Sleep, 19(3):248–254

EEG Frequency Changes During Sleep Apneas

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Summary: To study the effect of transient, apnea-induced hypoxemia on electrocortical activity, five patients with severe obstructive sleep apnea syndrome (OSAS) were investigated during nocturnal sleep. Polysomnographic and simultaneous digitized electro encephalographic (EEG) recordings for topographic and compressed spectral array analysis were made. The EEG recordings were timed exactly to respiratory events. During nonrapid eye movement (NREM) apneas, delta band amplitude increased, starting on average 13 seconds after the apnea onset. Average differences were 268% between initial and maximal values and 202% between initial and final values. In contrast, significant increases in delta amplitudes between the onset and end of REM apneas did not occur, although some caused deep oxygen desaturations. Changes in delta activity were not correlated to NREM apnea duration or degree of desaturation. These results indicate that the increased delta activity during NREM apneas may not be caused by arterial hypoxemia. It could instead be due to either an arousal mechanism, since arousals may be preceded by slow waves in EEG, or to a breakthrough of slow-wave-sleep activity. The sleep disturbance in severe OSAS may create such a propensity for slow-wave sleep that stages pass much more rapidly than in normal persons. **Key words:** EEG topography—Frequency analysis—Cerebral hypoxemia—Oximetry—Sleep apneas.

Even as early as 1925, rapid electroencephalographic (EEG) changes in response to cerebral anoxia were reported (1). Since then, the typical sequence of changes has been firmly established: 1) desynchronization, 2) appearance of 1–3-Hz waves of high amplitude and 3) after about 5 minutes of anoxia, electrical silence (2). There is also a strong correlation between the dominant EEG frequency and cerebral oxygen uptake (3). These investigations, however, were performed on awake subjects during inhalation of oxygen-poor or oxygen-free gas mixtures during ischemic anoxia or asphyxic anoxia. Very little is known about the influence of transient hypoxic events during sleep, such as those induced by obstructive sleep apneas (OSAs), on the EEG. OSA syndrome (OSAS) is associated with a variety of cerebral symptoms, such as excessive daytime sleepiness, impaired memory function, concentration difficulties, irritability and depression. The degree of excessive daytime sleepiness has been reported to be correlated not only with the number of apnea-induced arousals but also with indices of hypoxemia (4, 5). Since numerous and deep oxygen desaturations (levels sometimes below 50%) may occur in patients with severe OSAS, the question is raised as to the role of cerebral hypoxemia in the development of the above-mentioned symptoms.

It has previously been reported from visual analysis of polysomnographic recordings that apneas may be associated with the appearance of delta waves in the EEG. Krieger and Kurtz (6) described bursts of delta activity with frontotemporal dominance occurring toward the end of apneas in sleep stages 1 and 2 but not in rapid eye movement (REM) sleep. Guilleminault et al. (7) indicated that delta waves appeared at least 15 seconds after the onset of apnea.

The present investigation was performed to study whether EEG changes could be correlated to the severity of sleep apneas in terms of duration or accompanying oxygen desaturations. Digitized EEGs allowed detailed frequency analysis, and EEG topography (8) was employed to investigate the occurrence of regional differences in activity. Topographic recordings of sleep stages have previously been shown to be stable and reproducible during naps in normal subjects (9). Digitized EEG recordings were made simultaneously with conventional polysomnograms to enable exact coupling of respiratory events to the computed EEG signals.

PATIENTS AND METHODS

Five patients, three men and two women with a mean age of 53 (39–61) years, were examined. They

Accepted for publication December 1995.
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all suffered from heavy snoring and severe, excessive daytime sleepiness. Each had normal routine EEG recordings, blood gases and spirometric tests while awake. None had any history of central nervous system affliction or pulmonary or neuromuscular disease. On whole-night polysomnographic recordings, their mean respiratory disturbance index (RDI) was 61 (22–76), their mean oxygen desaturation index (ODI, total number of desaturations >3% divided by sleeping time) was 68 (36–110) and the mean lowest recorded SaO_2 level was 51 (20–73).

Nocturnal polysomnographic recordings were made on a Nihon Kohden 4321. Times of "lights out" and "lights on" were consistent (11 p.m. and 6 a.m.). The recordings included EEGs, electrooculograms (EOGs), chin electromyograms (EMGs), electrocardiograms (ECGs), respiratory movements, airflow and SaO_2 (Biox 3740, ear probe). During periods of sleep apneas, 16 channels of EEG were recorded simultaneously for frequency analysis using software version 2.31 on a Biologic Brain Atlas model 171, a microcomputer with internal amplifiers. EEG electrodes were in positions F_7, F_3, F_4, F_8, T_3, C_3, C_z, C_4, T_4, T_5, P_3, P_z, P_4, T_6, O_1 and O_2 according to the international 10-20 system. Activity corresponding to positions F_{p1}, F_{p2}, F_{pz} and O_z was interpolated by the software. Linked mandibles were used as reference. Low- and high-frequency filters were set at 1.0 and 30 Hz. Sampling rate was 128 Hz. Electrode impedances were kept below 5,000 ohm. The maximum length of a recording file was 12 minutes. Longer recordings were avoided because of anticipated difficulties with the exact timing of events to the polysomnogram. Start and stop times of Brain Atlas recordings were marked simultaneously in the polysomnogram, and the two types of recordings were time-locked using recognition of common wave form elements. Samples were chosen from several periods of the night.

Each section containing an apnea/hypopnea associated with an oxygen desaturation >3% was subjected to a Fourier transform (FFT) in 2-second epochs, starting 2 seconds before apnea onset and continuing another 4 seconds after the apnea terminated. Color-coded topographic maps of the scalp were made to show the distribution of amplitudes within the frequency bands of 0.5–3.5 Hz (delta), 4–7.5 Hz (theta), 8–11.5 Hz (alpha) and 12–15.5 Hz (beta). With the aid of a digitizer, the circumference of each area with a certain color (representing a certain amplitude) within a map was measured, and specially designed software gave the exact percentage of this area in relation to the total map area. The average amplitude of the investigated frequency band for each map was then calculated. Only epochs free from artifacts or K complexes were analyzed. Artifact rejection (from profound EOG or EMG changes due to eye movements or body movements) was done manually with visual analysis of both the polysomnogram and the raw EEG signal in the Brain Atlas. Since artifacts of various types were, as a rule, present during the postapneic phase, statistical comparisons were made at three points in time only: A) the 2-second epoch immediately after the onset of apnea (initial value), B) an artifact-free epoch during the apnea with the highest recorded delta amplitude (maximal value) and C) the 2-second epoch immediately preceding apnea termination (final value). B and C could be the same. If artifacts occurred at the onset or termination of epochs, the whole apnea was excluded from analysis. Compressed spectral array (CSA) analysis (10) was also employed to give an overview of activity changes during the entire length of the files. Using FFT, CSA displays the processed EEG data as a function of frequency and amplitude over time.

In three patients, an additional nocturnal recording, as described above, was made after 3 weeks of successful nasal continuous positive airway pressure (CPAP) treatment. The ODI was 0 in all cases. Each sleep stage was recorded for 9–15 minutes. Samples from baseline and treatment conditions were taken from the same nocturnal time segments. This procedure allowed within-subject comparisons of EEG frequency patterns before and during treatment (i.e. with unobstructed breathing). The remaining two patients interrupted their CPAP treatment before the required 3 weeks had passed.

Sleep stages were scored according to Rechtschaffen and Kales (11). Arousal was defined as the abrupt appearance of alpha or beta activity in the EEG for 3–10 seconds, accompanied by increased EMG activity. Apneas were scored according to the Stanford criteria (12).

RESULTS

One patient never entered REM sleep. None of the patients exhibited slow-wave-sleep (stages 3–4) apneas; three patients with continous, repetitive apneas never entered sleep stages 3 and 4, and two with lower RDIs had no apneas in those stages.

A total of 81 respiratory events were analyzed; 70 were apneas, and 11 were obstructive hypopneas with oxygen desaturations of 4% or more. Of the 70 apneas, three were central (diaphragmatic), seven were mixed and 60 were obstructive. Fifty-three events occurred during sleep stages 1 and 2, and 28 occurred during REM sleep. All central events were recorded in REM sleep. The non-REM (NREM) apneas/hypopneas had a mean duration of 28 seconds (range 12–66 seconds) with a mean desaturation of 8% (range 4–29%). REM

sleep apneas/hypopneas had a mean duration of 27 seconds (range 11–64 seconds) with a mean desaturation of 11% (range 4–24%).

NREM respiratory events

All patients exhibited a uniform pattern of EEG changes. Delta amplitudes progressively increased during all recorded respiratory events except one, beginning on average 13 seconds (range 6–24 seconds) after onset, when desaturations usually could not yet be recorded. At the end of the episode, delta amplitudes usually decreased again. As a rule, the EEG was obscured by movement artifacts at the beginning of post-apneic hyperventilation. The increase in delta amplitudes could be partly attributed to a diffuse increase in background EEG activity, but major increases were due to the occurrence of discrete delta waves.

Decreased delta amplitudes near the end of the respiratory event were closely linked to signs of arousal (13). However, delta amplitudes could also continue to rise simultaneously with the appearance of increased alpha activity.

The topographic maps showed that the increases in delta amplitudes were usually generalized over the scalp, without hemispheric differences or consistent regional initiation. There was, however, a tendency for the maximum delta amplitudes to show a square "table" distribution, insofar as they were dominant in the posterior frontal, central and parietal regions.

Fig. 1A shows a typical sequence of delta amplitude changes in consecutive topographic maps obtained during one obstructive apnea. Fig. 1B shows the simultaneously recorded polysomnogram. Fig. 2 shows CSA plots from three consecutive obstructive apneas in NREM sleep, demonstrating the changes in frequency spectra over time.

The average value of the delta amplitude in each map was calculated for comparison of initial, maximal and final values during the respiratory events. Individual values for each patient are given in Table 1. The mean initial delta value for all patients was 26 μV (range 8–50 μV, SD 8), increasing to a maximum of 65 μV (range 40–116 μV, SD 20) and decreasing to 50 μV (range 18–116 μV, SD 21) at the end of events. This corresponds to an average difference in delta amplitudes of 268% (range 100–1138%, SD 144) between initial and maximal values and 202% (range 56–500%, SD 91) between initial and final values. When initial, maximal and final amplitudes during all respiratory events were compared, the differences were highly significant ($p < 0.001$, Wilcoxon Rank Sign test).

Marked increases in delta amplitudes could also occur during comparatively short apneas (<20 seconds)

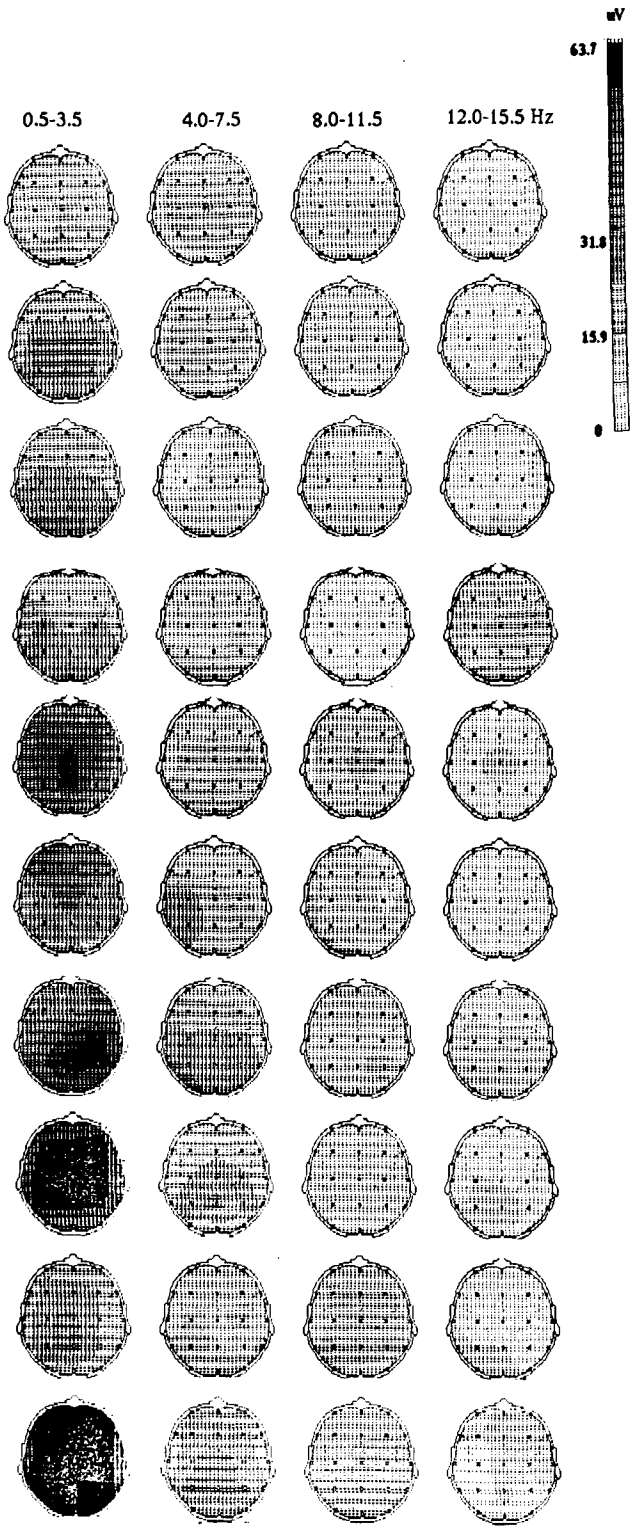


FIG. 1. (**A**, above) Consecutive topographic maps (top to bottom) displaying EEG amplitudes within delta, theta, alpha and beta bands in 2-second epochs during 20 seconds of an obstructive apnea in NREM sleep, causing a 5% desaturation. The amplitudes within the delta-band increase shortly after the onset of the apnea, indicated by darkening shades of grey. The color-code key is shown to the right. (**B**, opposite) Discrete delta-waves are also visible in the simultaneously recorded polysomnogram. The arrows mark the section subjected to topographic EEG analysis.

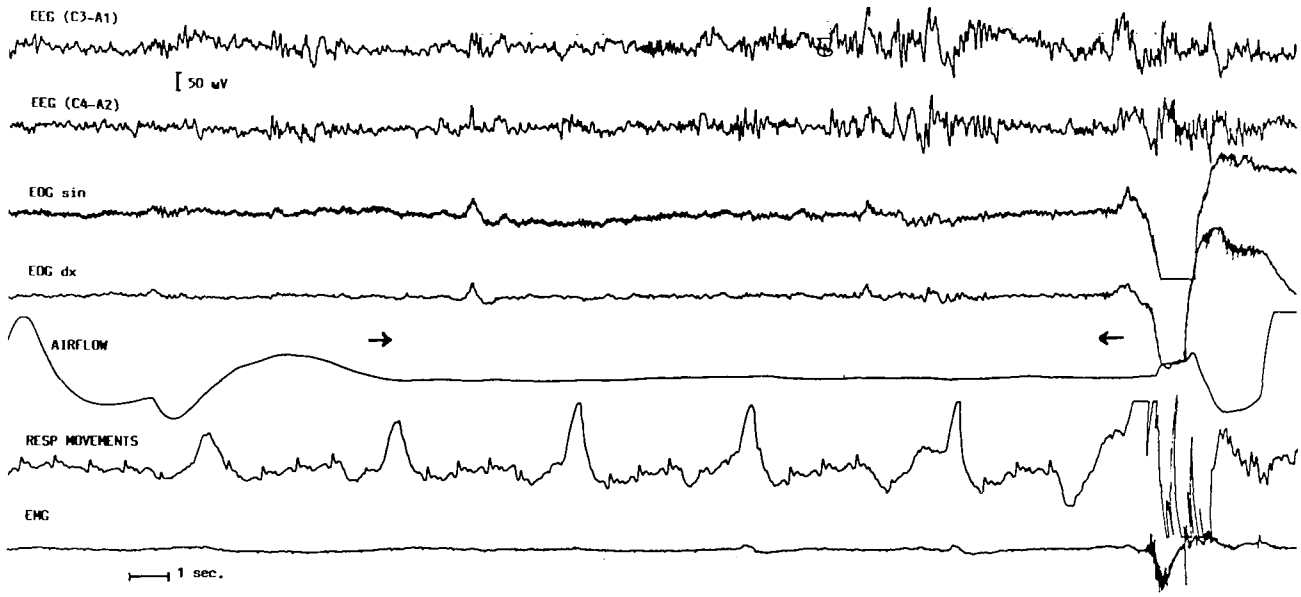


FIG. 1. Continued.

with minor desaturations. The same was true for hypopneas, in spite of the fact that they usually caused only slight desaturations (never exceeding 9%, mean value 6%). There was no statistically significant difference between increases in delta amplitudes during apneas and hypopneas, but this may be due to the fact that only a small number of hypopneas were studied.

REM respiratory events

The EEG pattern during REM apneas was different from the one described above during NREM apneas. When delta amplitudes in all 2-second epochs during each event were compared to initial values, there were increases during all respiratory events but four. These increases, however, did consist of isolated rises in single epochs, and there was no consistent regional maximum in the maps. Gradual progression did not occur. There was no significant difference between the initial and final delta amplitude values (mean value of 22 μV in both instances). This was also true during long apneas with major desaturations. The difference in delta amplitude change (initial–maximal values) between NREM and REM apneas was highly significant, expressed both as percentage and absolute amplitude (μV) ($p < 0.0001$, Mann-Whitney U test).

The percentage of change in delta amplitudes (both initial–maximal and initial–final) during all respiratory events was compared to their respective durations and degrees of desaturation (Spearman Rank Correlation test). There were no significant correlations among NREM events. In REM sleep, delta increase was not correlated to degree of desaturation but weakly to event duration ($p = 0.02$, tau = 0.44). Final delta values were not correlated to event duration.

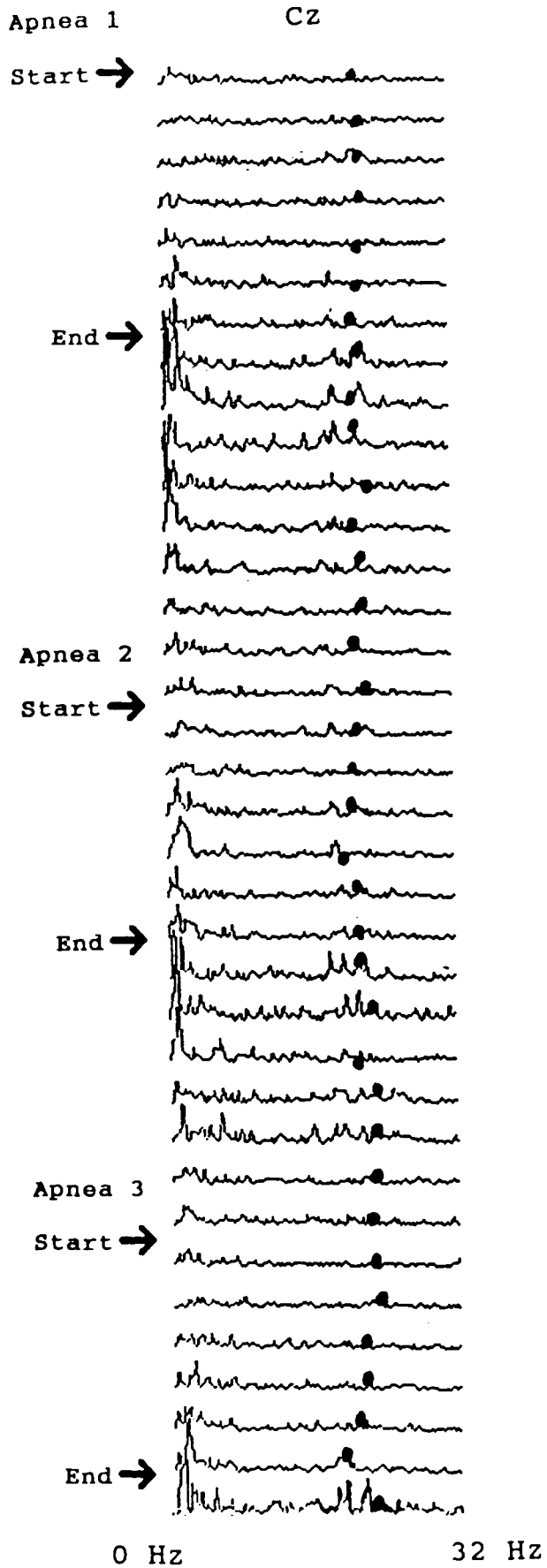
CPAP treatment

Recordings were repeated during CPAP treatment in three patients, i.e. during sleep without obstructed respiration. EEG analyses were performed on recordings of similar length made at the same times of night as those in the previous investigation. In these renewed recordings, none of the patients exhibited such rapid increases in delta amplitudes as during stage 1 and 2 apneas. In REM, there was a similar variability in delta amplitudes to the one previously recorded during apneas.

Table 2 presents mean delta amplitude values for stages 1–4 NREM and REM sleep in each CPAP-treated subject.

DISCUSSION

The main finding of this study was that delta-band activity increases progressively during NREM apneas but not during REM apneas. This increase during NREM apneas was generalized over the scalp with no consistent regional initiation or assymetry, but delta amplitudes tended to have a maximum in the posterior frontal, central and parietal regions. Such a distribution of delta amplitudes in spectral maps has also been shown during stage 2 sleep in non-OSAS patients (14), whereas it was found in an older study without FFT analysis that the average amplitude of delta waves dur-



ing sleep in young normal subjects was largest in the occipital region (15).

Increased activity in the delta range also occurred during REM apneas but was much less marked than during NREM apneas and occurred without progression, despite the fact that the accompanying desaturations tended to be greater. There were no significant correlations between increases in delta during NREM apneas and apnea duration or degree of desaturation. Based on these findings, we find it unlikely that the recorded delta increases in NREM were primarily due to hypoxemia.

The findings of this study may appear to be in contrast to those of Walsleben, et al. (16), who reported that the typical finding in EEG topography of obstructive apneas is a general decrease in activity. They studied epochs of 14 seconds before, during and after apnea. During the first 10–15 seconds of apneas, comparatively decreased amplitudes were usually seen in the present study as well. The probable reason for this is that apnea onset often coincides with sleep onset. The general EEG amplitude is significantly lower during stage 1 sleep than during arousals. In a study of EEG changes typical of obstructive apnea, the total duration of an episode needs to be taken into account. Also, 14-second epochs are too long to show the rapid changes which may be taking place.

Considering the magnitudes of some recorded desaturations (SaO_2 values down to 66%) in REM apneas, it may seem surprising that accompanying EEG changes did not occur. One may speculate whether sleep might protect the brain so that the effects of hypoxia are delayed compared to wakefulness. A hypoxic EEG response might also be different in the waking and sleep states or between REM and NREM sleep. Hypoxia may act primarily on neurotransmitter systems, which synchronize cortical activity and which may be preferentially activated during NREM over REM. However, the findings of this study indicate that cerebral hypoxia is an unlikely cause for the EEG changes observed during NREM apneas. Delta amplitudes started to rise, on average, only 13 seconds after the onset of apneas and often decreased in association with apnea termination when SaO_2 was still falling. These temporal relationships also argue against hypercapnia as the cause of the observed changes. Further-

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FIG. 2. CSA plots (amplitude vs. frequency spectra, electrode Cz) in consecutive 4-second epochs from an episode of NREM sleep with 3 obstructive apneas. Apnea 1: duration 28 seconds, desaturation 8%. Apnea 2: duration 23 seconds, desaturation 8%. Apnea 3: duration 23 seconds, desaturation 7%. The marker (dark dot) in each row represents the spectral edge, i.e. the point preceded by 80% of the total FFT amplitude.

Table 1. *Patient's mean initial, maximal, and final delta amplitude values (μV) during NREM and REM apneas (ranges are within parentheses)*

Patient no.	NREM onset	NREM max	NREM end	REM onset	REM max	REM end
1	25 (8–38)	72 (40–116)	44 (32–116)	18 (9–23)	35 (30–40)	21 (16–26)
2	15 (14–16)	45 (28–60)	24 (18–32)	18 (15–20)	20 (17–22)	17 (14–19)
3	30 (28–32)	60 (48–72)	40 (29–50)	31 (17–48)	42 (31–64)	29 (21–44)
4	26 (16–50)	51 (30–69)	37 (21–63)	22 (15–25)	38 (29–47)	22 (15–26)
5	32 (20–44)	75 (48–116)	60 (36–91)	—	—	—

more, the magnitudes of delta increases were not significantly related to the degree of desaturation.

Krieger and Kurtz (6) suggested that the bursts of delta waves which they observed toward the end of apneas were a manifestation of arousal. Increased delta activity is often seen preceding "normal" awakenings. An arousal response therefore remains a possibility. However, the frequency analysis in this study showed that delta waves appeared before increases in fast activity were seen and that delta amplitudes again decreased toward the end of apneas, when faster activities became prominent. If increased delta activity is a sign of arousal, it also remains to be explained why REM should be different from NREM in this respect. Some of the REM apneic events in this study were terminated by arousals.

A pattern of progressively increasing amplitudes in the delta range with a generalized topographic distribution is a normal finding in the transition stage to slow-wave sleep. One explanation for such an EEG finding during NREM apneas could therefore be a breakthrough of stage 3 or 4 slow-wave activity, even though all the investigated events started in stages 1 and 2 according to the conventional classification by Rechtschaffen and Kales (11). In normal subjects, the sleep stage is not supposed to change within a 30-second epoch, and the majority of the investigated apneas confined themselves to this period of time. Dijk et al (17) found that the mean rate of rise of slow activity per 2 minutes was 18.6% in the first NREM sleep episode in normal subjects and 41.2% in recovery sleep after sleep deprivation. They, like Kupfer et al. (18), also reported that delta activity rises gradually during a NREM episode and ceases abruptly at its end. Our patients all had a considerable diminution of slow-wave sleep, as judged by previous diagnostic polysomnograms. It may be speculated whether chronic deprivation of stages 3 and 4 could create such a propensity for slow-wave sleep that transition to deeper stages from sleep onset occurs much faster than normal. Penzel and Petzold (19) have suggested another method of sleep staging, i.e. introduction of trajectories in the parameter space of Fourier phase spectra. When they investigated OSAS patients with this method they found that most 30-second epochs, starting from sleep onset, displayed a higher proportion of low frequencies than what was seen in normal subjects. If OSAS patients pass through a series of "stages" during, for example, 30 seconds, the finding of increased delta activity during NREM apneas in this study would be explained. We therefore propose that a possible cause of rapidly increased, generalized delta activity during NREM apneas is a breakthrough of slow-wave sleep.

A fast transition to sleep stages 3 and 4 during NREM apneas could contribute to the pathophysiology of OSAS. A low general muscle tone is characteristic of slow-wave sleep, and it has been shown that a key feature of obstructive apneas is an inability of the oropharyngeal muscles to counteract the negative inspiratory pressure (20, 21), thus resulting in upper airway collapse. The chemical control of ventilation is prominent during slow-wave sleep (22), but hypoxic and hypercapnic responses are delayed (23–25). A rapid switch to a high delta activity state after a preceding arousal could allow some restorative sleep to occur but also be responsible for longer apneas, if their resolution depended on delayed responses to hypoxia and hypercapnia.

Acknowledgements: This study was supported by grants from the Karolinska Institute and the Swedish Society of Medicine.

Table 2. *Mean delta amplitudes (μV) in different sleep stages during CPAP treatment*

Patient no.	s1	s2	s3	s4	REM
1	20	28	42	51	25
2	22	30	49	52	31
3	20	21	45	50	23

FFT was made in 1.5-minute epochs for CPAP recordings. The values above are averages of 3 such analyses for each sleep stage.

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