal during each test.

**Fig. 3.** Slopes of the cerebrovascular oxygenation (A), cerebral reactivity (B), and ventilatory responsiveness (C) to hypoxia in each individual during the evening (PM) and morning (AM). Bold lines represent group average. No differences existed between the evening and morning cerebrovascular or ventilatory reactivity to hypoxia, while there was a greater cerebral desaturation for a given change in arterial \( \text{O}_2 \) saturation (\( \text{SaO}_2 \)) in the morning (shown in 18 out of 20 subjects). NS, not significant.
Reproducibility

Reproducibility of the two evening measurements was compared with that of the evening and morning measurements. If more variability exists between the evening and morning (i.e., reflected in a lower correlation) compared with the variability between the two evening tests, it suggests an altered physiological response between evening and early morning. The correlation coefficients (r value) for the slopes of the MCAV cerebral oxygenation and ventilatory responses to hypercapnia, between the two evening experiments, were 0.81, 0.79, and 0.62, respectively (P < 0.05). Conversely, there were lower correlations between the evening and morning values (r = 0.36; 0.42, 0.31, respectively; P < 0.05 vs. PM). The two evening correlation coefficients for the slopes of the MCAV and ventilatory responses to hypoxia were not different from the correlations between the evening and morning slopes. Conversely, the correlation between the slopes of the cerebral oxygenation to hypoxia for the two evening tests (r = 0.65; P < 0.05) was higher than the correlations between evening and morning slope (r = 0.42; not significant). These results indicate selective overnight alterations in cerebrovascular, oxygenation, and ventilatory response to hypercapnia and hypoxic-induced cerebral deoxygenation, but not in the cerebrovascular or ventilatory responses to poikilocapnic hypoxia.

DISCUSSION

This study has produced several novel observations regarding ventilatory and cerebrovascular responses to CO2 in the early morning, all occurring despite the lack of any significant overnight changes in resting parameters. First, in normal subjects without pharmacological intervention, the early morning reduction in cerebrovascular reactivity to hypercapnia was associated with a smaller increase in cerebral oxygenation and an increased hypercapnic ventilatory response. Second, while mild hypoxemia had no overall effect on MCAV, VE, or PETCO2 during the last minute of hypoxia, there was a greater decrease in cerebral oxygenation with hypoxemia in the morning than in the evening. Third, after a 20-s breath hold, we observed a marked increase in both cerebral oxygenation and MCAV, but both increases were of lesser magnitude in the morning compared with evening. Therefore, the increased ventilatory response to hypercapnia observed in our study is likely a result of the reduced cerebrovascular reactivity to CO2, especially given recent findings showing a direct effect of manipulating the cerebrovascular reactivity, via the use of indomethacin administration, on the hypercapnic response (45). Furthermore, our results suggest that morning cerebral tissue oxygenation might be reduced as a result of a decreased cerebrovascular responsiveness to CO2 or other factors, leading to a higher level of desaturation.

Methodological Considerations

Although not a direct measure of flow, the majority of research suggests that there is little or no change in the cross-sectional area of the MCA during either hypercapnia or hypoxia, suggesting that MCAV is a reliable index of CBF (13, 33, 39). Cerebral NIRS has been shown to track changes in jugular venous bulb saturation in healthy volunteers under conditions of isocapnic hypoxia (19) and has also been validated compared with PET scanning (30), with 133Xe washout methods (34) and with internal carotid artery stump pressures (42). Since there were no overnight changes in total-Hb (as an index of cerebral blood volume), the changes in cerebral oxygenation are unlikely to be related primarily to differential volume shifts between the proportions of blood in the arterial or venous part of the cerebrovascular bed. It should be acknowledged that NIRS measures only local (i.e., to one depth)
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Diurnal Rhythm in Ventilatory and Cerebrovascular Reactivity

Circadian rhythm has been shown to influence the chemical control of breathing in both animals (27, 32), as well as humans (36, 38). We found no significant differences in any cardiorespiratory or cerebrovascular parameters at rest between the evening and early morning, consistent with other reports (22, 31). Although hypoventilation leading to a 3- to 7-Torr increase in arterial PCO₂ can occur during sleep (28), in normal, awake humans, it has been demonstrated that arterial PCO₂ remains unchanged from morning and evening (8). This has been confirmed in other studies where subjects remain awake in constant light and bed rest (constant routine conditions), where it has been demonstrated that the changes in metabolic rate and VE observed during sleep are reduced considerably or eliminated, leading to only small changes (within 1–2 Torr) in PETCO₂ throughout a 24-h period (37, 38). Together, these observations indicate that the small circadian changes in VE are mediated almost exclusively by the changes in the state of arousal (23).

Consistent with these observations and others (22, 31), our data show no significant differences in PETCO₂ or VE at rest between the evening and early morning. PETCO₂ is a good reflection of arterial PCO₂ at rest, and data from our laboratory indicate that the change in PETCO₂ is closely related to the change in arterial PCO₂ during hypercapnia (R² = 0.79, P < 0.05; mean bias, −0.08; n = 12; Ainslie PN, et al., unpublished observations). That being said, we cannot rule out the possibility that an enhanced ventilatory response to hypercapnia in the morning, subsequently leading to a difference in arterial PCO₂/pH, results in the attenuated cerebrovascular response to CO₂ in the morning that we observed in our study.

Previous studies have shown that MCAV is reduced during sleep (2, 14) and that there is a marked reduction (~70%) in sleep-related cerebrovascular response to CO₂ in otherwise healthy humans (21). A postsleep reduction in blood flow velocity has been confirmed in normal volunteers in some studies using TCD ultrasound (20) and with H215O positron emission tomography (7), but not all studies (22). These findings provide evidence of some form of “sleep inertia” or “carryover” of sleep-related processes into waking. Conversely, there is also one report describing an endogenous circadian rhythm in MCAV (9), providing preliminary evidence that the decline in MCAV is present during wakefulness in the nighttime hours and therefore may not be attributed solely to sleep and associated changes that normally influence MCAV (including factors such as the shift to recumbency, and reduced activity, metabolic rate, and respiratory rate); however, it is unknown if there is a similar endogenous circadian rhythm in cerebrovascular reactivity independent of sleep.

Collectively, the extent to which the morning reduction in the “awake” cerebrovascular response to CO₂ can be attributed to a “carryover” effect from sleep or to an endogenous circadian rhythm in cerebrovascular reactivity, independent of sleep, remains to be examined.

Cerebrovascular Reactivity to CO₂ and the Implications for Breathing Stability

Our data indicate that the cerebrovascular reactivity to CO₂ in healthy subjects is significantly reduced in the morning and is strongly associated with an augmented ventilatory response to CO₂. It is likely that this reduction in MCAV CO₂ reactivity, by reducing blood flow through medullary respiratory control centers, increases both the arterial-brain tissue PCO₂ difference and the H⁺ concentration presented to the central chemoreceptor(s) (11, 44). In effect, it appears the brain tissue is more susceptible in the morning to changes in arterial PCO₂, which could increase the likelihood of ventilatory overshoots and undershoots. However, changes in cerebral responsiveness to CO₂ may not be sufficient to destablize breathing, as the carotid bodies play a significant role in the rapid ventilatory response to CO₂ challenge (35). In addition, the carotid bodies are an important determinant in breathing stability at rest through tonic inputs and by possibly compensating for a reduced central CO₂ sensitivity (12, 15, 25, 35). However, it is tempting to speculate that this decrease in the morning responsiveness of the cerebral circulation to CO₂, by increasing the central contribution to loop gain, might also increase the risk for unstable breathing during the morning hours, especially when occurring in a background of other risk factors, such as heart failure.

Cerebrovascular Oxygenation During Hypoxia

From evening to morning, there was no change in MCAV sensitivity to poikilocapnic hypoxia. Although levels of hypoxia-induced hypocapnia were statistically identical from evening to morning, it remains possible that a difference in the hypoxic sensitivity from evening to morning was counteracted by a difference in the cerebrovascular response to the ensuing mild hypoxemia. As we did not compare cerebrovascular responses to hypoxemia alone, it is not possible for us to determine whether this is the case. However, our finding is in agreement with data from Meadows and colleagues (22), who found no changes in the CBF responses to isocapnic hypoxia, and hypothesized that the maintenance of the cerebrovascular response to hypoxia in the early morning may be a protective mechanism against cerebral ischemia and stroke (22).

Interestingly though, despite an unchanged MCAV responsiveness to hypoxia from evening to morning, there was a smaller increase in cerebral oxygenation compared with the...
evening. This indicates that, despite there being no differences in the cerebrovascular response to poikilocapnic hypoxia, the cerebral tissue is more prone to desaturation in the morning. This could partially explain the increased risk for morning cerebral ischemia and stroke, especially when occurring in a background of other risk factors.

The Effect of Breath Hold on MCAV and Cerebral Oxygenation

Similarly to Xie et al. (45), we used a breath-hold protocol to mimic apnea and initiate endogenous changes in arterial blood gases. From evening to morning, equivalent changes occurred in $\text{SaO}_2$, $\text{BP}$, and $\text{PETCO}_2$ during the breath hold. However, as was the case with the hypercapnic challenge, subjects holding their breath in the morning experienced a significantly blunted increase in MCAV compared with evening, likely a result of a reduced cerebrovascular responsiveness to CO$_2$. Although there appears to be no difference in the cerebrovascular response to hypoxemia from evening to morning, the lower increase in cerebral oxygenation in the morning after a breath hold could be from either a reduced cerebrovascular responsiveness to CO$_2$ or to additional, yet-to-be-identified factors.

In conclusion, our results suggest that early morning reductions in cerebrovascular CO$_2$ reactivity strongly influence the magnitude of the ventilatory response to CO$_2$. This may have significant implications for breathing stability, increasing the chances of periodic breathing in the morning in patients with additional risk factors. The early morning reduction in cerebral oxygenation with hypercapnic challenge, mild hypoxemia, or during apnea may be a contributing factor in the high prevalence of early morning stroke. Whether differences in the responses of CBF, oxygenation, or $\text{Ve}$ to CO$_2$ challenge are associated with other risk factors for stroke, such as gender or age, remains to be elucidated.

REFERENCES