Perspectives in Medicine (2012) 1, 275—284

Bartels E, Bartels S, Poppert H (Editors):
New Trends in Neurosonology and Cerebral Hemodynamics — an Update.
Perspectives in Medicine (2012) 1, 275—284

journal homepage: www.elsevier.com/locate/permed

Cerebral blood flow velocity in sleep

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KEYWORDS
Transcranial doppler sonography;
Cerebral electrical activity;
CBF velocity during normal sleep and sleep disorders;
Sleep apnea syndrome

Summary Sleep is the most conspicuous alteration of cerebral function during the circadian rhythm. It is composed of a cyclic sequence of stages defined on the basis of electrophysiological parameters. The underlying functional activity of the human brain is reflected by sleep correlated changes of cerebral blood flow (CBF), CBF velocity and cerebral metabolism (CM). Transcranial Doppler sonography (TCD) allows to analyze the rapid adaptation processes of cerebral hemodynamics due to TCD capabilities for high temporal resolution and continuous recording during sleep using modern ultrasonic probes with special fixation devices. After the onset of sleep there is a significant progressive reduction of CBF velocity from the waking state to slow wave sleep. The beginning of REM sleep is accompanied by a marked increase in CBF velocity. Furthermore, TCD enables the assessment of perfusion changes in pathological sleep conditions. In sleep apnea syndrome an apnea-associated increase in CBF velocity occurs, which is attributed to apnea-related hypercapnia, whereas a rapid normalization of flow velocity occurs at the end of each apneic episode. TCD is a useful method for long-term and on-line monitoring of dynamic changes in cerebral perfusion during normal sleep and in sleep disorders.

Cerebral electrical activity, CBF and CM during normal sleep

The two basic types of sleep are non-rapid eye movement (NREM) and rapid eye movement (REM) sleep. In humans NREM sleep is further subdivided into four stages, each associated with distinct states of altered consciousness [1,2]. When compared with baseline levels during wakefulness, cerebral blood flow (CBF) and cerebral metabolism (CM) decrease with the onset of sleep and during sleep stages land I—II and reach minimum values in all brain regions during slow-wave sleep (SWS; sleep stages III and IV) [3—10]. These changes are not uniformly distributed. Against this global fall in CBF are important regional variations with some brain regions (frontal cortex, basal ganglia, thalamus, pons, cerebellum) affected to a greater degree while others (temporal cortex) are relatively affected to a minor degree [7,11]. CBF and CM rise to or even exceed waking levels during rapid eye movement (REM) sleep [3,4,6,11—14]. In a study of regional CBF during REM sleep, Madsen et al. [15] showed that during REM sleep CBF increases in the associative visual area while it decreases in the inferior frontal cortex.

Electroencephalography studies show that there is a hyperfrontal distribution of the electrical activity of the brain during wakefulness [16]. The electroencephalogram (EEG) pattern is closely coupled with the state of conscious awareness. With increasing depth of sleep [17], this regional differentiation is lost and the EEG shows a generalized decrease of frequency. During REM sleep, high mixed frequencies occur [2,18]. A close correlation between the EEG frequency, CBF and CM during human sleep has been reported [7,16,19,20], corroborating the notion of a tight coupling between cerebral electrical activity, CBF and CM [21—25]. The changes in EEG frequency, CBF and CM have been attributed to variations of brain activity during sleep.

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2211-968X/$ — see front matter
doi:10.1016/j.permed.2012.02.021

Transcranial Doppler sonography (TCD) allows continuous measurement of CBF velocity in the major cerebral arteries and with TCD the rapid adaptation processes of cerebral hemodynamics that occur during sleep may be analyzed with a high temporal resolution [26—29].

Ever since the beginning of clinical sleep research, the results of electroencephalographic recordings of the course of sleep have contradicted the findings of radioisotope tracer studies, which were obtained during a short sampling period for each sleep phase. The radioisotope studies revealed only a static picture of CBF and CM and were unable to demonstrate sleep as a dynamic state of changing cerebral function [3,30—32]. Because of TCD's capabilities for high temporal resolution and continuous recording using modern ultrasonic probes with special fixation devices, the relationship between EEG and cerebral perfusion changes over the course of the entire sleep period can now be recorded.

CBF velocity during normal sleep

In a study by Fischer et al. [33], the flow velocity (FV) in the right middle cerebral artery (MCA) was assessed during evening wakefulness, sleep stages II or IV of non-rapid eye movement (NREM) sleep and the morning waking stage in 5 healthy children (age: 5—13 years) and 6 adults (age: 24—42 years). Polysomnography was performed in all subjects. The MFV decreased during NREM sleep by an average of 21% in the adults and 32% in the children. An MFV increase was observed during awakening but, in both children and adults, the MFV was an average 19% less than during evening wakefulness. No significant change in pCO_2 was observed during sleep. From these findings, the authors concluded that the degree of wakefulness should be taken into account when assessing TCD study findings.

In another study by this group [34], the intracranial hemodynamics of sleep apnea syndrome (SAS) was assessed in 11 healthy adults (age: 37.1 ± 3.2 years), who served as the control group. The study design was the same as in the former study, except that, in this study, MFV measurements were also obtained during REM sleep. In this study, the MFV decreased by an average 17.5% during NREM sleep and a further slight decrease occurred in REM sleep. The MFV measured after awakening the next morning was an average 8.4% lower than the wakefulness value measured on the preceding evening. Changes in the pCO_2 during sleep were also detected in this test group; there was a 10.5% decrease during NREM sleep and a 3.2% decrease during REM sleep. The pCO_2 measured the next morning was 4.8% lower than the pCO_2 of the previous evening. After CO_2 correction of the MFV values [35], these researchers detected a significant MFV decrease during REM sleep and a slight MFV increase during NREM sleep compared with the values observed during evening wakefulness and after awakening the next morning. This group's findings on the MFV dynamics during sleep differ from those of other research groups [36—39].

Droste et al. [36], for example, obtained different results in their study of the MFV development in the MCA during nocturnal sleep in 10 healthy volunteers (age: 25—31 years). The MFV was significantly higher during REM sleep than in the

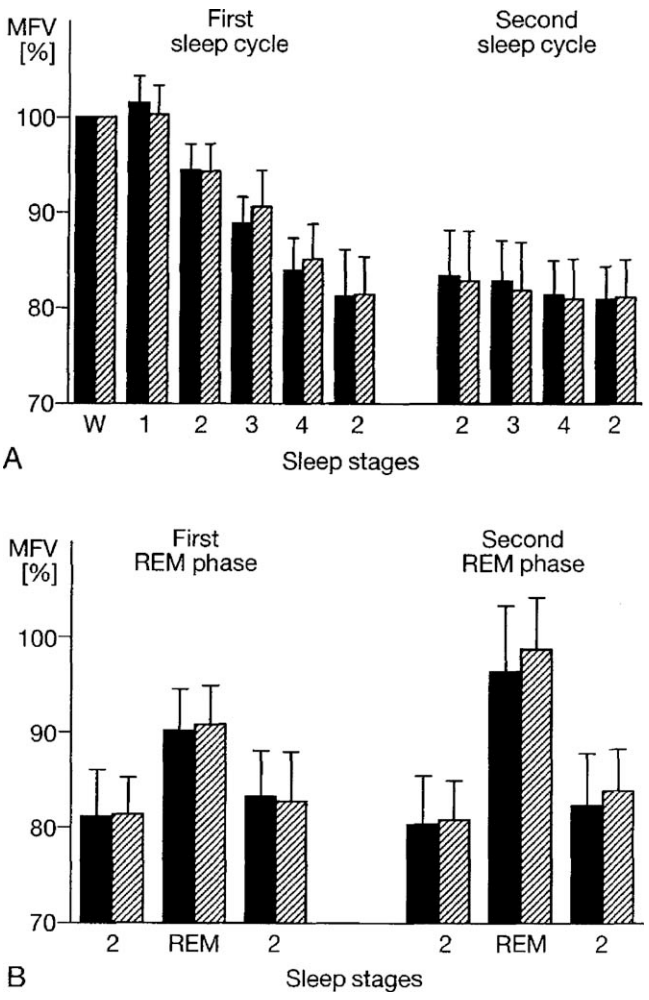

Figure 1 Relative mean flow velocities (related to the evening wakefulness values, *W*) detected in the middle cerebral artery (MCA). Black bars = left MCA, $n = 16$. Hatched bars = right MCA, $n = 18$. (A) During different NREM sleep stages (1st and 2nd sleep cycle) and (B) during REM sleep, together with sleep stage II prior to and after REM sleep (1st and 2nd sleep cycle). MFV: mean flow velocity (according to [39]).

NREM sleep stages and nocturnal wakeful states. After analyzing the results of their nocturnal TCD recordings using a fast Fourier transformation algorithm, they detected rhythmic fluctuations in the TCD curves, particularly during REM sleep, with wavelengths ranging from 20 to 75 s. Droste's group saw a causal relationship between the rhythmic oscillations and the B-waves of nocturnal intracranial pressure (ICP) fluctuations.

Klingelhöfer et al. [39] measured the MFV in the right ($n = 18$) and left MCA ($n = 16$) as well as heart rate, peripheral arterial blood pressure and pCO_2 in 18 healthy male volunteers (age: 24—34 years) during two nights. Polysomnography, performed in all volunteers, included an EEG, bilateral electrooculogram, electromyogram (submental and anterior tibial muscle), ECG, measurement of nasal and oral airflow during chest and abdominal wall respiratory movements, blood pressure, pulsoximetry and capnometry. The MFV changes and pCO_2 changes during the manually determined sleep stages of the first, second and last sleep

cycles were determined with reference to the evening wakefulness values (Fig. 1). For assessment of sleep events (EEG), all sleep spindles, K-complexes with and without sleep spindles, EEG arousals and movement arousals (EEG arousals with an increase in EMG activity) during the last sleep cycle were manually determined from polysomnograms obtained during 12 nights and time-correlated to the corresponding MFV values and vegetative parameters. After a total of 980 EEG events, the reactions of the MFV and autonomic nervous system were assessed.

Long-term analysis in healthy subjects (whole night period)

After the onset of sleep, there> was a significant ($p < 0.001$) progressive reduction of the MFV from the waking state to stage IVa of the first sleep cycle (Figs. 1 and 2). In spite of the subsequent decrease in the depth of sleep, MFV decreased further from stages IVa to IIc preceding the REM period. MFVs in stage IIa of the second and last sleep cycles were significantly ($p < 0.01$) lower than those in stage IIa during the first NREM cycle. A special pattern in the MFV profile was seen during passage through the second and subsequent NREM sleep cycles. MFV values were low during sleep stages IIa and IVa following REM sleep, increased moderately during intermediate sleep stage IIb and decreased again gradually with consecutive sleep stages IIIb, IVb and IIc. The decrease in MFV values was less during the second and last NREM sleep stages than during the first sleep cycle. MFV values in all sleep stages did not differ significantly during the NREM sleep stages in the second and last NREM sleep cycles studied.

The beginning of REM sleep was accompanied by a marked increase in MFV. MFV values markedly exceeded values of the preceding sleep stages II and IV but did not reach waking values in the first, second and last sleep cycle. The MFV during alpha-frequency wakefulness that follows NREM

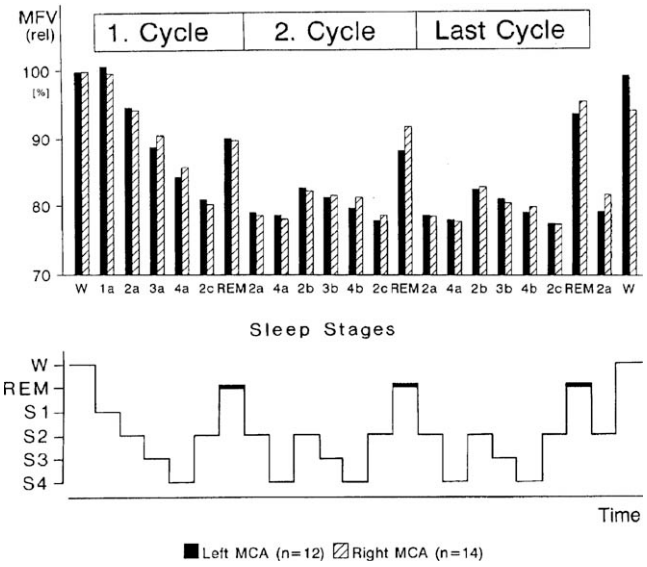

Figure 2 Relative MFV in the right ($n = 14$) and left ($n = 12$) MCA during different sleep stages in healthy male volunteers (according to [38]).

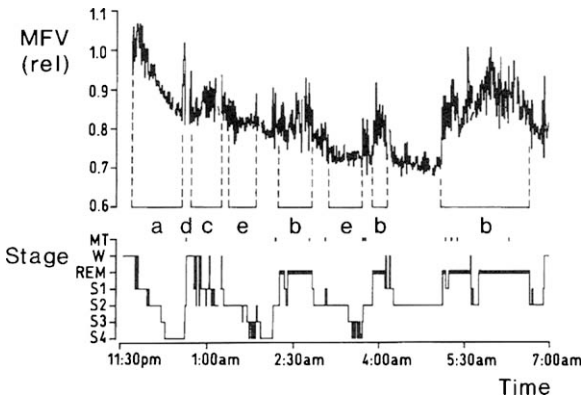

Figure 3 Course of the MFV (relative values) of the right MCA and the corresponding sleep profile in a 26-year-old healthy subject. Lower-case letters characterize (a) progressive MFV reduction; (b) increased MFV during REM sleep; (c) reduced MFV while awakening; (d) movement artifact; and (e) unaltered MFV during changes from stage II to slow-wave sleep (according to [66]).

sleep was lower than waking values preceding sleep onset (Fig. 3). After morning awakening, patients lying awake often required more than half an hour to reach MFV values corresponding to the waking state of the previous evening. MFV profiles were occasionally interrupted by movement artifacts in all healthy subjects (Fig. 3).

Short-term analysis in healthy subjects (dynamics of rapid FV fluctuations)

Rapid fluctuations in FV lasting seconds occurred during SWS as well as stage II and REM sleep. Fig. 4 shows the FV curve with corresponding sleep stages in a typical healthy subject [39]. There were no major fluctuations of FV during stage IV. Moderate fluctuations appeared during sleep stage II. During REM sleep, the amplitude and the duration of fluctuations were markedly increased. Large fluctuations in FV lasting seconds were accompanied by fluctuations

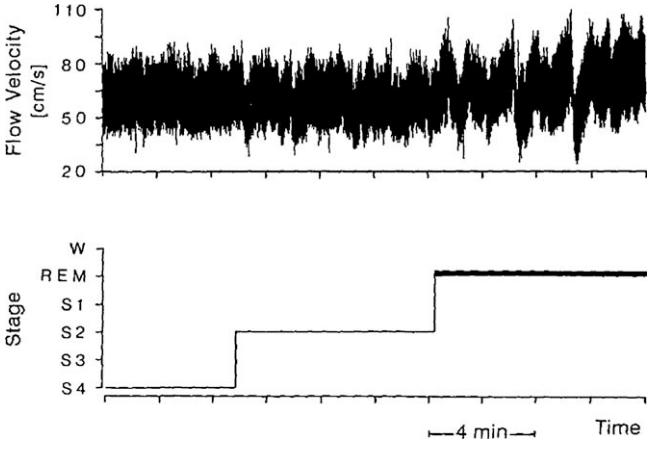

Figure 4 Dynamics of rapid FV fluctuations in the left MCA during the transition from sleep stage IV to REM sleep via stage II in the first sleep cycle in a 25-year-old healthy subject (according to [39]).

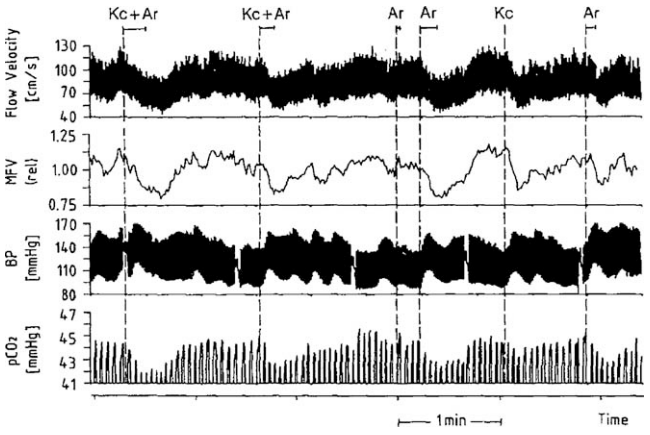

Figure 5 Relationship between FV (right MCA), MFV, blood pressure, end-expiratory CO_2 concentration, and sleep events (Kc, K-complex; Ar, arousal) in sleep stage II in a healthy 27-year-old subject (according to [39]).

in blood pressure. However, the changes in peripheral blood pressure and pulse were not always accompanied by corresponding changes in FV. Fluctuations in FV also occurred following sleep events such as K-complexes and arousal. Immediately after the sleep event there was a moderate increase followed by a pronounced decrease in MFV. During REM sleep, increases in velocity that appeared during phases of rapid eye movements (phasic REM) often persisted for several minutes.

Fig. 5, showing a typical recording of about 6 min duration during sleep stage II, illustrates FV fluctuations that correlated with cardiovascular and respiratory parameters. K-complexes and arousal initiated the observed alterations in FV, MFV, blood pressure and CO_2. Blood pressure increased in the subsequent cardiac cycles, reaching a maximum after about 5 s, then returned to normal during the next 5—15 s. Increases in MFV did not always occur despite rising blood pressure in stage II but were usually found with greater rises of blood pressure in REM sleep. Blood pressure and MFV curves did not follow a parallel course. Hyperventilation with 2—3 mmHg decrease in CO_2 often persisted for more than 30 s during sleep (Fig. 5). A close correlation was found between decreases in MFV and reduction of CO_2.

In their interpretation of these findings, the authors concluded that the reduction in MFV during NREM sleep is a reflection of reduced cerebral activity and that the later increase during REM sleep corresponds to the active brain processes associated with frequent dream phases. The findings in the first sleep cycle are in agreement with the results of CBF measurements and they confirm the close relationship between cerebral perfusion and brain electrical activity, even during human sleep. Continuous measurement over the entire sleep period, as permitted by TCD, demonstrated that, in the later sleep cycles, the course of MFV development is independent of the NREM sleep stages. This finding, together with the finding of delayed MFV increase after morning awakening, may indicate an uncoupling of brain electrical activity from cerebral perfusion in sleep. This suggests that other mechanisms besides locally active mechanisms may also be involved in the regulation of cerebral perfusion during sleep. The MFV changes after EEG events can be interpreted as a result of cardiovascular and respiratory reactions that occur during the waking reaction. Primary constriction of the cerebral arteries mediated by the activated sympathetic nervous system may also be hypothesized. Quantitative differences in the MFV fluctuations after K-complexes, EEG arousal and movement arousal correspond to the increasing intensity of the associated awakening reactions. The absence of MFV responses and autonomic nervous system responses during the occurrence of sleep spindles support the theory that sleep spindles are sleep-protective events.

Droste et al. [40] studied intracranial pressure B-waves and their association with rhythmic changes in CBF velocity (B-wave equivalents) by TCD monitoring. In overnight TCD recordings in 10 normal young adults, these rhythmic changes in CBF velocity were higher and more frequent during REM sleep and sleep stage I than during other sleep stages. B-wave equivalents also had a longer wavelength during REM sleep. These results support the hypothesis that ICP B-waves are caused by vasodilation.

The MFV dynamics in the right and left MCAs of 12 healthy volunteers (age: 25—34 years) was also studied by Hajak et al. [38] using the same test design. The MFV values measured during NREM sleep were lower than those detected during wakefulness and the values measured during the second and last sleep cycle were significantly lower than in the first sleep cycle. The MFVs in sleep stage II at the end of an NREM sleep period were lower than in the preceding slow-wave sleep. At the onset of REM sleep, the MFV increased rapidly and reached a level significantly higher than in the preceding NREM sleep period. MFV fluctuations occurred in all sleep stages; the most significant fluctuations occurred during REM sleep and the least pronounced fluctuations were observed in slow-wave sleep. In the later sleep cycles, the MFV changes from one sleep stage to another were less pronounced than in the first sleep cycle. During the transition from NREM sleep to wakefulness, the MFV remained lower than in the evening pre-sleep stage. Even after the patients awoke the next morning, it took several minutes for the MFV to reach the value measured during the pre-sleep phase of the previous evening. There were no significant side-to-side differences between the left and right MCA. When changes in the sleep stages were provoked using brief tone pulses or clicks, the EEG frequency rose, but the MFV remained low or even decreased for a few seconds before rising to the earlier level.

CO_2 reactivity during normal sleep

CO_2 retention by holding one's breath or CO_2 stimulation will lead to a vessel dilatation of the cerebral resistance vessels and to a decrease of vascular resistance. Therefore, the relative CO_2 reactivity can be defined as the percentage of FV change per percentage of mmHg CO_2 change. Although the CO_2 test is used as a matter of routine [41,42] and although approximately more than 30% of all cerebral ischemias occur at night time, so far little is known about CO_2 reactivity during normal sleep. We, therefore, tried to perform a CO_2 stimulation during sleep in healthy subjects. During 19 nights the authors [Klingelhöfer J et al., unpublished data] were able to evaluate on 106 CO_2 stimulation periods. In order to be admitted into evaluation, the healthy subjects had

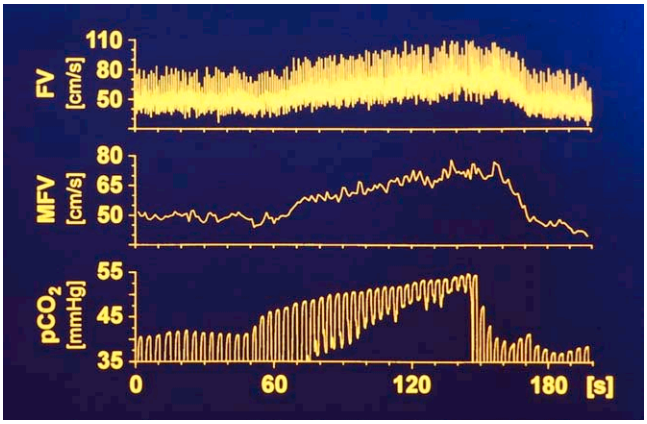

Figure 6 Original recording of the left MCA of a 23-year-old sleeping healthy subject during CO_2 stimulation: original envelope curve, course of MFV, end-expiratory CO_2 concentration. The increase of velocity during CO_2 stimulation is clearly visible (according to [Kingelhöfer J et al., unpublished data]).

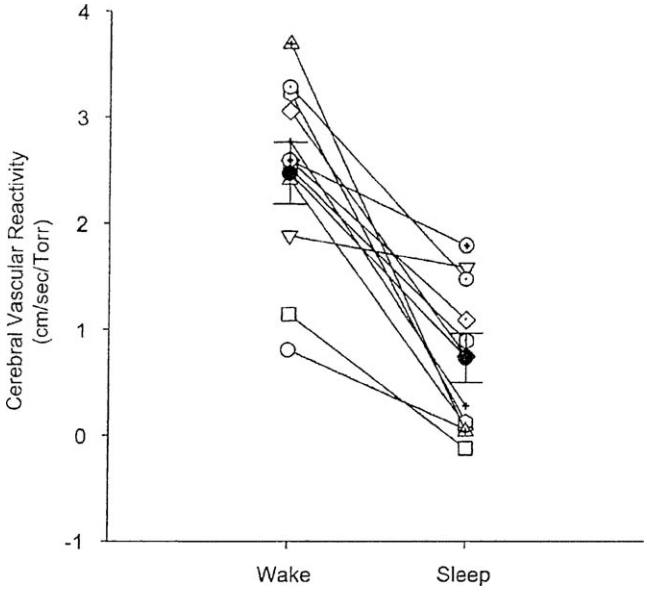

Figure 7 Changes in cerebral vascular reactivity from wake to sleep. The cerebral vascular reactivity to CO_2 from wake to NREM sleep is reduced in each individual. Open symbols: individual values; solid symbols: group mean values (according to [45]).

to reach at least an end-expiratory CO_2 concentration of more than 50 mmHg. They also had to be able to tolerate a CO_2 accumulation period for a minimum of 90 s. Fig. 6 shows an original recording of the left MCA of a 23-year-old subject during sleep. The topmost recording demonstrates the original envelope curve, the middlemost the course of MFV and the lowermost the CO_2 concentration during CO_2 stimulation. The increase of velocity is clearly visible. From these data the authors calculated the relative CO_2 reactivity during different sleep stages for the whole healthy collective. The results show that CO_2 stimulation presented no significant differences in light, slow wave and REM sleep as compared to the waking state in healthy subjects. The authors concluded that cerebrovascular CO_2 reactivity is maintained during normal sleep. In healthy subjects no significant differences as compared to the waking state have been revealed. During CO_2 stimulation in healthy sleepers an increase of mean EEG frequencies in slow wave sleep has been explained as a sign of growing activity within an arousal reaction.

A second study examining CO_2 reactivity in normal sleep was accomplished by Meadows et al. [43,44]. The authors investigated the effects of stable stage III/IV NREM sleep on the CBF response to CO_2 using TCD to determine MCA velocity as an index of CBF [43,45]. Meadows et al. determined that, in normal human subjects, hypercapnic cerebral vascular reactivity is reduced by 70% compared to wakefulness (Fig. 7). The authors concluded that this marked reduction in cerebral vascular reactivity during sleep indicates that the regulation of CBF is significantly altered compared with wakefulness. The functional advantage of such a reduction in the sleep-related cerebral vascular reactivity could not be explained by the authors.

Spontaneous hemodynamic behavior during normal sleep and sleep transitions characterized with near-infrared spectroscopy

In a current study Näsi et al. [46] carried out 30 all-night sleep measurements with combined near-infrared spectroscopy (NIRS) and polysomnography to investigate spontaneous hemodynamic behavior in slow wave sleep compared to light sleep and REM sleep. Their results indicated that slow spontaneous cortical and systemic hemodynamic activity was reduced in slow wave sleep compared to light sleep, REM sleep and wakefulness. This behavior was explained by neuronal synchronization observed in electrophysiological studies of slow wave sleep and a reduction in autonomic nervous system activity. Also, sleep stage transitions were asymmetric, so that the slow wave sleep-to-light sleep and light sleep-to-REM sleep transitions, which are associated with an increase in the complexity of cortical electrophysiological activity, were characterized by more dramatic hemodynamic changes than the opposite transitions. Thus, it appeared to the authors that while the onset of slow wave sleep and termination of REM sleep occurred only as gradual processes over time, the termination of slow wave sleep and onset of REM sleep may be triggered more abruptly by a particular physiological event or condition.

Pathophysiology, cerebral hemodynamics and CBF in sleep apnea syndrome

All sleep apnea syndromes — whether of the central, the obstructive, or the mixed type — are characterized by a disorder of breathing during sleep. For diagnostic purposes, apnea is defined as a cessation of airflow at the nose and mouth lasting at least 10 s [47]. The diagnosis of SAS is made when at least 30 apneic episodes are observed during REM and NREM stages over 7 h of nocturnal sleep. Some of the apneic episodes must appear in a repetitive sequence during NREM sleep [48]. Sleep apnea syndromes have been associated with medical complications such as pulmonary and arterial hypertension, cardiovascular disease, excessive

daytime sleeping, fatigue and morning headache [48,49], as well as increased risk of cerebral infarction [50—54].

The etiology of SAS remains equivocal, but several mechanisms (e.g., instability of central respiratory regulation, reduction in the responsiveness of medullary chemoreceptors and relaxation of the upper airway musculature during sleep) have been proposed as factors in the genesis of nocturnal apnea phases [55—60]. Longobardo et al. [56] believe that an increase in circulation time between receptors in the brainstem respiratory centers and controlled alveolar ventilation is the cause of periodic cessation of breathing. Because apnea is accompanied by hypoxia and hypercapnia and pCO_2 and perivascular pH are major regulatory determinants of CBF and flow velocity, changes in cerebral hemodynamics are to be expected in patients with SAS [35,41,42,61]. These theoretic considerations have been confirmed by a limited number of studies. Meyer et al. [62] performed CBF measurements during daytime sleeping and waking states in 13 patients with narcolepsy and 7 with SAS. In the waking state, brainstem, cerebellar and bihemispheric flow were below normal in both patient groups. After sleep onset, CBF decreased further; maximum changes of regional flow values were seen in brainstem regions, indicating a critically reduced brainstem functional activity during sleep in SAS. Alterations of flow velocities during apnea-associated changes of CO_2 were also reported in obstructive SAS [63].

CBF velocity during sleep apnea syndrome

Now that several studies have shown that transcranial Doppler sonography is a useful method for long-term and on-line monitoring of dynamic changes in cerebral perfusion during sleep, researchers have begun using TCD for the assessment of perfusion changes in pathological sleep conditions. Various studies have been performed to assess cerebral flow velocity changes during nocturnal apneic episodes in patients with SAS. Siebler et al. [64] were the first to observe a cerebral flow velocity increase during nocturnal apneic phases in a patient with obstructive SAS and their findings have since been confirmed by various independent work groups in larger numbers of patients [65—67]. Fischer et al. [34], who compared the MFV changes in SAS patients with those of a comparable control group, observed lower MFV values in SAS patients during wakefulness, NREM sleep and REM sleep than in normals. They therefore concluded that altered cerebral perfusion occurs in SAS patients.

However, a sleep stage-correlated CBF velocity assessment in SAS patients and normal control subjects determined that the course of CBF velocity changes in apneic patients during night sleep were comparable to those observed in healthy control subjects. These findings indicate that the general pattern of cerebral perfusion changes associated with sleep remains preserved in SAS and they contradict the hypothesis of the existence of cerebral hypoperfusion in SAS [65,66]. Klingelhöfer et al. [66] observed MFV increases of 19—219%, reaching a maximum in REM sleep, during apneic episodes in 6 patients with SAS (age: 34—55 years, mean age: 49 years) (Fig. 8). There was also a significant increase in blood pressure (12.5—83.1%) during apneic episodes. A multiple linear regression analysis revealed that the flow velocity increase was not only attributable to the blood pressure increase alone, but was significantly linked to apnea.

Siebler and Nachtmann [67] compared the flow velocity responses during apneic episodes in SAS patients with those observed during arbitrary apnea in healthy control subjects. They detected comparable MFV increases in both groups and concluded that cerebral CO_2 reactivity is preserved in SAS. Klingelhöfer et al. [66] also observed normal CO_2 reactivity ($4.4 \pm 1.2\%$) in SAS patients during wakefulness, but the reactivity values increased significantly during sleep stages I and II and reached a maximum during REM sleep with rises of CO_2 reactivity up to three times the waking values. The authors interpreted the increase in CO_2 reactivity during sleep as hypersensitivity of intracranial CO_2 or pH receptors in SAS patients and attributed this to a possible disorder of the central catecholaminergic and cholinergic systems in SAS. They presume that the marked flow velocity fluctuations during apneic episodes and the associated changes in vessel wall tension place a chronic strain on the cerebral blood vessels, thereby promoting the development of micro- and macroangiopathy. This, among other factors, could be a reason for the increased incidence of cerebral ischemia in patients with SAS.

In addition to the apnea-associated increase in CBF velocity, which most authors attribute to apnea-related hypercapnia [64—67], it is also notable that a rapid normalization of flow velocity occurs at the end of each apneic episode. Hajak et al. [65] demonstrated in 10 patients (mean age: 37 years) that, in addition to its connection with the restoration of breathing and the associated occurrence of normocapnia, this flow velocity reduction is also regularly associated with the occurrence of EEG arousal or movement arousal. Because arousals represent a type of neuronal activation, the authors concluded that this indicates a direct neuronal influence on flow velocity during apneic episodes.

Franklin [68] compared cerebral hemodynamics in obstructive sleep apneas and central sleep apneas. Cerebral and cardiovascular changes display a different pattern during central and obstructive sleep apneas. By means of their study they revealed that the CBF velocity according to TCD increases during an obstructive apnea and decreases after apnea termination concomitant with changes in arterial pressure. Their interpretation of the results was: the changes in cerebral circulation during obstructive apneas could be an immediate effect of rapid changes in blood pressure because cerebral autoregulation is overridden. The opposite pattern was seen during a central apnea, with a decrease in CBF velocity during apnea and an increase after apnea termination (Fig. 9). Changes during obstructive apneas are probably hazardous, with adverse cardiovascular effects including stroke. This may not be the case during central apneas, as Cheyne—Stokes respiration with central apneas is a result of an underlying disorder such as heart failure and stroke and is not a disease entity in itself.

Contrary to every study using TCD during obstructive sleep apnea [65—67,69,70], Netzer et al. reported in 1998 [71] that the CBF velocity declined during 80% of obstructive sleep apneas. They also recorded a decline in CBF velocity during central apnea but only in 14% of central apneas, which contradicts the studies by Franklin et al. [68,72],

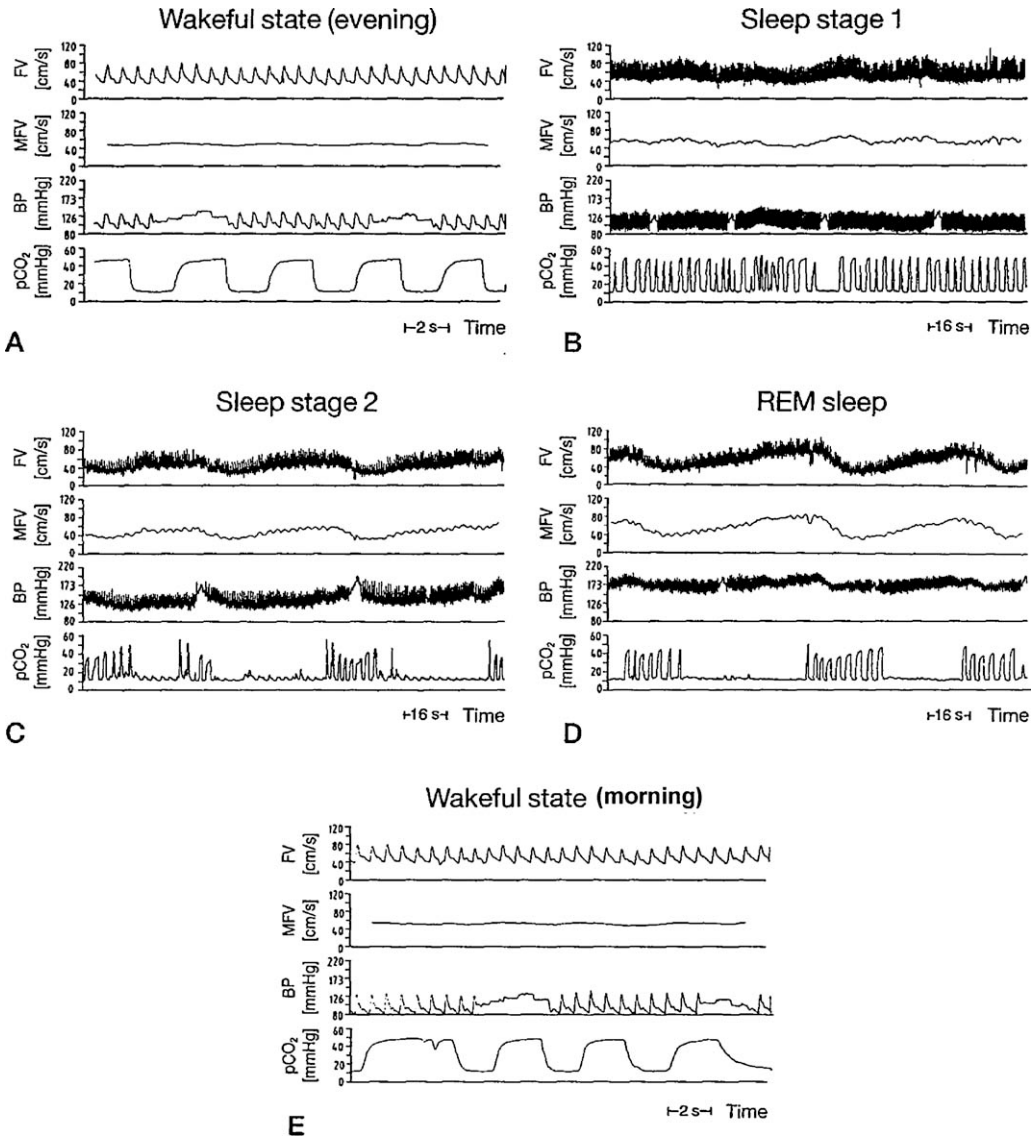

Figure 8 Changes in flow velocity (FV) and mean flow velocity (MVF) of the right middle cerebral artery (MCA), and changes in blood pressure (BP) and end-tidal CO_2 concentration (pCO_2) in a 35-year-old man with severe sleep apnea syndrome (A, E) during the wakeful state and (B—D) during different sleep stages. Due to methodological reasons, the measured rise in pCO_2 is too low after some apneic episodes. In these cases, expiration of air did not take place exclusively through the nose, where the sensor for the end-tidal pCO_2 determination was located. These apneic episodes were excluded from the CO_2 reactivity calculations. FV: flow velocity; BP: blood pressure; MFV: mean flow velocity (according to [66]).

which reports a consistently low CBF velocity during central apnea. The reason for these contradictory results is unclear and the authors do not discuss their findings in comparison with others.

The cerebral vascular reactivity to hypercapnia in patients with obstructive sleep apnea syndrome (OSAS) was investigated by Diomedi et al., 1998 [73] and Placidi et al., 1998 [74] to evaluate the influence of hemodynamic changes caused by OSAS. They studied cerebral vascular reactivity to hypercapnia calculated by means of the breath holding index. The investigation was performed in the early morning, soon after awakening and in the late afternoon. OSAS patients showed significantly lower breath holding index values with respect to controls both in the morning (0.57 vs. 1.40; $p < 0.0001$) and in the afternoon (1.0 vs. 1.51; $p < 0.0001$). In patients, breath holding index values in the afternoon were significantly higher than in the morning. The authors concluded that the data demonstrate a diminished vasodilator reserve in obstructive OSAS patients, particularly evident in the morning. This reduction of the possibility of cerebral vessels to adapt functionally in response to stimulation could be linked to hyposensitivity of cerebrovascular chemoreceptors after the continuous stress caused by nocturnal hypercapnia.

Droste et al. [75] studied the potential effect of continuous positive airway pressure (CPAP) on cerebral perfusion. They investigated 23 patients with OSAS and 16 healthy young adults in the waking state. As compared with

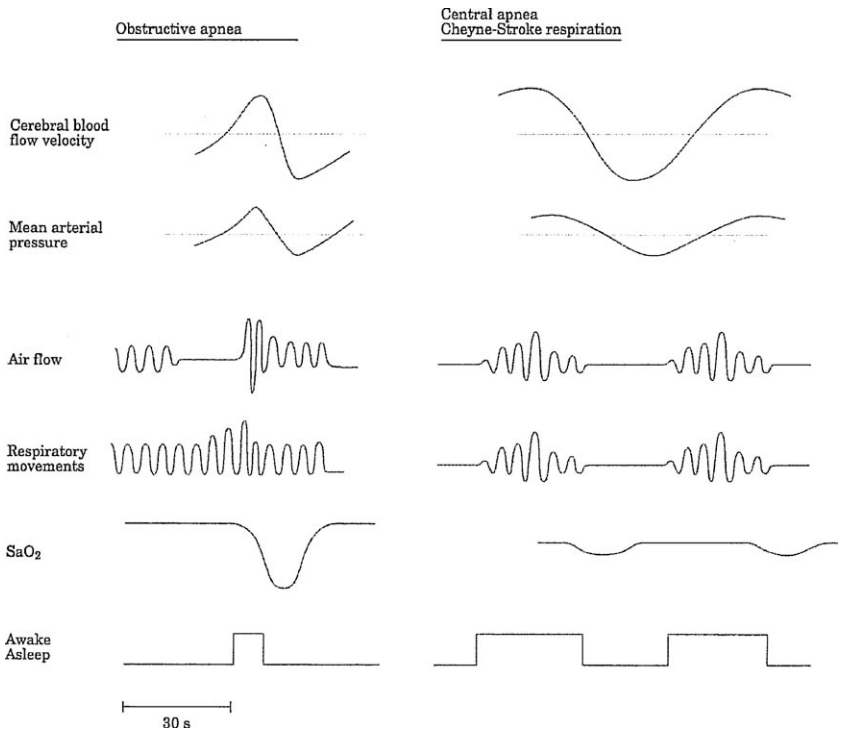

Figure 9 Outline of the hemodynamic pattern during obstructive and central apnea (according to [68]).

normal breathing CBF velocity of MCA and pCO_2 remained unchanged during CPAP. Systolic and diastolic blood pressure increased slightly by 1.2 mmHg and 1.1 mmHg, respectively. Cerebrovascular reactivity did not differ in the two groups. From their findings the authors concluded that nasal CPAP of 9 cmH_2O is a safe treatment with respect to the maintenance of CBF. The study gives further evidence for the autoregulation's capacity to maintain CBF velocity constant during different levels of intrathoracic pressure and different cerebral perfusion pressures.

Another group of scientists [76] analyzed whether increasing levels of CPAP may affect cerebral hemodynamics, assessed by TCD in normal humans. They found that even low levels of CPAP delivered through a mouthpiece in awake, young volunteers led to a decrease in CBF velocity, measured by TCD. This fall in CBF velocity was associated with hypocapnia and with an increase in both cerebrovascular resistance and anxiety due to breathing against positive pressure.

In a recent study Furtner et al. [63] investigated CBF velocity changes and vascular compliance in patients with OSAS using TCD and cerebral pulse transit time. Cerebrovascular reactivity was assessed by calculation of apnea and hypopnea-related CBF velocity changes. Arterial compliance was characterized by cerebral pulse transit time derived from phase difference analysis between ECG and TCD signals. Sleep time was dichotomized into periods with high density of consecutive respiratory events vs. periods with low density of consecutive respiratory events. TCD measurements of CBF velocity showed a regular, undulating pattern with flow minima immediately before apneas or hypopneas and maxima closely after their termination, reciprocally to peripheral O_2 saturation. CBF velocity reactivity was significantly diminished in consecutive respiratory events compared to non-consecutive respiratory event periods. The authors discussed severe disturbances of cerebrovascular reactivity in OSAS patients and interpreted their data as a sign of loss of vasoreactivity and increase of arterial stiffness.

Conclusion

The combined long-term recordings of intracranial flow patterns and polysomnography constitute an important method for evaluating dynamic aspects of brain function and cerebral perfusion during sleep. Numerous studies concerning this scientific field using this technique have contributed to a better understanding of the physiology of the normal sleep and the pathophysiology of sleep disorders as well as that of nocturnal stroke.

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