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Relationship Between Cerebral Blood Flow Velocities and Cerebral Electrical Activity in Sleep

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Summary: The dynamics of cerebral blood flow velocity during sleep were measured in the right and left middle cerebral artery of 12 and 10 healthy male volunteers, respectively. A computer-assisted pulsed (2-MHz) Doppler ultrasonography system was modified for continuous long-term and on-line recording of cerebral hemodynamics in combination with polysomnography. Mean flow velocity (MFV) decreased steadily during deepening nonrapid eye movement (NREM) sleep and increased suddenly during rapid eye movement sleep, corresponding to changes in brain function. However, spontaneous or provoked changes in sleep stage patterns as well as awakenings from NREM sleep were not regularly accompanied by corresponding changes in MFV. Differing values for MFV in subsequent sleep cycles could be shown for several sleep stages. Furthermore, MFV values in sleep stage II at the end of an NREM-sleep period were lower than in preceding slow-wave sleep. After application of short acoustic signals the electroencephalogram frequency rose, indicating an arousal, whereas MFV rapidly decreased for several seconds and then gradually returned to the prior level. These results imply an uncoupling between cerebral electrical activity and cerebral perfusion during sleep and support a dissociation in the activity of central regulatory mechanisms. In light of the proposal that cortical energy consumption can be accounted for by cerebral electrical activity, the concept that cerebral perfusion during sleep is regulated solely by the metabolic rate must be reconsidered. **Key Words:** Cerebral blood flow velocity—Doppler—Electroencephalogram—Sleep—Ultrasonography.

Sleep represents a dynamic physiologic process with cyclic alterations of varying functional states. Rapid eye movement (REM) sleep and four stages of nonrapid eye movement (NREM) sleep show quickly changing patterns in electroencephalographic (EEG) recordings of brain electrical activity. EEG frequencies decrease evenly with deepening NREM sleep and increase to mixed high frequencies during REM sleep (1). Measurements of cerebral blood flow (CBF) and cerebral metabolic rate (CMR) have been used to investigate the underlying functional activity of the human brain. CBF and CMR of glucose and oxygen decreased during NREM sleep stages I and II and reached minimum values during slow-wave sleep (SWS) stages III and IV when compared with wakefulness (2–13). In contrast, CBF and CMR rose to nearly waking values during REM sleep (2,6,7,14) or even exceeded levels obtained during wakefulness (3,5,8–10,12,13). Serial measurements of CBF during sleep have recorded different subtypes of flow patterns for stage II sleep, dependent on whether CBF measurements followed sleep onset or SWS (10,12). These results raise the question of whether the dynamic feature of sleep stage-related EEG patterns has influence on cerebral perfusion. However, radioisotope tracer techniques, which have been used to determine CBF and CMR during human sleep, are limited to very few recordings per sleep period because of the high expense and the long half-life of the applied tracer substances (9,15–18). Methods capable of continuous registration of the time course of cerebral perfusion are, therefore, of particular importance. Transcranial Doppler ultrasonography (TCD) is an established method for noninvasive monitoring of the direction and velocity of blood flow in large basal intracranial arteries in a time course of seconds (19,20). In the present study, a computer-assisted TCD system was modified for continuous long-term

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and on-line recording of cerebral hemodynamics during human sleep.

MATERIALS AND METHODS

Subjects

The main study included 18 subjects. Six subjects and two recordings of two subjects were excluded from data analysis because of movement artifacts with subsequent probe dislocation. Recordings of the left and right middle cerebral artery (MCA) of 12 subjects aged 25–34 years (mean age 28.2 years) were used for data analysis. All subjects were healthy and had normal flow conditions in the cranial arterial system as evaluated by clinical Doppler control determination. Each underwent two investigation nights following one night recording to adapt to technical conditions. Recordings were performed simultaneously with polysomnography and TCD during spontaneous sleep over the whole night period.

Sleep evaluation

Recordings of EEG, right and left electrooculogram, submental electromyogram, electrocardiogram, nasal and oral airflow, abdominal and thoracic respiratory movements, and electromyogram of the anterior tibialis muscle were registered on a polysomnograph (Nihon Kohden, Japan) and stored on a personal computer system. Polysomnography as well as manual evaluation of sleep parameters followed standard criteria (1).

Low-frequency impulse noise with peak levels of 30 to 70 dB was presented at intervals of 30 or 60 seconds to provoke changes in depth of sleep. This was done in subjects not being used for stage-correlated TCD statistics.

TCD evaluation

A computer-assisted, 2-MHz pulsed Doppler system (TC 2-64B, EME, FRG) was used to investigate the MCA. The Doppler instrument incorporated a 64-point fast Fourier transformation to analyze the received velocity spectra. The AD-converted envelope curve of the Doppler frequency spectrum was stored on-line on a personal computer. The mean flow velocity (MFV) was calculated in the course of one cardiac cycle on the basis of the original registration using a computer-assisted integration procedure.

The TCD examination techniques have been described in detail elsewhere (19–21). In this study, the MCA was insonated through the temporal bone window. The MCA segment with the maximal reflected signal was recorded. The probe was mechanically locked in position with a specially developed probe holder after detection and manual optimization of the Doppler signal. Attachment to the subject's head was maintained with elastic bands and tape in a manner that did not interfere with additional fixation of polysomnographic registration sensors. For each nocturnal study, the TCD measurement began during relaxed wakefulness with closed eyes in a darkened room, when the EEG showed continuous alpha frequency. The Doppler examination continued after morning awakening to rule out possible probe dislocation. Only those recordings of the left MCA were used for data analysis if the MFV after morning awakening did not differ significantly from waking values preceding sleep onset. During recordings of the right MCA, the probe was removed in six subjects shortly after morning awakening and before the increase of MFV to waking values of the preceding evening. Consequently, the averaged MFV value of the right MCA during morning awakening was below the waking level of the previous evening and is not included in our results (Table 1). Nevertheless, the subjects were used for statistical evaluation of sleep stage-related MFV values, because MFV in corresponding sleep stages of all six probands differed less than 1 SD.

Data analysis

The associated TCD sleep evaluation was performed by computer adaption of cerebral blood flow velocity (CBFV) measurements to computerized polysomnographic recorded data. MFV values were estimated in intervals of 30 seconds from the computerized data, in relation to corresponding sleep epochs. Sleep-epoch correlated MFV values were averaged (mean ± SD) for sleep stages Ia, IIa, IIIa and IVa during deepening periods of sleep following sleep onset or REM sleep periods, for sleep stages IIb, IIIb and IVb in the middle of NREM sleep cycles (period from beginning of NREM sleep to end of the following REM period), for sleep stage IIc preceding REM periods and for REM sleep. Averaged MFV values were determined for sleep stages in the first, second and last NREM sleep cycle. Relative intraindividual changes of MFV in relation to wake values were used for statistical evaluation. Influences of sleep cycle (first, second or last sleep cycle), type of sleep (NREM or REM sleep) and side of probe location (left or right MCA) on MFV were analyzed by multifactor analysis of variance (ANOVA). Differences between MFV values in corresponding sleep stages of different sleep cycles were calculated separately by one-way ANOVA for left and right MCA. If the overall F-value was significant, subsequent post hoc analysis was performed using the Newman-Keuls test for multiple comparisons. The test was performed for signif-

TABLE 1. *Relative mean flow velocity (rMFV) in the right (n = 12) and left (n = 10) middle cerebral artery during different sleep stages in healthy male volunteers (mean age 28.2 years)*

	A	B	C		D	
Sleep stage	**Right MCA** rMFV (%) (mean ± SD)	**Left MCA** rMFV (%) (mean ± SD)	Comparison to corresponding sleep-stages in the first sleep cycle **Right MCA**	**Left MCA**	Comparison to preceeding sleep-stage in the same cycle **Right MCA**	**Left MCA**
W	100	100				
Ia	99.7 ± 2.4	101.0 ± 2.5			N.S.	N.S.
IIa	94.3 ± 2.5	94.7 ± 2.9			**	**
IIIa	91.3 ± 3.9	88.5 ± 3.0			N.S.	**
IVa	86.4 ± 3.8	84.3 ± 4.8			*	N.S.
IIc	78.8 ± 3.9	81.1 ± 6.5			**	N.S.
REM	89.5 ± 4.1	90.4 ± 4.7			**	*
IIa	78.1 ± 3.5	79.3 ± 6.1	**	**		
IVa	77.5 ± 4.6	78.6 ± 3.6	*	N.S.	N.S.	N.S.
IIb	82.7 ± 6.7	85.5 ± 6.2	**	*	N.S.	N.S.
IIIb	81.9 ± 5.8	82.7 ± 5.1	**	N.S.	N.S.	N.S.
IVb	81.7 ± 4.9	80.8 ± 6.1	N.S.	N.S.	N.S.	N.S.
IIc	79.4 ± 4.5	77.1 ± 2.9	N.S.	N.S.	N.S.	N.S.
REM	93.3 ± 6.2	86.3 ± 6.8	N.S.	N.S.	**	*
IIa	78.4 ± 5.1	78.2 ± 4.6	**	**		
IVa	77.4 ± 3.9	78.3 ± 4.7	*	N.S.	N.S.	N.S.
IIb	84.4 ± 7.2	81.3 ± 7.6	**	**	N.S.	N.S.
IIIb	81.8 ± 6.8	80.6 ± 7,5	**	N.S.	N.S.	N.S.
IVb	80.5 ± 6.9	77.8 ± 4.9	N.S.	N.S.	N.S.	N.S.
IIc	76.7 ± 4.6	76.6 ± 5.7	N.S.	N.S.	N.S.	N.S.
REM	96.3 ± 5.8	92.0 ± 7.5	*	N.S.	**	**
IIa	82.8 ± 3.6	78.4 ± 5.7	**	**		
W	93.2 ± 7.5	99.8 ± 5.4	see text	N.S.	**	**

Significance of differences: NS not significant; * $p<0.05$; ** $p<0.01$

icance levels $p \leq 0.05$ and $p \leq 0.01$. Comparison of MFV values in subsequent sleep stages was performed for each sleep cycle by a Bonferroni adjusted *t* test.

RESULTS

Each volunteer exhibited a steadily progressive reduction in MFV as compared to wake values during deepening NREM sleep in the first sleep cycle (Figs. 1a and 2a). MFV continued to decrease in the course of sleep stage IVa following sleep onset (Figs. 1b and 2b). In spite of a subsequent rise in depth of sleep from sleep stage IVa to sleep stage IIc preceding the first REM period, MFV continued to decrease (Fig. 2a) and was lower in sleep stage IIc than in preceding sleep stage IVa (Table 1, Fig. 3).

From the first to the following sleep cycles MFV mean levels during NREM sleep remained low. MFV values were significantly ($p \leq 0.01$) below wake values during sleep stages II to IV in the second and last sleep cycle (Fig. 3, Table 1). Averaged MFV values during NREM sleep in the second and last sleep cycle were significantly lower than in the first sleep cycle (first sleep cycle: 90.1% ± 6.5%; second sleep cycle: 80.8% ± 6.4%; last sleep cycle: 79.8% ± 6.5%; $p \leq 0.001$; multifactor ANOVA). Furthermore, the MFV in sleep stages during the second and last sleep cycle was lower than MFV in corresponding sleep stages during deepening sleep in the first sleep cycle (Table 1, Fig. 3). Initiation of REM sleep was accompanied by sudden increases in MFV compared with NREM sleep within several seconds (Figs. 1f, h and i; 2f, g and j). MFV values were significantly higher than in NREM sleep (REM sleep: 91.5% ± 6.4% ± 6.4%; NREM sleep: 83.6% ± 7.9%; $p \leq 0.001$). They rose notably above values of preceding sleep stages IVa, IVb and IIc, tending to increase from the first to later REM periods, attaining values that did not differ significantly from

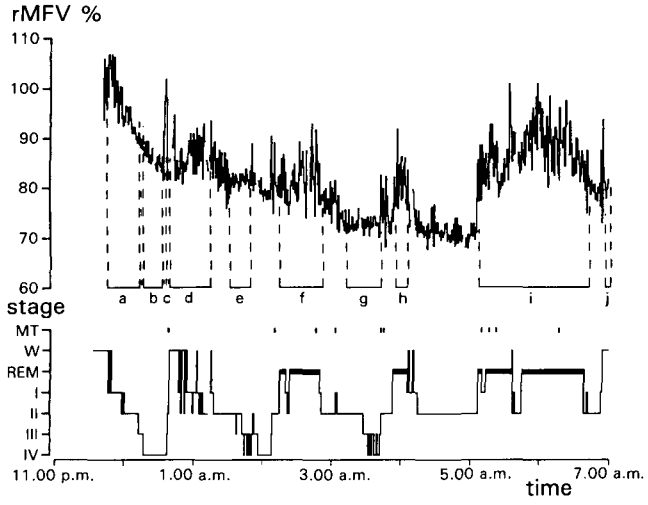

FIG. 1. Relative mean flow velocity (rMFV) in the right middle cerebral artery and sleep profile of one normal volunteer. a) Progressive MFV reduction during NREM sleep; b) continuous MFV reduction during SWS; c, j) movement artifact; d) reduced MFV during nighttime awakening; e, g) constant mean level of MFV during changes from sleep stage II to SWS; f, h, i) rapid increase in MFV during REM sleep.

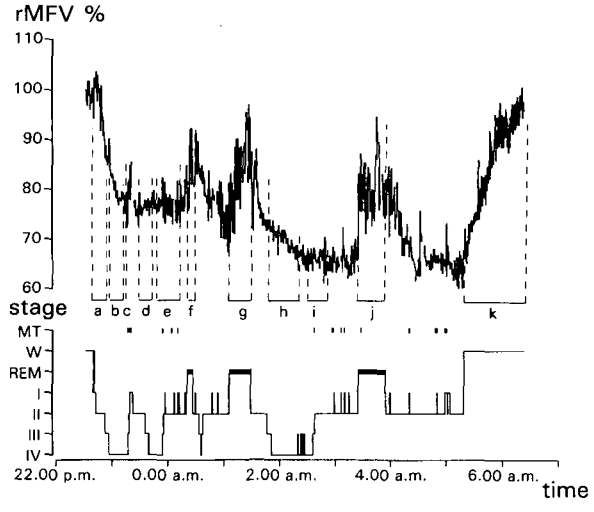

FIG. 2. Relative mean flow velocity (rMFV) in the right middle cerebral artery and sleep profile of one normal volunteer. a) Progressive MFV reduction during NREM sleep; b, h) continuous MFV reduction during SWS; c) movement artifact; d) constant mean level of MFV during changes from sleep stage II to SWS; e, i) constant mean level of MFV during changes from SWS to sleep stage II; f, g, j) rapid increase in MFV during REM sleep; k) delayed increase in MFV after morning awakening.

comparable waking levels (Table 1, Fig. 3). There were no significant side differences between left and right MCA. Rapid fluctuations in MFV were superimposed on the mean MFV level during all sleep stages. The time course ranged from seconds to minutes. Slight alterations of MFV appeared during SWS, and moderate changes were seen during sleep stages I and II, whereas large fluctuations were frequent during REM sleep. REM sleep-correlated fluctuations were pronounced during the last REM period. Even in night profiles of 30-second samples of MFV, the fast-alternating MFV was seen (Figs. 1f, h and i; 2f, g and j).

In regard to the dynamic pattern of MFV, comparison of MFV values during different sleep cycles showed that sleep stage changes during NREM sleep caused fewer changes in MFV in later sleep cycles than in the first sleep cycle (Table 1). Changes in the mean level of MFV disappeared completely in several volunteers, in spite of distinct changes in sleep stage patterns (Figs. 1e and g; 2d, e and i). MFV remained lower than waking values preceding sleep onset during changes from NREM sleep into alpha frequency wakefulness (Fig. 1d). Upon awakening in the morning, patients required several minutes to half an hour to reach MFV values corresponding to the waking state of the previous evening (Fig. 2k).

Series of short acoustic signals were also used to provoke changes in sleep stage patterns. They accelerated the EEG frequency and changed the depth of sleep gradually from sleep stage IV to sleep stage II in less than 3 minutes. Flow velocity and MFV remained low or rose for a short time but returned quickly to the preceding level in spite of the corresponding change in sleep stages (Fig. 4). After application of clicks during sleep stage II, the EEG frequency rose, indicating an arousal, whereas CBFV and MFV rapidly decreased for several seconds and then gradually returned to the prior level (Fig. 5).

DISCUSSION

Transcranial Doppler ultrasonography provided a noninvasive method for determining rapid alterations of blood flow velocities in the large basal intracranial arteries during sleep (22–25). The present technique offers important advantages compared with other techniques commonly used for measuring cerebral perfusion during human sleep, such as on-line noninvasive monitoring, high temporal resolution for measuring rapid alterations of cerebral perfusion, continuous long-term recording during an entire sleep period and simultaneous registration of associated variables.

Relationship between CBFV and CBF

Transcranial Doppler ultrasonography measurements during sleep raise the question of whether this technique records volume flow when measuring flow velocity. In this study, relative changes in CBFV were assumed to be changes in cerebral perfusion. The validity of this assumption was based on the hypothesis of a linear relationship between blood flow velocity and blood volume within the large basal arteries in normal volunteers. This presupposes that changes in

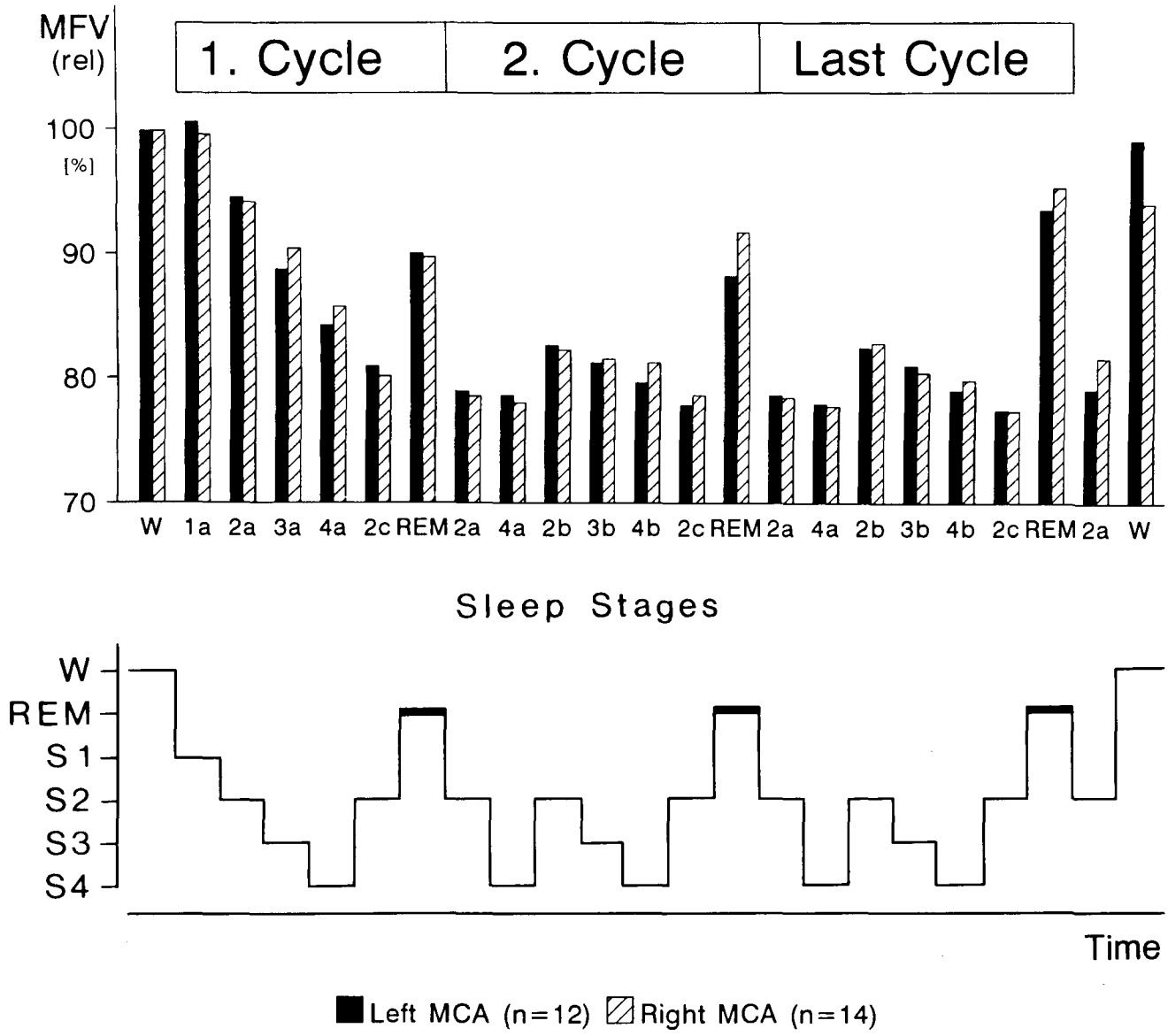

FIG. 3. Relative mean flow velocity (rMFV) in the right (n = 12) and left (n = 10) middle cerebral artery during different sleep stages in healthy male volunteers

the cerebral vascular bed mainly occur in small cortical vessels in the brain parenchyma. This assumption is supported by the findings of very stiff walls of large intracranial human arteries (26). Accordingly it was demonstrated that the caliber of large intracranial arteries and of arterioles with diameters of more than 322 μm remains constant or changes only minimally in response to changes of the arterial blood pressure (27) or partial pressure of carbon dioxide (pCO_2) (28). Furthermore, a good relationship between flow velocity and flow volume has been shown for the MCA (29) and the internal carotid artery (30) upon alterations of blood pressure. The main autoregulatory activity, therefore, has been located in the small brain vessels (27,31,32). In particular, recent studies have not only failed to find significant changes in the human MCA cross-sectional area by analyzing the Doppler signal power during changes in arterial blood pressure (33), but also have demonstrated that changes in the MCA diameter did not invalidate the use of CBFV measurements for the study of cerebral autoregulatory dynamics (34). These data suggest that diameter changes in large basal arteries are negligible for various conditions such as hypercapnia or moderate changes in arterial blood pressure in normal subjects. Although under physiological conditions the cerebral perfusion is as a rule affected only for 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.

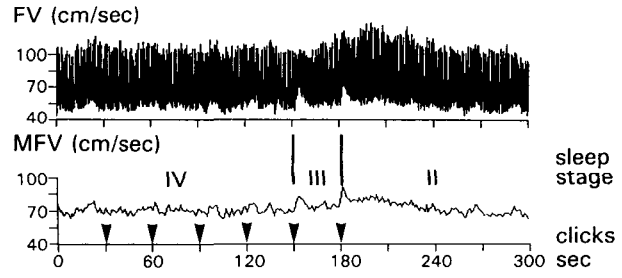

FIG. 4. Effect of acoustic arousal signals (clicks) on flow velocity (FV) and mean flow velocity (MFV) during sleep stages III and IV in one normal volunteer.

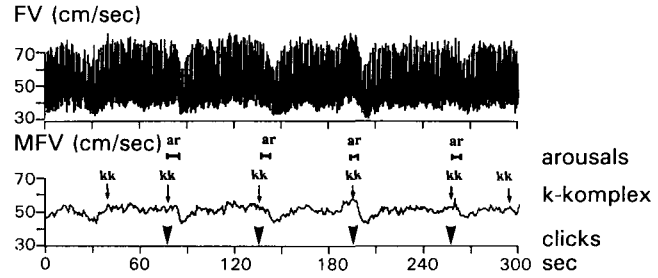

FIG. 5. Effect of acoustic arousal signals (clicks) on flow velocity (FV) and mean flow velocity (MFV) during sleep stage II in one normal volunteer.

Nevertheless, validation of TCD with ^{133}xenon inhalation technique showed a correlation coefficient of 0.849 for MCA velocity reactivity in response to hypercapnia when compared with mean hemispheric CBF (35). One has to consider that in some studies the correlation between absolute values of CBFV and CBF was poor (35,36) or existed only at low flows (37). Some authors improved the correlation for absolute flow parameters by normalizing to a standard pCO_2 (38) or considering the patient's age and hematocrit (39). It must be conceded that absolute CBFV values appear to be insufficient for describing CBF. Nevertheless, it can be assumed that relative changes in CBFV appear to be a reliable parameter for measuring dynamics of cerebral perfusion in normal human sleep.

Coupling of CBFV, NREM and REM sleep stage patterns

The whole night sleep profile of MFV showed a dynamic pattern of brain perfusion during human sleep. An arched course of MFV was modulated by changes of MFV corresponding to changes in depth of sleep. A fall in MFV of 6% below the waking level during sleep stage IIa following sleep onset and at the most of 23% during sleep stage II in the subsequent sleep periods corresponds to reported decreases in global levels of CBF and CMR of 5–15% during sleep stages I and II (4,10,12) and 13–23% during nonspecified NREM sleep (2,5). Decreases in MFV of 16–22% during sleep stage IV were in the range of decreases in CBF and CMR of 14–44% during SWS (3,6–8,10,12,13). Increases in MFV during REM sleep to 4–10% below wake values generally agree with reported levels of CBF and CMR from 10% below to 41% above levels obtained during wakefulness (2–8,10,12,14).

Corresponding changes between EEG-indicated depth of sleep and MFV support the concept of a functional association of brain electrical activity, brain perfusion and brain metabolic action (40–44). The hypothesis that each of these parameters may reflect neuronal activity had been widely accepted (43–46). A variety of studies performed during the wake state confirmed a close relationship between cerebral perfusion, cerebral metabolism and brain activity. CBF and CMR have been shown to increase in corresponding brain structures during motor activation (9), cognitive activity (47,48) and sensory stimulation (49–53), whereas lowest rates of CBF and CMR were observed during resting state (9,47,48). TCD measurements of dynamic reactions of CBFV also revealed increases in flow velocity during cognitive tasks and visual stimuli (54,55).

Together these data constitute, although in part indirectly, evidence that NREM sleep reflects a resting state of the brain (10) with reduced neuronal activity (2), decreased synaptic transmission (8) and depressed energy metabolism (5). Consequently the results support the assumption that REM sleep may be attributed to an activation of brain function (2,10) with increased neuronal activity (56), resumption of synaptic events (8) and higher metabolism (5). In anesthetized rabbits spontaneous shifts from high-voltage to low-voltage EEG were accompanied by increases in CBF and CMR of oxygen similar to MFV increases during desynchronized low-voltage EEG in REM sleep. Administration of the cholinergic blocker scopolamine rapidly abolished the increase in CBF. The results had been interpreted as evidence that cholinergic mechanisms mediate increases in CBF and decreases in EEG amplitude (57). Increases in MFV during REM sleep may, therefore, be due to cholinergic stimulation, which is in good agreement with the reciprocal interaction model of sleep regulation (58,59).

Uncoupling of CBFV and cerebral electrical activity

Because TCD offers the unique opportunity to continuously record CBFV throughout the entire sleep period, it was possible to elucidate sleep stage-related alterations of MFV and their dependence on a given sleep stage and sleep cycle. Differing values for sleep stage-related MFV in subsequent sleep cycles and lower MFV values in light sleep stage II than in preceding sleep stage IV indicate that a tight coupling between

CBFV and sleep stage-related EEG frequency is only present during increasing sleep depth in the first sleep cycle. Diminished or absent alterations in MFV during transitions between NREM sleep stages in later sleep cycles, constant MFV levels during provoked sleep stage changes, rapid decreases in MFV during EEG arousals and delayed increases in MFV after awakening at night and in the morning make it increasingly clear than an altered state of consciousness is not regularly accompanied by simultaneous changes in cerebral perfusion. These findings are in agreement with observations during serial measurement of CBF that showed higher flow patterns during sleep stage II following sleep onset compared with CBF values after transition from SWS to sleep stage II and reduced CBF values after awakening from SWS (10,12). The sleep stage-independent bell curve of the mean MFV level during the night supports the hypothesis of an uncoupling of cerebral perfusion and brain electrical activity during sleep.

Our current knowledge concerning brain electrical activity suggests that EEG-indicated changes of functional activity represent the cerebral synaptic activity, which reflects the state of consciousness. Consequently, EEG parameters are used for the definition of sleep. In this continuum, the observed uncoupling of MFV and sleep patterns provides evidence that measurements of the cerebral perfusion do not regularly reflect neuronal processes responsible for the generation of sleep. Furthermore, the uncoupling phenomenon provides a new understanding of the brain's mode of regulating CBF by mechanisms other than oxidative metabolic ones. Concepts concerning the cerebrovascular regulatory action are still controversial (60). It is a well-established idea that increased neuronal metabolism causes an accumulation of vasoactive catabolites, which decrease vascular resistance and thereby increase CBF (41,43). On the other hand, neurotransmitters, as well as central neurogenic control mechanisms localized in the brainstem, may directly influence the tone of cerebral vessels (41,60,61). In this context, the delay of change in MFV during changes in NREM sleep patterns can be interpreted as a persistence of activity of central neuronal mechanisms regulating cerebral perfusion that is independent of the local coupling between flow and oxidative metabolism. Abolition of regional differences in the mean EEG frequency and the CBF during NREM sleep that can be found in the waking state (62) are indicative of such a displacement from a local to a global regulation. This hypothesis is supported by a diffuse reduction in CBF in all cerebral regions during SWS (12).

The possibility of central CBF-regulating structures arises from animal experiments. Destruction of the nucleus coeruleus blocked the increase in CBF in raised neuronal activity (63). This nuclear area is known for reduced activity during sleep (64). There are also indications from autoradiographic studies that stimulation of the dorsal medullary reticular formation is closely coupled to metabolism in certain cortical regions (65). Furthermore, it was demonstrated that electrical stimulation of the dorsal medullary reticular formation caused an increase in regional CBF that was not coupled to EEG activation. This increase could neither be attributed to an affect secondary to systemic factors, such as blood gases or arterial blood pressure, nor to a global metabolic stimulation, because stimulation at adjacent sites in the brainstem failed to alter CBF. In addition, transection experiments showed that the blood flow increase was the result of excitation of pathways intrinsic to the brain (66). The existence of neuronal networks emanating from the basal forebrain and the fastigial nucleus of the cerebellum, which produce increases in CBF without accompanying increases in CMR, has already been established (67). One interpretation of sleep regulation suggests that complex interactions in the pontine and bulbar reticular formation control sleep as well as other physiological processes, including CBF (68). Rhythmically firing neurons in interpenetrating neuronal fields (58) may be loci mediating these complex interactions. If indeed the basic rhythmicity of a network of neurons accounts for many sleep phenomena, the uncoupling of cerebral perfusion and cerebral electrical activity reflects a dissociation in the activity of central regulatory mechanisms during parts of the sleep process.

The abrupt increase in MFV with the beginning of REM sleep and fast alterations in MFV during REM sleep point to a dramatic change in functional regulation, which is supported by distinct regional differences in CBF and CMR during this sleep period (3,5,6,10,11,13–15). In the context of the studies reviewed, the results of the present examination indicate that the interaction of the mechanisms involved in blood flow regulation are organized differently for the waking state, NREM sleep and REM sleep.

CONCLUSIONS

The presented dynamic feature of CBFV obtained by TCD indicates that changes in the EEG-defined state of sleep are not regularly accompanied by changes in cerebral perfusion. These results do not completely contradict reports finding reduced levels of CBF during NREM sleep and elevated levels during REM sleep. However, in contrast to previous studies, this paper stresses an uncoupling of cerebral electrical activity and cerebral perfusion during human sleep. This could reflect the impact of central neurogenic control mechanisms on the regulation of cerebral perfusion as well as a dissociation in the activity of central regulatory

centers during sleep. Low cerebral perfusion values during the transition from NREM sleep to wakefulness are a possible consequence of this phenomenon.

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