# Cerebrovascular Response to Arousal from NREM and REM Sleep

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**Study Objective:** To determine the effect of arousal from sleep on cerebral blood flow velocity (CBFV) in relation to associated ventilatory and systemic hemodynamic changes.

**Participants:** Eleven healthy individuals (6 men, 5 women).

**Measurements:** Pulsed Doppler ultrasonography was used to measure CBFV in the middle cerebral artery with simultaneous measurements of sleep state (EEG, EOG, and EMG), ventilation (inductance plethysmography), heart rate (ECG), and arterial pressure (finger plethysmography). Arousals were induced by auditory tones (range: 40-80 dB; duration: 0.5 sec). Cardiovascular responses were examined beat-by-beat for 30 sec before and 30 sec after auditory tones.

**Results:** During NREM sleep, CBFV declined following arousals (-15% ± 2%; group mean ± SEM) with a nadir at 9 sec after the auditory tone, followed by a gradual return to baseline. Mean arterial pressure (MAP; +20% ± 1%) and heart rate (HR; +17% ± 2%) increased with peaks at 5 and 3 sec after the auditory tone, respectively. Minute ventilation ($V_E$) was increased (+35% ± 10%) for 2 breaths after the auditory tone. In contrast, during REM sleep, CBFV increased following arousals (+15% ± 3%) with a peak at 3 sec. MAP (+17% ± 2%) and HR (+15% ± 2%) increased during arousals from REM sleep with peaks at 5 and 3 sec post tone. $V_E$ increased (+16% ± 7%) in a smaller, more sustained manner during arousals from REM sleep.

**Conclusions:** Arousals from NREM sleep transiently reduce CBFV, whereas arousals from REM sleep transiently increase CBFV, despite qualitatively and quantitatively similar increases in MAP, HR, and $V_E$ in the two sleep states.

**Keywords:** cerebral blood flow, rapid-eye-movement sleep, non-rapid-eye-movement sleep

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SLEEP DISORDERED BREATHING IS ASSOCIATED WITH ELEVATED ARTERIAL PRESSURE AND AN INCREASED RISK OF STROKE[1,2]; THIS INCREASED RISK MAY be related to changes in the regulation of cerebral blood flow. Numerous factors contribute to cerebral blood flow regulation, among them cerebral metabolism, arterial carbon dioxide tension, and cerebral perfusion pressure.[3-5] Sleep state has profound direct and indirect effects on cerebral hemodynamics. Several studies using a variety of methods (transcranial Doppler ultrasonography,[133] Xe inhalation, and single-photon emission computerized tomography) have shown a reduction in cerebral blood flow during NREM sleep and an increase during REM sleep as compared to the awake state in healthy persons.[1,6-13]

Arousal from sleep, per se, causes abrupt hemodynamic and respiratory changes characterized by increases in sympathetic nervous system activity, blood pressure, heart rate,[14] and ventilation.[15,16] Moreover, arousal from sleep accentuates the hemodynamic changes produced by upper airway obstruction.[17] Although changes in cerebral blood flow associated with arousal[12] and with spontaneous theta-alpha transitions during the sleep onset period[18] have been characterized, the interaction of hemodynamic, ventilatory, and cerebrovascular responses to arousal from stable sleep has not been rigorously studied thus far.

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In this study we investigated arousal-induced changes in cerebral blood flow velocity (CBFV) in healthy young adults. In addition, we investigated the temporal relationships among the cerebrovascular, ventilatory, and systemic hemodynamic perturbations associated with arousal from NREM and REM sleep.

## METHODS

### Subjects

Six men and 5 women (aged 26 ± 5 [SD] yr) served as subjects for the sleep study (Table 1). Six additional subjects (4 males and 2 females [aged 37 ± 12 yr]) were enrolled in a separate daytime study where the effects of voluntary hyperventilation on CBFV were studied during wakefulness. All subjects were non-obese (BMI < 25 kg/m$^2$) nonsnorers. Participants were not taking any medication, and none had a history of pulmonary, neurological, or cardiovascular disease. All subjects provided informed consent prior to participation. The experimental protocol was approved by the University of Wisconsin Center for Health Sciences Human Subjects Committee.

### General Procedures

The nighttime sleep studies took place in a quiet, darkened, temperature- controlled (20-22 ºC) room between 23:00-06:00. Physiological responses were monitored from an adjacent room. Subjects were instructed to abstain from caffeine and alcohol consumption for 24 hours prior to the study. In addition, we asked the subjects to sleep deprive themselves by obtaining no more than 4 hours of sleep the night prior to study.

An additional daytime study was performed to determine the time course of the CBFV and $P_{ET}CO_2$ responses to brief

**Table 1**—Demographic Characteristics, Distribution of Auditory Arousals Across Sleep States, and Mean Duration of EEG Perturbations for Each Subject

| Subject | Age/Gender | # Stage 2 Events (duration) | # Stage 3-4 Events (duration) | # REM events (duration) |
|---|---|---|---|---|
| 1 | 21/F | 16 (8.8 sec) | 11 (8 sec) | 4 (5 sec) |
| 2 | 22/M | 6 (8.5 sec) | 1 (7 sec) | 6 (8.2 sec) |
| 3 | 24/F | 2 (7.3 sec) | 0 | 2 (5 sec) |
| 4 | 20/F | 8 (6.6 sec) | 6 (8.3 sec) | 2 (7.7 sec) |
| 5 | 20/M | 5 (6.5 sec) | 7 (8.8 sec) | 2 (8 sec) |
| 6 | 29/F | 12 (6.9 sec) | 0 | 3 (6.6 sec) |
| 7 | 24/M | 9 (6.5 sec) | 0 | 6 (6 sec) |
| 8 | 28/F | 4 (9.4 sec) | 2 (8 sec) | 7 (6.2 sec) |
| 9 | 26/M | 11 (6. 8 sec) | 2 (9.3 sec) | 7 (6.4 sec) |
| 10 | 35/M | 8 (8 sec) | 10 (7.8 sec) | 9 (6 sec) |
| 11 | 29/M | 11 (8.6 sec) | 2 (5.5 sec) | 15 (6 sec) |
| Mean±SEM | 26 ± 2 yr | 7.7 ± 0.3 sec | 7.0 ± 0.9 sec | 6.5 ± 0.3 sec |

periods of hyperventilation. The daytime studies were carried out between the hours of 13:00 and 14:30 in all subjects. In these studies, subjects were coached to take 3 consecutive large breaths, using a real-time visual feedback display of tidal volume and auditory tones to cue the timing and depth of each breath, so that the amplitude and duration of the breaths produced a change in minute ventilation that was as least as great as that observed following acoustic arousal in the nighttime sleep study (approximately 140% of the baseline value). After the 3 large breaths, the subjects were instructed to relax and breathe normally. Each subject performed this maneuver 3 times.

### Acoustic Interventions During Sleep

Transient arousals from stable NREM (stage 2, 3, or 4) and REM sleep were induced using brief computer-generated auditory tones (1000 Hz, 0.5 second) delivered via 2-inch diameter audio speaker, which was positioned 15 cm above the forehead of the supine subject. A sound level meter placed 25 cm from the speaker was used to calibrate the gain control on the amplifier so that a range of audio stimuli at 40-80 dB was produced. The first trial was at 40 dB, and if no arousal was induced, further trials at 5 dB increments were delivered until arousal was induced or a level of 80 dB was reached. We allowed at least 2 min of stable sleep between successive stimuli. All tones were delivered during late expiration.

### Measurements

Subjects were instrumented and continuous overnight polysomnography recordings of EEG (C3/A2 and O2/A1), left and right EOG, submental EMG, and a single lead ECG were obtained. Tidal volume was measured by inductance plethysmography (Respitrace, Ambulatory Monitoring, Ardsley, NY). The two wired elastic bands were carefully positioned around the subject, encircling the rib cage just below the axilla and the abdomen just below the umbilicus. Both bands were secured with adhesive tape. The inductance plethysmograph output was calibrated by the isovolume technique[19] in conjunction with a rolling seal spirometer (Ohio 800, Ohio Intruments, Madison, WI). Respiratory cycle timing was measured using the inductance plethysmography signal. Arterial blood oxygen saturation was measured continuously with an ear oximeter (Model 3740, Ohmeda, Louisville, CO).

Beat-by-beat arterial pressure was measured by photoelectric plethysmography (Finapres, Ohmeda, Louisville, CO). Heart rate (HR) was measured from the electrocardiogram. A 2 MHz pulsed Doppler ultrasound system (Neurovision 500 M, Multigon Industries, Younkers, NY) was used to measure peak CBFV in the proximal (M1) segment of the middle cerebral artery. The middle cerebral artery was insonated through the right temporal window using search techniques that have been described previously.[20] After obtaining the best-quality signal, the probe was secured using a headband device to provide a fixed angle of insonation.

During the daytime study, subjects breathed through a nasal mask connected to a pneumotachograph (Model 3700, Hans Rudolph) to measure ventilation. CBFV was measured as described above. End-tidal $CO_2$ was sampled with a catheter inserted in the mask and analyzed with an infrared gas analyzer (Model CD3A, Ametek, Pittsburgh, PA).

All variables were recorded continuously on paper (Astro-Med K2G, Grass Instruments, West Warwick, RI) and videotape (#400A PCM, Vetter, Rebersburg, PA). These signals were also routed to a computer (sampling rate, 120 Hz) for off-line analysis using custom-written software.

### Data Analysis

#### Sleep Staging and Arousal Scoring

A single trained observer performed the EEG analysis. Sleep stages were scored according to standard criteria.[21] Thirty-sec segments of EEG record following the auditory tones were examined to assess arousal responses. A 30-sec segment prior to arousal was used as baseline for comparison. Arousals during both NREM and REM sleep were identified as transient increases in EEG frequency, which were 3-14 sec in duration. Trials in which the auditory stimulus did not cause EEG change or produced a full awakening were not included in the data analysis.

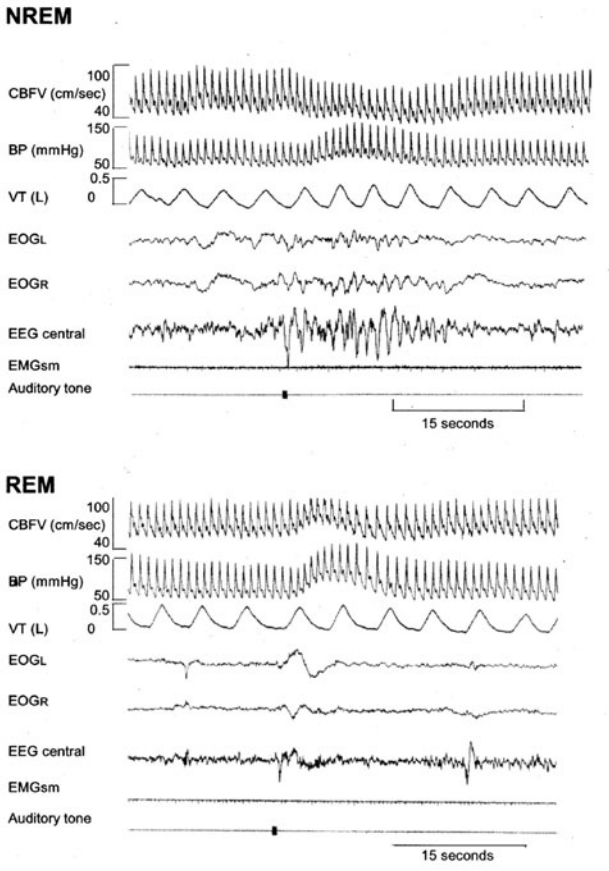


**Figure 1**—Original polygraph records showing typical cardiovascular and ventilatory responses to auditory arousals from NREM (top panel) and REM (bottom panel) sleep. CBFV, cerebral blood flow velocity; BP, blood pressure; VT, tidal volume; EOG, electrooculogram; EEG, electroencephalogram; EMG, electromyogram.

### Vascular Responses

Hemodynamic and cerebrovascular variables in the 30 sec preceding and 30 sec following auditory stimuli were acquired on a beat-by-beat basis using custom developed software. HR was determined from the ECG R-R interval. Mean CBFV for each cardiac cycle was determined from the integral of the maximal frequency shift over one cardiac cycle divided by the length of the corresponding cardiac cycle (i.e., velocity-time integral). MAP was calculated as one-third pulse pressure + diastolic pressure. The beat-by-beat values for CBFV, HR, and MAP were placed into 1-sec bins.

Data from each trial were carefully inspected and outlying data points (differing from a neighboring point > 2 standard deviations of the pre-stimulus values), usually associated with movement artifact, were removed. Post-tone responses were expressed as percentage of the 30-sec pre-tone mean. For each subject, hemodynamic responses to auditory tones during NREM and REM sleep were averaged, and these average values were used in computation of the group means.

### Ventilatory Responses

Ventilatory parameters in the 30 sec preceding and 30 sec following an auditory tone were analyzed on a breath-by-breath basis. Ventilation ($V_E$), tidal volume, and respiratory frequency were measured using custom-developed software. Post-tone responses were expressed as percentage of the 30-sec pretone mean. For each subject, ventilatory responses to auditory tones during each sleep stage were averaged, and these average values were used in computation of the group means.

**Table 2**—Heart Rate (HR) and Cerebral Blood Flow Velocity (CBFV) Values During Wakefulness and Stable NREM and REM Sleep (n = 11 Subjects)

| | Awake | NREM Baseline | REM Baseline |
|---|---|---|---|
| HR(beats/min) | 71 ± 4 | 62 ± 3 | 66 ± 3 |
| CBFV(cm/sec) | 56.5 ± 4.3 | 53.9 ± 3.7 | 58.9 ± 5.7 |

The differences in HR and CBFV were not statistically significant (P >0.05 by ANOVA).

### Daytime Hyperventilation Study

Beat-by-beat measurements of CBFV were signal-averaged for each breath. For each subject, breath-by-breath measurements of $V_E$, CBFV, and $P_{ET}CO_2$ during the 3 hyperventilation trials were averaged, and these average values were used in computation of the group means.

### Statistical Analysis

All data are reported as means ± SEM. Steady-state baseline values for HR and CBFV during wakefulness, NREM, and REM sleep were compared by 1-way ANOVA. For the arousal responses, binned data were analyzed for CBFV, HR, and MAP, whereas breath-by-breath analysis was performed for ventilation. Averaged trial data, with each subject contributing one data point, were used in the statistical analyses. The values for CBFV, HR, MAP and ventilation before and after the arousal induced by an auditory tone in NREM sleep were compared by Wilcoxon signed-ranks tests to determine if the percent change from baseline was different from 100%. To compare these values across sleep states, we used a Wilcoxon signed-ranks test at each time point. We felt that this conservative nonparametric testing procedure would offset some of the potential problems associated with multiple testing and did not make any further multiple testing adjustments. P-values less than 0.05 were considered significant. All analyses were performed using SAS statistical software version 9.1, SAS Institute Inc. (Cary, NC).

## RESULTS

### Effect of Sleep on Heart Rate and Cerebral Blood Flow Velocity

Sixteen percent of the observed sleep time was spent in stage 1, 45% in stage 2, and 22% in stages 3 and 4. REM sleep was achieved in all subjects, and it accounted for 17% of the observation period. Steady-state baseline values of HR and CBFV were not statistically different during wakefulness, NREM, or REM sleep (Table 2). The distribution of auditory arousals across sleep states and mean durations of EEG perturbations are

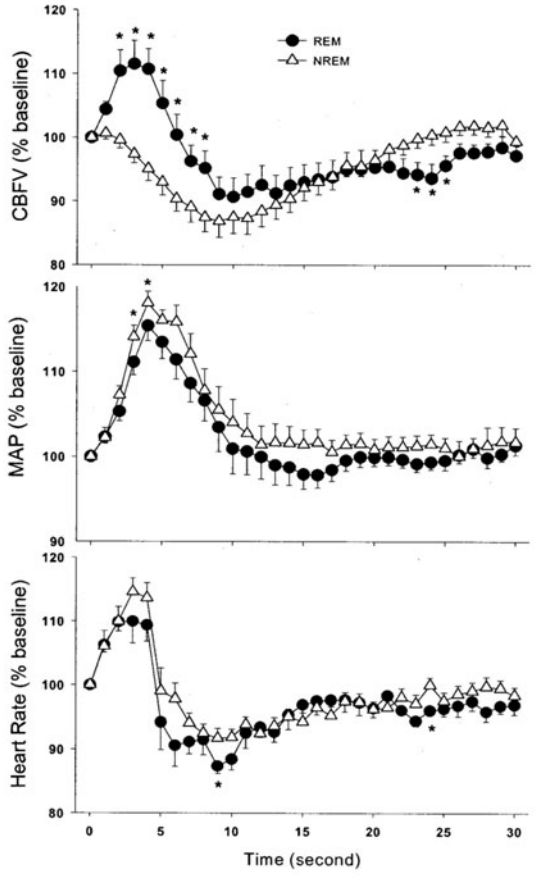


**Figure 2**—Cerebral blood flow velocity (CBFV), mean arterial pressure (MAP), and heart rate (HR) after arousal from NREM and REM sleep, expressed as percentages of the pre-arousal baseline means. Points represent mean values±SEM. * P < 0.05, NREM vs. REM (n = 11 subjects).

shown in Table 1. The durations of arousal were comparable in stage 2, slow wave, and REM sleep (7.7 vs. 7.0 vs. 6.5 sec, P > 0.05 by ANOVA) (Table 1).

### Hemodynamic, Cerebrovascular, and Ventilatory Responses to Auditory Arousals from NREM Sleep

A representative polygraph record showing the 30 sec before and after presentation of the auditory stimulus during NREM sleep is shown in Figure 1 (top panel). Mean data for all 11 subjects are shown in Figure 2. On average, CBFV declined by –15% ± 2% (P < 0.05) during arousals from NREM sleep. The nadir occurred 9 sec after the auditory tone. HR and MAP increased after arousal from NREM sleep (+17% ± 2% and +20% ± 1% respectively; P < 0.05) with peaks at 3 and 5 sec after the auditory tone, respectively. $V_E$ increased significantly in the first 2 breaths following arousals from NREM sleep (+35% ± 10%, P < 0.05), secondary to increases in both tidal volume and frequency (Figure 3).

To investigate the possibility that the CBFV response to auditory arousal was variable within NREM sleep, we compared events that occurred in Stage 2 sleep with those that occurred in slow wave sleep in a subset of subjects (n = 4) who had relatively equal numbers of events in the 2 sleep stages. Arousal-induced decreases in CBFV were comparable in Stage 2 and slow wave sleep (Figure 4).

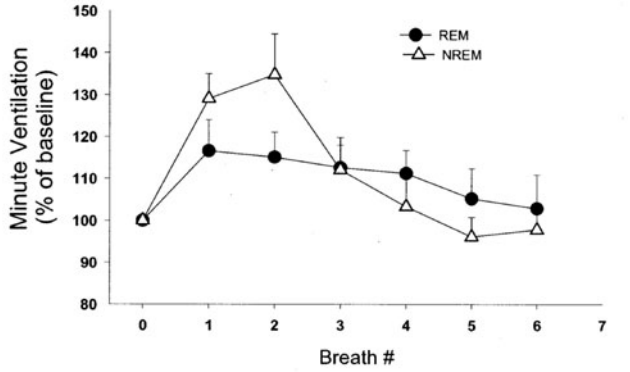


**Figure 3**—Changes in minute ventilation after arousal from NREM and REM sleep. Points represent mean values ± SEM. *P < 0.05, NREM vs. REM (n = 11 subjects).

### Hemodynamic, Cerebrovascular, and Ventilatory Responses to Auditory Arousals from REM Sleep

Figure 1 (bottom panel) is an original polygraph record showing the 30 sec before and after presentation of the auditory stimulus during REM sleep in the same subject shown in the top panel. In contrast to NREM sleep, CBFV increased during arousals from REM sleep. Group mean data showing the NREM vs. REM comparison are shown in Figure 2. The between-state differences in CBFV were statistically significant during seconds 2-8 and 22-27 after the tone. MAP rose slightly more after arousal from NREM vs. REM sleep. This difference was statistically significant at 3 and 4 sec after the tone. There were no significant between-state differences in HR (Figure 2) or $V_E$ (Figure 3) following auditory arousal.

### Effect of Time of Day on CBFV Responses to Auditory Arousal

To investigate the possibility that diurnal variations in CBFV might contribute to the observed NREM vs. REM differences in CBFV response to arousal, we compared "early" REM events (i.e., those that preceded NREM events) with "late" REM events (those that that occurred after at least one NREM period). This analysis was possible in 8 of 11 subjects. Auditory arousals from REM sleep caused increases in CBFV regardless of the time of night at which the tones were administered. Likewise, arousals from NREM sleep caused decreases in CBFV regardless of the time of night; therefore, we combined the REM trials and the NREM trials in each subject to yield a single mean value for each sleep state.

### Time Course of Changes in CBFV Caused by Voluntary Hyperventilation during Wakefulness

With the onset of voluntary hyperventilation, the decrease in $P_{ET}CO_2$ preceded the decrease in CBFV, reaching a nadir during the third large breath (approximately 10 sec). In contrast, CBFV rose slightly during the first large breath, then declined,

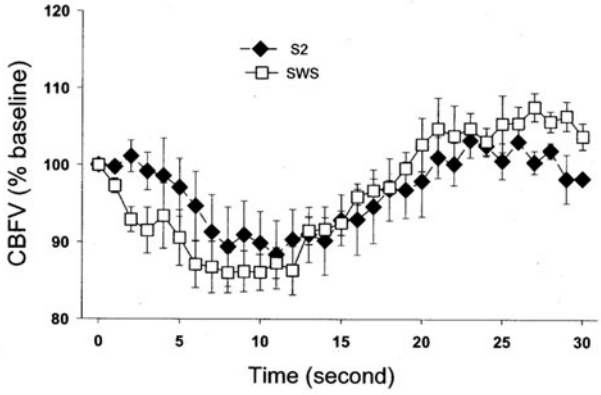


**Figure 4**—Changes in cerebral blood flow velocity (CBFV) during stage 2 sleep (S2) and slow wave sleep (SWS) in 4 subjects who experienced relatively equally numbers of auditory stimuli in the 2 sleep stages.

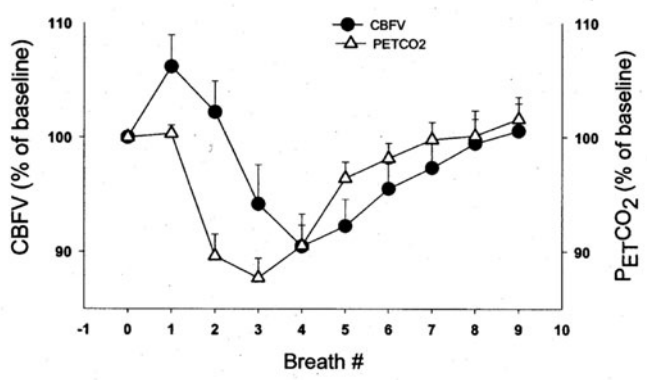


**Figure 5**—Breath-by-breath changes in ventilation, cerebral blood flow velocity (CBFV), and end-tidal $PCO_2$ ($P_{ET}CO_2$) caused by voluntary hyperventilation during wakefulness. Unlike the immediate decrease in CBFV observed after arousal from NREM sleep, the decrease in CBFV following the onset of hyperventilation in the awake state was delayed relative to the decrease in $P_{ET}CO_2$ (n = 6 subjects).

reaching a nadir approximately 18 sec after the onset of hyperventilation (Figure 5). Both $P_{ET}CO_2$ and CBFV had returned to baseline levels by the sixth post-hyperpnea breath.

## DISCUSSION

The major finding of this study is that the cerebrovascular response to transient arousal from sleep is dependent on the underlying sleep stage. In all subjects, we observed a rapid significant decline in CBFV following arousal from NREM sleep, whereas an immediate increase in CBFV was observed during REM sleep. The NREM-REM difference in CBFV response to auditory arousal was evident despite qualitatively and quantitatively similar hemodynamic and ventilatory responses. To our knowledge, this study is the first to systematically analyze the interaction of hemodynamic, ventilatory, and cerebrovascular response to acoustic arousal from stable NREM and REM sleep.

### Methodological Issues

Doppler ultrasound measures of flow velocity are reflective of volume flow only when the cross-sectional area of the vessel under study remains constant. Although we do not know whether middle cerebral artery diameter remains constant during change in sleep state, previous investigators have shown that middle cerebral artery diameter does not vary more than 4% during changes in arterial pressure, $CO_2$ tension[22,23] or gravitational stress.[24] For this reason, and because other investigators have demonstrated that velocity and flow through the middle cerebral artery are highly correlated,[25,26] we believe we are justified in using velocity as a surrogate for flow in our experiments. We acknowledge, however, that inability to quantify middle cerebral artery diameter is a limitation of our study. Nevertheless, we believe that this limitation is greatly outweighed by the excellent temporal resolution of Doppler ultrasonography, which allowed us to detect rapid changes in cerebral blood flow that would have been missed by techniques that are unable to track beat-by-beat changes.

Because we measured CBFV only in the middle cerebral artery, our data do not speak to the effects of auditory arousal on perfusion in other brain regions, where the hemodynamic profile may be different. Nevertheless, because the auditory cortex is located within the middle cerebral artery perfusion territory, we believe that our measurements of flow velocity in this artery provide important information about cerebrovascular regulation during acoustic arousals.

To increase comfort, we did not require that subjects remain in the same body position throughout all observations. Therefore, calibrations of the respiratory impedance plethysmograph, made before the onset of sleep in the supine position, may not have remained valid throughout all observations as body position changed. We acknowledge this as a limitation of our study. We are confident, however, that body position did not change within trials. We believe that we have overcome this limitation by expressing $V_E$ as a percent of the preceding baseline period of stable sleep.

The majority of our REM sleep observations were made during tonic REM sleep. Further investigation is required to characterize the CBFV responses to auditory arousal from phasic REM sleep.

### Effect of Sleep on Cerebral Blood Flow

Prior studies performed to monitor cerebral blood flow with a variety of techniques have shown a dynamic pattern of brain perfusion over the course of a night's sleep.[1,6-13] In one previous study using transcranial Doppler, the investigators observed a progressive reduction of CBFV from waking state to stage 4 NREM sleep, but only for the first sleep cycle of the night.[13] Thereafter, CBFV continued to decline, even in the lighter sleep stages of subsequent cycles, suggesting that EEG-measured cerebral activity and cerebral perfusion are uncoupled in NREM sleep. In this and other previous studies, marked increases in CBFV were consistently observed at NREM-to-REM transitions,[10,12,13] suggesting a close coupling between cerebral activity and cerebral perfusion in REM sleep. Taken together these findings suggest that metabolic mechanisms of cerebral blood flow regulation are more important in REM vs. NREM sleep.

### Mechanism of CBFV Response to Arousal from NREM Sleep

The decline in CBFV after auditory arousal from all stages of NREM sleep that we observed in our subjects cannot be explained on the basis of hemodynamic and/or ventilatory responses. Both blood pressure and heart rate were rising at the time when CBFV was falling during the first 10 sec after the acoustic tone. Thus, it is unlikely that decreased perfusion pressure or decreased cardiac output was the underlying cause of the decrease in CBFV. The decline in CBFV occurred too rapidly to result from hypocapnia caused by arousal-induced hyperventilation. In a separate study of the time interval between onset of hyperventilation, development of hypocapnia, and decline in CBFV in awake subjects, we found that the nadir in CBFV occurred 18 sec after the onset of voluntary hyperventilation. In contrast, the nadir in CBFV after acoustic arousal from NREM sleep occurred an average of 9 sec after the tone stimulus. On the basis of this analysis we postulate that hyperventilation-induced decreases in arterial $PCO_2$ may have prolonged the decreases in CBFV caused by auditory arousal from NREM sleep, but they clearly did not initiate them. Therefore, we conclude that the rapid reduction in CBFV was mediated by neural events associated with auditory arousal. This interpretation is consistent with the findings of previous investigators who observed decreases in CBFV during spontaneous theta-alpha transitions in the sleep onset period.[18]

Previous investigators have shown that the transition from wakefulness to NREM sleep is accompanied by a transient rise in CBFV that is independent of slowing of the EEG and the expected reduction in cerebral metabolism.[18,27] Thus, neural regulation of cerebral blood flow independent of cerebral metabolism is evident during NREM sleep and could potentially contribute to the abrupt decreases in CBFV that we observed during the auditory arousals. Neurons in several subcortical regions (e.g., locus ceruleus and raphe nucleus) provide important vasoconstrictor inputs to the cerebral circulation through direct projections and also via cortical interneurons that are thought to function as integrators of sensory information.[28]

Does the sympathetic nervous system contribute to the reduced CBFV after arousal from NREM sleep? The extraparenchymal cerebral arteries are diffusely innervated with sympathetic nerve fibers,[29] and in anesthetized animals, electrical stimulation of them can elicit substantial reductions in cerebral blood flow.[30-33] The current concept is that sympathetic nerves in the cerebral circulation serve mainly a protective role by increasing the upper limit of autoregulation in situations where a generalized increase in sympathetic outflow and consequent surge in cerebral perfusion pressure might otherwise threaten the blood brain barrier.[28,34] In humans, auditory arousal from NREM sleep augments sympathetic outflow to the skeletal muscle vascular bed,[14] causes peripheral vasoconstriction,[35-37] and raises arterial pressure.[14] Thus, it is possible that the decrease in CBFV that we observed following arousal from NREM sleep was caused, at least in part, by an increase in sympathetic vasoconstrictor activity.

### Why are CBFV Responses to Arousal Qualitatively Different in REM vs. NREM Sleep?

In REM sleep, high levels of cortical activity are accompanied by increases in cerebral blood flow; thus, cerebral blood flow regulation is thought to be heavily influenced by metabolic rate.[13] At the same time, vasoconstrictor neurons in the locus ceruleus and the raphe nucleus cease firing completely.[38,39] REM-related abolition of activity in these neurons may alter baseline vascular tone and/or result in divergent responses to perturbing stimuli. We speculate that the increases in CBFV observed following arousal from REM sleep were initiated by abrupt increases in cortical metabolic rate and/or perfusion pressure and that the absence of vasoconstrictor restraint may have played a permissive role. This scenario is not necessarily inconsistent with the relatively high levels of sympathetic vasoconstrictor outflow to the skeletal muscle circulation that have been observed during REM sleep.[40] Neuronal activity in the locus ceruleus and raphe nucleus exerts a powerful influence on the cerebral circulation, whereas interventions that increase sympathetic outflow to skeletal muscle have little influence on cerebral blood flow.[41]

### Does Arousal from REM Sleep Compromise Cerebrovascular Autoregulation?

In our subjects, the immediate increase in CBFV after arousal from REM sleep occurred in parallel with the increase in mean arterial pressure. To our knowledge, we are the first to report this finding, which suggests a transient failure of autoregulation. We know that autoregulation is not perfect; in fact, prior studies indicate that autoregulation can be overridden, at least in part, by relatively rapid changes in arterial pressure.[42] It has been reported that cerebral autoregulation responds more effectively to low- vs. high-frequency changes in blood pressure.[43] In addition, autoregulation is much less effective in the presence of hypercapnia,[44] which would be present at the time of arousal due to the sleep-related elevation in arterial $PCO_2$.

### Summary

This study demonstrated a qualitative difference in the CBFV response to arousal in NREM vs. REM sleep. The reduction in CBFV during NREM and the increase in REM sleep raise the possibility that the cerebral vasculature is regulated by different pathways depending on sleep state. The clinical significance of the present findings requires further investigation. Arousal-induced increases and decreases in CBFV could increase the susceptibility to periodic breathing by altering the chemical milieu at the central chemoreceptor. If autoregulation is compromised during REM sleep, the susceptibility to adverse cerebrovascular events during this sleep stage could be increased.


### ACKNOWLEDGMENTS

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