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
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 sufficiently in the sleep laboratory during spontaneous sleep throughout the whole night were evaluated after giving informed consent. Right and left middle cerebral artery recordings were made during two consecutive nights. Data from a total of 12 whole night periods were analyzed. 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, Uberlingen, 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 Po₂ and PcO₂ (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 \( \times 10/duration \) 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, 6.27±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...
(evening and morning) and various stages of sleep are shown for a 35-year-old patient with SAS in Figure 1. There was 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
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. Fast functional changes of cerebral
perfusion during sleep could be measured with the high
time resolution of TCD.\textsuperscript{18,19,21} The continuous registrati-
on 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\textsubscript{2}. The respiration model of Longobardo et al\textsuperscript{8}
describes an increased circulation time between the
neurons in medullary respiratory centers and the con-
trolled alveolar ventilation or a decreased controller
gain of the CO\textsubscript{2}-dependent neurons as the cause of
periodic breathing. Previous studies\textsuperscript{11-14} have demonstrat-
ed that brain perfusion depends mainly on Pco\textsubscript{2}.
Our findings of a tight coupling between the CBF
velocity increase and hypercapnia during apneic epi-
sodes suggest that the cerebrovascular CO\textsubscript{2} receptors or
the pH receptors are functionally intact. An explana-
tion based on delayed perfusion times is not supported
by these data. The increase in the respiratory CO\textsubscript{2} thresh-
old and the decrease in respiratory CO\textsubscript{2} sensitivity
during sleep found in SAS suggest that receptors of the
respiration-sensitive area in the brain stem were dis-
turbed.\textsuperscript{26,27} Thus, a structural difference between cere-
brovascular receptors and respiration-sensitive neurons
has to be postulated.

Our results show that CO\textsubscript{2} reactivity and the TCD
apnea score changed depending on the stage of sleep in
all patients investigated. There were rises in CO\textsubscript{2} reac-
tivity 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\textsubscript{2} reactivity averaging 4.4±1.2% in all pa-
tients during the waking state. It might be argued that
the calculated rise in CO\textsubscript{2} reactivity was based on
end-expiratory CO\textsubscript{2} values that were measured too low
in part. However, previous studies\textsuperscript{28-30} have reported an
increase in Paco\textsubscript{2} of 6-10 mm Hg during an apnea
period of 30 seconds. The average values for the rise of
CO\textsubscript{2} (normed to 30 seconds) that we calculated during
the three sleep stages were in this range. In addition,
the alterations in CO\textsubscript{2} reactivity are similar to the
alterations of vessel wall tension resulting from the CBF
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\textsubscript{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 hypersen-
sitivity of the cerebrovascular CO\textsubscript{2} or pH receptors
entails a compensatory regulation in reduced chemo-
sensitivity of peripheral and central respiratory CO\textsubscript{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 exper-
iments suggest that the central catecholaminergic and
cholinergic systems, which arise from the brain stem,
are involved in cerebrovascular reactivity to changes in
PacO\textsubscript{2}.\textsuperscript{34-38} 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\textsubscript{2} reactivity.\textsuperscript{36-38} In patients with
SAS, there is a critically reduced brain stem blood flow
during sleep, indicating a disturbance of the ascending
reticular activating function including that of the ascend-
ing reticular activating system.\textsuperscript{35} Our data showing an increased CO\textsubscript{2}
reactivity during sleep in the investigated patients with
SAS may therefore be further explained by a disturb-
bance of the central catecholaminergic and cholinergic
systems that coregulate CO\textsubscript{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{18,19,21}
although the patients only rarely reached slow-wave
sleep due to the abnormal structural staging of their
sleep. Beyond that, alterations of vessel wall tension
of healthy subjects,\textsuperscript{18,19} 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 pres-
sure and CO\textsubscript{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\textsubscript{2} reactivity during
sleep, alterations in CO\textsubscript{2} concentrations associated with
apneic episodes lead to pronounced CBF velocity fluc-
tuations 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 mac-
roangiopathies. Second, rises of blood pressure level
depending on the sleep stage were found in four pa-
tients who showed normotensive or only slightly hyper-
tensive blood pressure values during the day. And,
third, under certain conditions, the complex hemody-
namic 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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