Slow-Wave Activity in Sleep Apnea Patients Before and After Continuous Positive Airway Pressure Treatment*

Contribution to Daytime Sleepiness

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Study objectives: To estimate the course of slow-wave activity (SWA), its amount during the night, and its correlation with daytime sleepiness in sleep apnea syndrome (SAS) patients. This study also verified whether continuous positive airway pressure (CPAP) treatment also restores a normal pattern of SWA in severe SAS patients.

Participants: Ten patients with a diagnosis of severe SAS who showed a good clinical response to CPAP after approximately 9 months of treatment were included in this study. These patients were matched for sex and age with 10 control subjects.

Design: All subjects underwent 1 night of polysomnography (PSG), followed by the multiple sleep latency test (MSLT) the next day. For the SAS patients only, the same procedure was repeated after 9 ± 0.7 months of CPAP treatment. In addition to traditional scoring of sleep stages, apneas, hypopneas, and microarousals, the SWA, defined as the power in the 0.75- to 4.5-Hz frequency band, was evaluated.

Results: A positive correlation between SWA of the first cycle and the MSLT (r = 0.56; p = 0.045) was found before treatment. Moreover, SAS patients significantly increased their mean SWA after CPAP treatment in the first (p = 0.024) and second (p = 0.002) sleep cycles and restored a more physiologic decay of SWA across the night.

Conclusions: These results suggest that daytime sleepiness in SAS patients may be the result of a lack of SWA during the first part of the night, and show that CPAP restores a more physiologic pattern of SWA across the night.

Key words: continuous positive airway pressure; quantitative EEG; sleep apnea syndrome; sleepiness; slow-wave activity

Abbreviations: AHI = apnea plus hypopnea index; ANOVA = analysis of variance; BMI = body mass index; CPAP = continuous positive airway pressure; EDS = excessive daytime somnolence; MSLT = multiple sleep latency test; NREM = nonrapid eye movement; NS = not significant; process C = circadian process; process S = homeostatic process; PSG = polysomnography; REM = rapid eye movement; SaO2 = arterial oxygen saturation; SAS = sleep apnea syndrome; SWA = slow-wave activity

Sleep apnea syndrome (SAS) is a chronic illness characterized by recurrent apneas and hypopneas during sleep, resulting in repetitive arousals and disruption of normal sleep architecture. Several studies have shown a strong deprivation of nonrapid eye movement (NREM) sleep in SAS patients, even though their sleep efficiency seems to be preserved1,2 or minimally changed3,4. Among the various symptoms associated with this condition, the most prevalent is excessive daytime sleepiness (EDS).5 SAS is commonly treated with nasal continuous positive airway pressure (CPAP), which was found to restore normal airflow and sleep architecture and to suppress episodes of nocturnal hypoxemia6-8 CPAP

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also improves daytime sleepiness as measured by the multiple sleep latency test (MSLT), especially with long-term use, although some degree of daytime somnolence remains.

According to a proposed model of sleep regulation, sleep and vigilance are regulated by two processes: a circadian process (process C) and a homeostatic process (process S). Slow-wave activity (SWA) is considered a marker or an objective measure of process S and has been shown, in normal subjects, to increase with the duration of prior wakefulness and to decline exponentially during the night from the first to the last sleep cycle. Unlike the quantification of slow-wave sleep, which requires an amplitude criterion (> 75 μV) and a minimum quantity of these slow waves (20% of the epoch), SWA has no such criteria (thus also takes into account lower-amplitude slow waves and slow waves present in stage 2 sleep) and has a broader frequency definition (0.75 to 4.5 Hz).

Few studies have looked at the functioning of process S in various medical conditions except in narcolepsy, for which it was found to be enhanced. To our knowledge, the dynamics of SWA have never been studied across the night in SAS patients. It is expected that SWA will be decreased in SAS patients and the habitual dynamic of SWA decline across the night will be disrupted. We will also verify whether the EDS of untreated SAS patients is related to the decrease in SWA and whether CPAP treatment will restore a normal amount and pattern of SWA.

**Materials and Methods**

**Subjects**

Ten men (mean age, 42.7 ± 1.87 years; age range, 36 to 57 years; mean body mass index [BMI], 37.54 ± 1.98 kg/m²) with a diagnosis of severe SAS who showed a good clinical and polysomnography (PSG) response to CPAP after 9 ± 0.7 months of treatment were included in the study. Inclusion criteria were as follows: (1) an apnea plus hypopnea index (AHI) of ≥ 30 events/h during the diagnosis night; (2) a good response to CPAP treatment, defined as an AHI of < 10 events/h; and (3) an index of periodic limb movements during sleep of < 10 movements/h of sleep. Exclusion criteria were the presence of any other sleep disorder or pulmonary disease and the use of any medication likely to affect sleep, EEG, or respiratory functions in the month prior to entering the study. Ten normal male subjects (mean age, 43.9 ± 2.2 years; age range, 36 to 55 years; mean BMI, 26.9 ± 1.15 kg/m²) were used as control subjects and were studied with the same procedure. None of the control subjects had a AHI > 5 events/h. Exclusion criteria were the same as those of the SAS group. All subjects signed a consent form prior to starting the experiment, and the study was approved by the ethics committee of the hospital and university.

**Nocturnal Sleep Studies**

All subjects underwent 1 night of PSG, followed by a modified MSLT the next day; for the SAS patients, the same procedure was repeated after 9 ± 0.7 months of CPAP treatment (Tranquility Plus T100; Healthdyne; Marietta, GA). Sleep was monitored using two EEG leads (C3-A2, O2-A1), right and left electrooculogram, chin electromyogram, and ECG. To assess apneas and hypopneas, nasal and oral airflow were recorded with thermistors, and respiratory movements with abdominal and thoracic strain gauges. An apnea was defined as a cessation of the respiratory airflow of at least 10-s duration, and an hypopnea as a reduction of the airflow > 50% (lasting ≥ 10 s). The AHI represents the number of apneas and hypopneas per hour of sleep. Arterial oxygen saturation (SaO₂) was measured continuously with a finger oximeter (Biopac III; Ohmeda; Boulder CO); both time < 90% and minimum SaO₂ were calculated. Surface electromyogram of anterior tibialis muscles was recorded to quantify periodic leg movements during sleep.

Sleep was recorded and scored manually according to the criteria of Rechtschaffen and Kales using 20-s epochs. The use of the 20-s epoch is essential when performing all-night quantitative EEG analysis on signals recorded at 128 Hz (analysis window of 4 s), to keep the time course of sleep staging and quantitative EEG values aligned. The following variables were calculated: total sleep time; sleep efficiency; number and index of microarousals; percentage of stages 1, 2, 3, and 4; and REM sleep, and mean and lowest oxygen saturation levels. Sleep efficiency was defined as the percentage of time spent asleep over the total recording time from sleep onset to the last awakening. A microarousal was defined as a return to α or θ frequency well differentiated from the background EEG activity lasting at least 3 s but < 10 s.

**MSLT**

The MSLT consists of five opportunities to nap administered at 10:00 AM, 12:00 noon, 2:00 PM, 4:00 PM, and 6:00 PM. As for PSG, sleep onset in the modified MSLT was defined as three consecutive epochs (1 min) of stage 1 sleep or one epoch (20 s) of any other sleep stage. Participants were awakened after 10 min of sleep, or the test was stopped after 20 min if they did not fall asleep. Participants were not allowed to drink alcohol or beverages containing caffeine, nor were they allowed to sleep between the five tests.

**EEG Spectral Analysis**

EEGs were low-pass filtered and digitized on-line at a sampling rate of 128 Hz. Quantitative analysis of the EEG was performed by fast Fourier transform calculated on 4-s mini-epochs for the nights preceding the MSLT. SWA was defined as the power (in microvolts squared) in the 0.75- to 4.5-Hz frequency band. The 4-s mini-epochs containing an artifact were rejected and were considered as missing data to preserve sleep continuity. Two visual inspections were performed according to two different criteria. First, “classical artifacts” such as movement, ocular, or muscle artifacts were removed. The second time, “prearousal” slow waves distinguishable from the background activity that occurred from 4 s prior, to 8 s after the end of the respiratory events were also removed. An example of these prearousal slow waves is shown in Figure 1. Interrater reliability between two experienced scorers was tested for the two patients with the highest AHI. To do so, a homemade computer program compares the scorings of the two scorers epoch by epoch and determines the percentage of similarly scored epoch. Between-scorer correlation rates of 98% and 93% were obtained for the first and the second patients, respectively.
Total SWA was calculated by adding the power of all valid NREM sleep epochs for the entire night. The time course of SWA was standardized for each subject by subdividing each NREM episode into 20 equal intervals and each REM episode into 5 intervals. Data were then averaged per subject to also obtain the mean SWA per sleep cycle. Sleep cycles were scored according to the criteria of Feinberg and Floyd. A cycle was defined by the succession of a NREM sleep episode lasting at least 15 min followed by a REM episode of at least 5-min duration. A NREM episode was defined as the time interval between the first occurrence of stage 1 sleep and the first occurrence of REM within a cycle. It has to be followed by a REM episode to be considered complete. Only the first three completed NREM episodes were included in the calculations.

**Statistical Analyses**

Between-group differences in sleep variables and in total SWA were assessed by either Mann-Whitney $U$ tests (control subjects vs SAS patients) or Wilcoxon matched-pair tests (treated vs untreated SAS patients). A two-way analysis of variance (ANOVA) with one independent and one repeated measure was used to compare SWA between SAS patients and control subjects for three successive NREM episodes. A two-way ANOVA with two repeated measures was used to compare SAS patients before and after treatment for three successive NREM episodes. The degrees of freedom were corrected according to Huynh-Feldt adjustments for sphericity violation. Post hoc comparisons were performed for the three episodes. Because 3 untreated patients did not complete their third cycle, the ANOVAs were performed using only 7 patients (before and after treatment and for all cycles) and 10 control subjects.

In order to assess the relationship between the MSLT and different sleep parameters including SWA, Pearson product-moment correlations (unilateral) were used. Wilcoxon matched-pair tests were performed to compare sleep parameters and MSLT results before and after CPAP treatment, and Mann-Whitney $U$ tests to compare control subjects with SAS patients before treatment and with patients after CPAP treatment. Data are presented as mean ± SEM. All statistic analyses have been performed using a software package (Statistica 5.1; StatSoft; Tulsa, OK).

**Results**

Results of PSG recordings are shown in Table 1. A shorter total sleep time was seen in SAS patients before treatment, compared to normal control subjects. SAS patients also had more stage 1 sleep and less stage REM sleep; they also fell asleep more rapidly on the MSLT. Stage 2 sleep, stages 3 and 4 sleep, and sleep efficiency were not statistically different between groups. SAS patients presented respiratory impairments (a mean AHI > 50 events/h, a mean time spent with $\text{SaO}_2 < 90\%$ of 115 min, and a mean minimum of $\text{SaO}_2$ of 63.9%) obviously not present in the control group. After CPAP treatment, both respiratory and sleep variables returned to normal values; there was no significant difference between posttreatment values and those of control subjects (Table 1).

The accumulation of all SWA during NREM sleep for the entire night was not statistically different for controls and untreated SAS patients. A statistically significant difference in total SWA was found, how-
ever, between pretreatment and posttreatment values in SAS patients (1,164,390 ± 528,219 μV² vs 1,425.031 ± 591.825 μV²; Wilcoxon, p = 0.05).

The distributions of SWA for three sleep cycles for control subjects vs untreated SAS patients and for treated vs untreated patients are presented in Figure 2, top and bottom, respectively. There was no interaction effect between group (control subjects and untreated patients) and NREM episode (1, 2, 3). However, an effect of NREM episode (F[2,30], 13.1; Huynh-Feldt, p = 0.0001) was found, as can be seen in Figure 2, top.

A second ANOVA with two repeated measures (SAS patients before and after CPAP treatment and SWA in successive NREM episodes) showed an interaction between the two factors (F[2,12], 4.97; Huynh-Feldt, p = 0.027). To decompose this interaction effect, an analysis of simple effects was performed and showed a significant pretreatment to posttreatment difference for the first (p = 0.024) and second NREM episodes (p = 0.002); the difference for the third NREM episode was not significant.

As shown in Table 2, the mean sleep latency on the MSLT was significantly correlated with SWA in the first NREM cycle (r = 0.56; p = 0.045) before treatment. The microarousal index was significantly correlated (negatively) with the SWA in the first NREM episode and the total accumulation of SWA for the entire night. There was no significant correlation between the MSLT and either the percentage of REM sleep, the AHI, the SaO₂ minimum, or the time spent with SaO₂ < 90%.

**DISCUSSION**

One of the major difficulties in studying SWA in SAS patients results from the numerous artifacts associated with repetitive microarousals or awakenings closely related to respiratory impairments. To our knowledge, this is the first study of all-night SWA in patients with SAS, and there is no easy way and no validated or standard method to reject artifacts in this population.

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**Table 1—Sleep Parameters for SAS Patients (Pretreatment), CPAP-Treated SAS Patients, and Control Subjects**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>SAS</th>
<th>CPAP</th>
<th>SAS vs CPAP, Wilcoxon</th>
<th>SAS vs Control Subjects, Mann-Whitney</th>
<th>CPAP vs Control Subjects, Mann-Whitney</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST, min</td>
<td>426 ± 11.8</td>
<td>420 ± 12.0</td>
<td>465 ± 9.7</td>
<td>NS</td>
<td>0.02</td>
</tr>
<tr>
<td>Sleep efficiency, %</td>
<td>88.68 ± 1.58</td>
<td>91.22 ± 0.92</td>
<td>90.3 ± 1.43</td>
<td>NS</td>
<td>0.05</td>
</tr>
<tr>
<td>Stage 1, %</td>
<td>21.71 ± 2.88</td>
<td>10.42 ± 0.85</td>
<td>11.9 ± 1.19</td>
<td>0.005</td>
<td>0.0008</td>
</tr>
<tr>
<td>Stage 2, %</td>
<td>64.40 ± 2.15</td>
<td>65.43 ± 1.74</td>
<td>63.3 ± 2.26</td>
<td>NS</td>
<td>0.03</td>
</tr>
<tr>
<td>Stage 3 and 4, %</td>
<td>3.21 ± 1.05</td>
<td>4.82 ± 1.22</td>
<td>4.86 ± 1.88</td>
<td>NS</td>
<td>0.03</td>
</tr>
<tr>
<td>Stage REM, %</td>
<td>10.66 ± 1.06</td>
<td>19.33 ± 1.36</td>
<td>19.39 ± 1.41</td>
<td>0.005</td>
<td>0.0003</td>
</tr>
<tr>
<td>Microarousals index</td>
<td>43.50 ± 7.34</td>
<td>9.0 ± 1.35</td>
<td>10.6 ± 1.82</td>
<td>0.005</td>
<td>0.007</td>
</tr>
<tr>
<td>AHI, events/h</td>
<td>54.65 ± 7.18</td>
<td>1.68 ± 0.81</td>
<td>0.66 ± 0.33</td>
<td>0.005</td>
<td>0.0004</td>
</tr>
<tr>
<td>SaO₂ &lt; 90%, min</td>
<td>115.6 ± 33.8</td>
<td>0.12 ± 0.12</td>
<td>0.07 ± 0.05</td>
<td>0.005</td>
<td>0.001</td>
</tr>
<tr>
<td>Minimum SaO₂, %</td>
<td>63.8 ± 4.4</td>
<td>90.8 ± 0.5</td>
<td>91.8 ± 0.6</td>
<td>0.005</td>
<td>0.001</td>
</tr>
<tr>
<td>MSLT, min</td>
<td>3.99 ± 0.54</td>
<td>9.97 ± 1.43</td>
<td>12.71 ± 0.79</td>
<td>0.005</td>
<td>0.0006</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SEM. TST = total sleep time.*
We decided to exclude bursts of δ activity occurring at the end of the apneic episodes in close association with microarousals, since it was previously reported that these bursts are part of an arousal response\textsuperscript{20,21} rather than physiologic SWA associated with the restorative functional sleep as SWA seen during SWS. One may question whether the criteria used for artifact rejection, including the rejection of “prearousal δ waves” occurring at the end of apneic episodes, may have influenced the calculation of the total SWA across the night. To assess this possibility, we also calculated SWA across sleep cycles without rejecting these bursts of SWA. We obtained the same results. Correlations between EDS, as measured by the MSLT, and SWA in the first NREM-REM sleep cycle, also remained significant when the calculations were made without rejection of bursts of δ activity occurring at the end of the apneic episodes.

Results of the present study show that there is a lower amount of SWA across the night, and especially in the first two NREM episodes, before treatment compared to posttreatment values. Comparison between control subjects and untreated apneic patients did not reach the significance, even though control subjects had values that were even higher than those of treated apneic patients. This result can first be explained by the small sample size and large SDs in SWA values for each group. The latter could be related to the large age range of subjects selected for the study, since it is known that SWA varies greatly with age.\textsuperscript{22,23} The lack of statistically significant differences is also due to the different statistical tests used to assess the differences between conditions in apneic patients (within-group test) on one hand and between control subjects and untreated apneic patients (between-group test) on the other hand. Nonetheless, these results showed that SWA is a more sensitive index of change in slow-wave sleep organization throughout the night than is the proportion of stages 3 and 4 sleep, which was not different from pretreatment to posttreatment recordings. These results show that the general pattern of SWA distribution across the night is normal in CPAP-treated apneic patients. These results also suggest that the decrease in SWA found in untreated apneic patients is at least partly reversible with CPAP treatment. This is consistent with previous findings of an increase in SWS with CPAP treatment.\textsuperscript{24–26} Similarly, a slowing of the EEG during wakefulness had been found in untreated apneic subjects\textsuperscript{27} in frontal, central, parietal, occipital, and temporal regions, which was corrected after CPAP.\textsuperscript{28}

One question that is often raised with regard to SAS is the identification of factors responsible for EDS. Many studies on SAS patients have shown a correlation between the number of arousals due to respiratory events during the night and the severity of EDS measured with the MSLT.\textsuperscript{29,30} One study (n = 1,146) showed that the AHI was positively correlated with daytime sleepiness, but AHI explained only 11% of the variance in MSLT results.\textsuperscript{31} A study of 466 patients showed that arousals resulting from respiratory disturbances were a good predictor of daytime sleepiness, explaining 13% of the variance in MSLT results.\textsuperscript{32} Daytime sleepiness was also positively correlated with oxygen desaturation,\textsuperscript{33} increased respiratory efforts,\textsuperscript{34} and parasympathetic activation.\textsuperscript{35} However, another study (n = 100) failed to show any correlation between MSLT and AHI, or oxygen desaturation.\textsuperscript{36} It has also been shown that oxygen desaturation induced experimentally by CO\textsubscript{2} inhalation in apneic patients treated with CPAP did not decrease sleep latency at the MSLT.\textsuperscript{37} However, experimentally induced microarousals in healthy subjects resulted in daytime sleepiness.\textsuperscript{38,39} In the present study, although the microarousal index was highly correlated (negatively) with the total amount of SWA (r = −0.75; p = 0.007), it was not significantly correlated with the MSLT (r = −0.04; not significant [NS]). No

### Table 2—Pearson Product-Moment Correlations Between MSLT, SWA, and Sleep Disruption Indexes in 10 SAS Patients

<table>
<thead>
<tr>
<th>Correlations</th>
<th>SAS Patients (Pretreatment)</th>
<th>SAS Patients (Posttreatment)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>p Value</td>
</tr>
<tr>
<td>MSLT and total SWA</td>
<td>0.3</td>
<td>NS</td>
</tr>
<tr>
<td>MSLT and NREM 1 SWA</td>
<td>0.56</td>
<td>0.045</td>
</tr>
<tr>
<td>MSLT and stage REM%</td>
<td>0.29</td>
<td>NS</td>
</tr>
<tr>
<td>MSLT and AHI</td>
<td>0.09</td>
<td>NS</td>
</tr>
<tr>
<td>MSLT and SaO\textsubscript{2} minimum</td>
<td>−0.39</td>
<td>NS</td>
</tr>
<tr>
<td>MSLT and time with SaO\textsubscript{2} &lt; 90%</td>
<td>0.38</td>
<td>NS</td>
</tr>
<tr>
<td>MSLT and microarousal index</td>
<td>−0.04</td>
<td>NS</td>
</tr>
<tr>
<td>Microarousal index and total SWA</td>
<td>−0.78</td>
<td>0.004</td>
</tr>
<tr>
<td>Microarousal index and NREM 1 SWA</td>
<td>−0.64</td>
<td>0.024</td>
</tr>
</tbody>
</table>
correlation was found between the number of respiratory events (AHI) and the severity of EDS. The MSLT test could have indeed been more sensitive to drowsiness if 30 s instead of 1 min (three epochs of 20 s) would have been used as the sleep onset criterion and if subjects had not been allowed to sleep for 10 min when they fell asleep. These points may have had an effect on the lack of correlation between the MSLT and the microarousal index or the AHI. Despite the low percentage of REM sleep found in untreated patients, which is restored after CPAP treatment, it does not appear that REM sleep percent plays a role in EDS. On the other hand, a significant correlation was found between results of the MSLT and SWA during the first sleep cycle. These results suggest that SWA may have a major predictive value of EDS as measured by the MSLT in SAS patients. Since it was not possible to match the control subjects for BMI to the apneic patients, one should keep in mind that obesity might be a confounding factor. However, this had no bearing on the fact that both MSLT and SWA values improved after treatment compared to before treatment in the apneic group, irrespective of a weight change.

This study also shows the importance of the nocturnal distribution of SWA across the night. It is not the total amount of SWA that was best correlated with the daytime vigilance, but rather the peak of SWA noted in the first part of the night. Indeed, the first NREM episode probably has a special role in sleep physiology since it is the period most affected by age,25 sleep loss,40 or sleep extension.41

Taken altogether, these results suggest that the occurrence of respiratory events at night, associated with repetitive microarousals, decreases the amount of SWA across the night in patients with SAS. As a consequence of the decreased SWA, patients experience more EDS during the day. However, there was a lack of correlation between SWA and the MSLT after treatment with nasal CPAP. The MSLT value increased remarkably after successful CPAP treatment to a near normal value (mean, 9.97 ± 1.43). This result suggests that SWA may not be a major determinant of the mean sleep latency on the MSLT when there is no major residual somnolence.

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