Assessment of Intracranial Hemodynamics in Sleep Apnea Syndrome

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Background and Purpose: Sleep apnea syndrome may lead to changes in cerebral hemodynamics due to altered alveolar ventilation. We investigated the dynamics of CO₂- and blood pressure–regulated alterations of cerebral blood flow velocities during apneic episodes and evaluated CO₂ reactivity during different sleep stages.

Methods: A computer-assisted pulsed Doppler system (2 MHz) was used for continuous overnight recordings of middle cerebral artery flow patterns together with simultaneous polysomnography, continuous blood pressure recordings, and measurements of end-expiratory CO₂ in six patients with sleep apnea syndrome.

Results: Increases in mean flow velocity of 19–219% and in blood pressure of 12.5–83.1% could be observed during the apneic episodes, with maximum increases during rapid eye movement (REM) sleep. CO₂ reactivity was in the normal range (4.4 ± 1.2%) in the waking state and was markedly increased during sleep stages 1 and 2 (p < 0.005 compared with awake). The greatest increase was found during REM sleep, with a rise of up to three times the waking value (p < 0.0001 compared with sleep stage 2).

Conclusions: The changes of mean flow velocity could be interpreted as reactive adaptation processes because of CO₂ and blood pressure increases corresponding to apnea. The increased CO₂ reactivity during sleep may indicate a “hypersensitivity” of intracranial vascular CO₂ or pH receptors and a disturbance of central catecholaminergic and cholinergic systems. The pronounced velocity changes during apneic episodes and the concomitant alterations of vessel wall tension might lead to microangiopathies and macroangiopathies due to chronic strain on the brain vessels. (Stroke 1992;23:1427–1433)

KEY WORDS • blood flow velocity • carbon dioxide • sleep apnea syndromes • ultrasonics

Specific disorders of breathing during sleep are described in patients with sleep apnea syndrome (SAS). Obstructive, central, mixed, and subobstructive types are distinguished. Apnea has been defined as a cessation of airflow through the nose and mouth lasting at least 10 seconds.1 SAS is diagnosed if at least 30 apneic episodes are observed during both non–rapid eye movement (NREM) and rapid eye movement (REM) sleep over 7 hours of nocturnal sleep. Some apneic episodes must appear in a repetitive sequence during NREM sleep.2 Severe complications (e.g., hypoxia, hypercapnia, pulmonary and systemic hypertension, right heart failure, cardiac arrhythmias, secondary polycythemia, respiratory failure, excessive daytime sleep, fatigue, and morning headache have been described in SAS.3,4 SAS is therefore a major cardiovascular risk factor and may be accompanied by an increased risk of stroke.4–6 So far, the etiology of SAS has not been unequivocally clarified. Various theories have been discussed to explain the genesis of the nocturnal apneic episodes.7–10 Longobardo et al8 consider that periodic breathing is caused by the increased circulation time between brain stem respiratory center receptors and controlled alveolar ventilation. Because the episodes of apnea are accompanied by hypoxia as well as hypercapnia and PCO₂ as well as the perivascular pH constitute a major regulatory parameter to control cerebral blood flow (CBF)11 and CBF velocity,12–14 it is likely that an effect on cerebral hemodynamics is to be found in patients with SAS. Due to technical limitations, the alterations of CBF and cerebral hemodynamics associated with apnea have been investigated in very few studies up to now.15 Transcranial Doppler ultrasonography (TCD) is a well-proven method detecting changes of cerebral perfusion within seconds.16,17 Recently studies established TCD as a method for continuous long-term and on-line recordings of cerebral perfusion during human sleep concomitant with simultaneous polysomnography.18–20 Another study reported the effect of sleep on intracranial hemodynamics in children and adults using 33 single TCD measurements.21 Alterations of CBF velocities were recently reported in one patient with obstructive SAS.22 We studied patients with SAS to investigate the dynamics of CBF velocities during the whole night’s sleep and analyzed the CO₂ and blood pressure–regu-
lated CBF velocity alterations during apneic episodes recorded by using continuous long-term and on-line TCD recordings in combination with polysomnography.

Subjects and Methods
Data from six men with severe SAS (age range, 34–55 years; mean, 48.8 years) who could be investigated with polysomnography and TCD throughout the night. None of the patients had a history of cerebral infarction or myocardial infarction. Hemodynamically relevant stenoses or occlusions of the extracranial and intracranial arteries supplying the brain were ruled out by Doppler determination before the beginning of sleep registrations. All patients abstained from alcohol and nicotine from 24 hours before up to the end of the examination. Recordings were performed continuously with polysomnography and TCD throughout the night.

Standard polysomnography was used to monitor the electroencephalogram, right and left electro-oculogram, submental electromyogram, electrocardiogram, and electromyogram of the anterior tibialis muscle. Respiratory parameters were assessed by measuring airflow through nasal and oral thermistors. Breathing effort was determined with abdominal and thoracic strain gauges measuring chest and abdominal wall respiratory movements. Body position and movements were detected by infrared video monitoring. The different stages and parameters of sleep were evaluated manually from polysomnograms (Nihon Kohden, Tokyo, Japan) in accordance with the criteria of Rechtschaffen and Kales and stored on a personal computer system.

The intracranial blood flow patterns were continuously recorded overnight with a computer-assisted pulsed 2-MHz Doppler system (TC 2-64B, EME, Ueberlingen, FRG). After detection and manual optimization of the Doppler signal, the probe was fixed mechanically with a specially developed probe holder using elastic bands and fixation strips in such a way that the additional attachment of polysomnographic registration sensors was possible. This fixation method permitted continuous long-term estimation of the CBF velocity in the middle cerebral artery with minor impairments for the sleeper and few movement artifacts during the recording. The analog-to-digital–converted envelope curve of the Doppler frequency spectrum was stored on-line on the hard disk of a personal computer. The mean flow velocity (MFV) was calculated from cardiac cycle to cardiac cycle on the basis of the original registration using a computer-assisted integration procedure. For each nocturnal study, the TCD measurement was started during relaxed wakefulness with closed eyes in the darkened room when the electroencephalogram showed a continuous alpha frequency. The TCD investigation was performed continuously after morning awakening until the MFV reached values comparable to the waking values preceding sleep onset. This was done to rule out possible dislocation of the probe.

Simultaneous with the TCD measurements, end-expiratory CO2 was measured with a capnometer (Normokap, Datex, Finland). In three patients, transcutaneous P02 and PC02 (Micro GAS 7640, Kontron, England) were also measured. Arterial oxyhemoglobin saturation was measured by ear pulse oximetry (Biox 37003, Ohmeda, Tokyo, Japan). Blood pressure was continuously monitored noninvasively by measurements of finger pulse pressure according to the Penaz methodology (Finapress, Ohmeda). All parameters including TCD data were continuously stored on the computer system.

The sleep evaluation was done by computer-assisted adaptation of CBF velocity measurements to computerized polysomnographic data. MFV values were taken at 30-second intervals from the computerized data and time-correlated to corresponding sleep periods. Statistical analysis was established by one-way analysis of variance and by linear regression analysis using the least-squares approximation. A calculated difference of p<0.05 was considered to be significant.

The CO2 reactivity during apneic episodes was defined as the ratio of the percentage increase of MFV and the difference between end-expiratory CO2 measurements before and after the apneic episodes. The CO2 reactivity during the waking phase was defined as the ratio of the percentage change of MFV and the difference between end-expiratory CO2 measurements before and after hypercapnia. However, an exact determination of the rise in CO2 concentration during an apneic episode was possible only when expiration after apnea was performed exclusively through the nose, where the sensor for end-expiratory CO2 was located. This was the case in only 62.1% of the apneic episodes. Only these apneic episodes were used to calculate CO2 reactivity. It was not possible to use the transcutaneous CO2 values in consequence of the inadequate time resolution of this method. To obtain a parameter for cerebrovascular reactivity during all apneic episodes that is independent of end-expiratory CO2, we also used a TCD apnea score. The score was defined as the percentage rise of MFV for an apnea duration of 10 seconds. This corresponded to the minimum time during which an apnea was included in the evaluation (TCD apnea score = percentage increase of MFV during apneic episodes / 10 / duration of apneic episode).

Average CO2 reactivity and the TCD apnea score calculated during the waking state were normed to 1. Average CO2 reactivity and the TCD apnea score of representative sleep stages were related to values during the waking state.

Results
A total of 969 apneic episodes occurred. Because the patients rarely reached slow-wave sleep and thus only 21 episodes of apnea were recorded during slow-wave sleep, this was not considered in the further evaluation. We observed 248 episodes of apnea during sleep stage 1, 521 during sleep stage 2, and 179 during REM sleep. A prolongation of the average duration of apnea and a consequent increasing mean end-expiratory CO2 could be observed from stage 1 to stage 2 to REM sleep (sleep stage 1; mean±SD duration of apnea, 24.7±9.6 seconds; mean±SD CO2 increase due to apnea, 6.2±4.10 mm Hg; sleep stage 2; 30.8±11.3 seconds and 7.96±5.74 mm Hg, respectively; REM sleep: 33.7±14.6 seconds and 8.07±5.21 mm Hg, respectively).

Alterations of CBF velocity, MFV, blood pressure, and end-expiratory CO2 during the waking state...
Figure 1. Tracings of changes in flow velocity (FV) and mean flow velocity (MFV) of right middle cerebral artery, blood pressure (BP), and end-expiratory CO₂ concentration (pCO₂) during waking state (panel A, evening; panel E, morning) and different sleep stages (panel B, stage 1; panel C, stage 2; panel D, rapid eye movement sleep) of a 35-year-old man with sleep apnea syndrome. For methodological reasons, measured rise of pCO₂ is too low after some apneic episodes. Here, expiration did not take place exclusively through the nose, where the sensor for pCO₂ determination was located. These apneic episodes were not used to calculate CO₂ reactivity.

Even a slow, even rise of CBF velocity during the apneic episodes in every sleep stage (Figures 1B, 1C, and 1D). With onset of breathing, MFV fell rapidly to or below the initial value (Figures 1C and 1D). Analogous to the reaction of CBF velocity, a rise of blood pressure could be observed during the apneic episodes. However, the relative increase of blood pressure was less than the relative increase of CBF velocity (Figures 1C and 1D). In addition to these fluctuations in blood pressure during apneic episodes, a rise of blood pressure to distinctly hypertensive values could be observed during the night. Thus, a rise of blood pressure was found with increasing depth of sleep, starting from normotensive resting values in the evening. This rise reached its maximum with values of 210/160 mm Hg during REM sleep (Figure 1D). Blood pressure values at rest in the morning were again almost comparable to the initial normotensive values of the previous evening (Figure 1E).

Despite these conspicuous blood pressure profiles, the patients displayed alterations of CBF velocities during sleep similar to those of healthy subjects. The night profile of MFV and the corresponding sleep stages of the same patient are compared with those of a typical healthy volunteer in Figure 2. This patient showed a greater reduction of MFV during deepening sleep
stages than the healthy subject, although he only rarely reached slow-wave sleep. The beginning of REM sleep in the patient was comparable to that in the healthy subject, accompanied by a marked increase in MFV compared with that during NREM sleep. In contrast to values in the healthy subject, in the patient averaged MFV values during REM sleep clearly exceeded waking values. REM sleep showed the greatest instability of all sleep stages. This was manifested in pronounced fluctuations of CBF velocity. CBF velocities that might be less than the awake values for a short time were hence found during REM sleep. In analysis of all REM sleep stages, however, a marked preponderance of CBF velocities that were above the awake values could be observed.

In all patients investigated, there was an even rise in MFV of 19–219% during the apneic episodes in each stage of sleep, with a maximum during REM sleep. The rise in blood pressure varied between 12.5% and 83.1% within one apneic episode. The average rises of MFV associated with apneic episodes showed a significant difference among the sleep stages (sleep stage 1: 66.8±29.3%, sleep stage 2: 81.5±38.1%, REM sleep: 108.1±50.1%; p<0.01). Average rises of blood pressure associated with apneic episodes did not show a significant difference among the sleep stages (sleep stage 1: 17.5±13.8%, sleep stage 2: 26.8±18.3%, REM sleep: 25.8±16.7%). The effect of apnea duration on the rise of MFV and the effect of the rise of blood pressure on the rise of MFV were analyzed separately. A significant correlation between duration of apnea and rise of MFV was shown for every sleep stage, whereas there was no significant correlation for rise of blood pressure within one apneic episode and rise of MFV. To detect a possible combined effect of duration of apnea and rise of blood pressure on the rise in MFV, a multiple linear

FIGURE 2. Tracings of mean flow velocity (MFV, relative values) of right middle cerebral artery and corresponding sleep profile in 35-year-old man with sleep apnea syndrome (panel A) and in 26-year-old healthy subject (panel B). Respective sleep stage is shown on vertical axis: MT, movement time; W, wake; REM, rapid eye movement (REM) sleep; S1–S4, stages 1–4. Lower-case letters characterize a, progressive MFV reduction; b, increased MFV during REM sleep; c, reduced MFV while awakening; d, movement artifact; and e, unaltered MFV during changes from stage 2 to slow-wave sleep.
regression analysis was carried out (Figure 3). A significant linear correlation was found among the three parameters (sleep stage 1: $r=0.49$, $p<0.001$; sleep stage 2: $r=0.63$, $p<0.001$; REM sleep: $r=0.73$, $p<0.001$). The slope of the regression curve increased both between the rise of MFV and duration of apnea and between the rise of MFV and rise of blood pressure from sleep stage 1 over sleep stage 2 to REM sleep. This phenomenon was more pronounced between the rise of MFV and duration of apnea than between the rise of MFV and rise of blood pressure (Figure 3).

The $CO_2$ reactivity and the TCD apnea score evidently depended on the sleep stage (Figure 4). In the waking state, patients showed a $CO_2$ reactivity in the normal range (4.4±1.2%; range, 3.01–6.27%); the TCD apnea score was 11.0±4.38% (range, 5.3–16.3%). In sleep stages 1 and 2, there was a pronounced rise of both parameters (Figure 4; $p<0.005$ compared with awake values). The greatest increase was found during REM sleep, with rises of $CO_2$ reactivity and TCD apnea score up to three times the waking values ($p<0.0001$ compared with sleep stage 2). On the other hand, the increases of $CO_2$ reactivity and TCD apnea score were independent of the sleep cycle. Thus, comparable increases of the two parameters could be demonstrated, for example, during the first as well as the last REM sleep cycle.

Discussion

SAS is characterized by the occurrence of various cardiovascular and respiratory changes during sleep. For methodological reasons, only a few studies have investigated the effect of SAS on nocturnal cerebral hemodynamics.15 Fast functional changes of cerebral
perfusion during sleep could be measured with the high time resolution of TCD.\textsuperscript{18,19,21} The continuous registration of cerebral perfusion changes even during the relatively short episodes of apnea was possible with long-term (whole night) TCD monitoring.\textsuperscript{20,22}

In all patients investigated, CBF velocity and MFV increased during the apneic episodes in direct relation to Pco\(_2\). The respiration model of Longobardo et al\textsuperscript{8} describes an increased circulation time between the neurons in medullary respiratory centers and the controlled alveolar ventilation or a decreased controller gain of the CO\(_2\)-dependent neurons as the cause of periodic breathing. Previous studies\textsuperscript{11-14} have demonstrated that brain perfusion depends mainly on Pco\(_2\).

Our findings of a tight coupling between the CBF velocity increase and hypercapnia during apneic episodes suggest that the cerebrovascular CO\(_2\) receptors or the pH receptors are functionally intact. An explanation based on delayed perfusion times is not supported by these data. The increase in the respiratory CO\(_2\) threshold and the decrease in respiratory CO\(_2\) sensitivity during sleep found in SAS suggest that receptors of the respiration-sensitive area in the brain stem were disturbed.\textsuperscript{26,27} Thus, a structural difference between cerebrovascular receptors and respiration-sensitive neurons has to be postulated.

Our results show that CO\(_2\) reactivity and the TCD apnea score changed depending on the stage of sleep in all patients investigated. There were rises in CO\(_2\) reactivity and the TCD apnea score with increasing depth of sleep. Both parameters showed the maximum value during REM sleep. On the other hand, there was a normal CO\(_2\) reactivity averaging 4.4±1.2% in all patients during the waking state. It might be argued that the calculated rise in CO\(_2\) reactivity was based on end-expiratory CO\(_2\) values that were measured too low in part. However, previous studies\textsuperscript{28-30} have reported an increase in Paco\(_2\) of 6-10 mm Hg during an apnea period of 30 seconds. The average values for the rise of CO\(_2\) (normed to 30 seconds) that we calculated during the three sleep stages were in this range. In addition, the alterations in CO\(_2\) reactivity are similar to the alterations in TCD apnea score. The TCD apnea score is in turn a parameter for cerebrovascular reactivity, which is independent of end-expiratory CO\(_2\). In our opinion, these results may indicate a hypersensitivity of the cerebrovascular CO\(_2\) or pH receptors during sleep compared with wakefulness. Moreover, it must be borne in mind in the interpretation of these findings that there were simultaneous rises of both blood pressure during the apneic episodes and the blood pressure level depending on the sleep stage. Besides other factors,\textsuperscript{31} this correlates with an increased level of circulating catecholamines accompanying sleep apnea.\textsuperscript{32,33}

Although under physiological conditions the cerebral perfusion is as a rule affected for only a short time by fluctuations of blood pressure due to cerebral autoregulation, it must remain an open question whether these mechanisms also apply in the same way during sleep and sleep apnea. The multiple linear regression analysis showed significant effects of both duration of apnea and percentage rise of blood pressure on the percentage rise of MFV linked to apnea. An increasing slope of the regression curve could also be demonstrated in this model between percentage rise of MFV and duration of apnea from sleep stage 1 over stage 2 to REM sleep. This increase in the slope of the regression curve seems not to be attributable exclusively to the rise of blood pressure associated with apnea.

To our knowledge, there have been no systematic investigations up to now as to whether healthy subjects also show a physiologically increased controller gain of cerebrovascular CO\(_2\) receptors during sleep compared with wakefulness. Thus, the possible pathophysiological significance of these findings in SAS is at present unresolved. It is conceivable that the possible hypersensitivity of the cerebrovascular CO\(_2\) or pH receptors entails a compensatory regulation in reduced chemosensitivity of peripheral and central respiratory CO\(_2\)-dependent neurons\textsuperscript{9,10} within a complex feedback-regulated system to maintain an adequate pH of the neuronal environment. Beyond that, a number of experiments suggest that the central catecholaminergic and cholinergic systems, which arise from the brain stem, are involved in cerebrovascular reactivity to changes in Paco\(_2\).\textsuperscript{34-36} It has been reported that the denervation of these systems by destruction of the locus ceruleus, by destruction of the ascending reticular activating system, or by intraventricular injection of 6-hydroxydopamine causes an increased CO\(_2\) reactivity.\textsuperscript{36-38} In patients with SAS, there is a critically reduced brain stem blood flow during sleep, indicating a disturbance of brain stem function including that of the ascending reticular activating system.\textsuperscript{15} Our data showing an increased CO\(_2\) reactivity during sleep in the investigated patients with SAS may therefore be further explained by a disturbance of the central catecholaminergic and cholinergic systems that coregulate CO\(_2\) reactivity.

Besides the changes of CBF velocities in the range of seconds during apneic episodes, all patients displayed alterations of CBF velocities during sleep similar to those of healthy subjects in long-term analysis of the entire night. The patients showed a similar or greater decrease of MFV during deepening sleep stages in the first sleep cycle compared with healthy subjects,\textsuperscript{16,19,21} although the patients only rarely reached slow-wave sleep due to the abnormal structural staging of their sleep. Beyond that, the TCD apnea score in healthy subjects\textsuperscript{16,19} a sleep stage-independent fall of the mean MFV level could be observed during the night so that a decoupling of cerebral electrical activity and cerebral perfusion during NREM sleep\textsuperscript{18,19} was also observed in the patients with SAS. Reduction of the mean MFV level occurred despite rises in blood pressure and CO\(_2\) level during the whole night.

With reference to the possible increased risk of stroke in SAS patients,\textsuperscript{4-6} several clinical implications are of interest. First, owing to the raised CO\(_2\) reactivity during sleep, alterations in CO\(_2\) concentrations associated with apneic episodes lead to pronounced CBF velocity fluctuations in the cerebral arteries. It can be assumed that alterations of vessel wall tension resulting from the CBF velocity fluctuations lead to a chronic strain on the brain vessels with consequent microangiopathies and macroangiopathies. Second, rises of blood pressure level depending on the sleep stage were found in four patients who showed normotensive or only slightly hypertensive blood pressure values during the day. And, third, under certain conditions, the complex hemodynamic changes during sleep and the substantially re-
duced CBF velocity during the early morning hours might lead to a critical reduction in cerebral perfusion, resulting in ischemia. This is consistent with the high rate of cerebral infarction at this time.39,40

Long-term and on-line recordings of intracranial blood flow patterns in combination with polysomnography as a new method for the detection of dynamic aspects of brain function and cerebral perfusion during sleep at any given time may be a useful tool for studying sleep disorders such as SAS. In the future, such knowledge may contribute to better understanding of the pathogenesis of nocturnal stroke.

References


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