Marked Reduction in Obstructive Sleep Apnea Severity in Slow Wave Sleep

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Introduction: Obstructive sleep apnea (OSA) is widely accepted to improve during slow wave sleep (SWS) compared to lighter stages of NREM sleep. However, supporting data to establish the magnitude and prevalence of this effect is lacking. Consequently, we examined this phenomenon, controlling for posture, in a large group of patients investigated for OSA at an academic clinical sleep service. Method: A detailed retrospective analysis was conducted on data obtained from each 30-sec epoch of sleep in 253 consecutive full-night diagnostic polysomnography studies performed over a 3-month period. Respiratory and arousal event rates were calculated within each stage of sleep, in the supine and lateral postures, and across the whole night, with OSA patients classified on the basis of the overall apnea-hypopnea index (AHI) ≥ 15 events/h. Central sleep apnea (CSA) patients were defined by a central apnea index ≥ 5/h. Sleep latency and time, and respiratory and arousal event rates in OSA, CSA, and non-OSA patients were compared between sleep stages and postures using linear mixed model analysis. The numbers of patients achieving reduced event rates in SWS and in the lateral posture were also examined.

Results: There were 171 patients with OSA, 14 with CSA, and 68 non-OSA patients. OSA patients took significantly longer to achieve slow wave and REM sleep (p < 0.001) than non-OSA patients and had less stage 4 sleep (p = 0.037). There were striking improvements in AHI and arousal index (AI) from stage 1 to 4 NREM sleep (p < 0.001), with intermediate levels in REM sleep. AHI and AI were also markedly reduced in lateral versus supine sleep in all sleep stages (p < 0.001), with an effect size comparable to that of the slow wave sleep effect. The majority of OSA patients achieved low respiratory event rates in SWS. Eighty-two percent of patients achieved an AHI < 15 and 57% < 5 events/hour during stage 4 sleep.

Conclusion: Although OSA patients demonstrate both a delayed and reduced proportion of SWS compared to non-OSA subjects, once they achieved SWS, AHI, and AI markedly improved in most patients.

Keywords: Obstructive sleep apnea, slow wave sleep, ventilatory control, posture, delta sleep, arousal, sleep stage

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Obstructive sleep apnea (OSA) is a common disorder. Twenty-four percent of adult males and 9% of adult females experience at least 5 events of disordered breathing per hour of sleep.1 The diagnosis and severity of obstructive sleep apnea is typically determined from the apnea hypopnea index (AHI),2 a measure of the total number of complete or partial upper airway obstruction (apnea or hypopnea) events lasting 10 sec or more, divided by total sleep time. AHI is known to be strongly influenced by factors such as sleep posture,3-5 head position,6,7 and REM sleep.4,5 In clinical studies, OSA severity frequently changes substantially over the course of a night, even in severely affected patients. It has also been widely accepted that obstructive sleep apnea improves during slow wave sleep (SWS). However, with the exception of a few preliminary reports based on small patient samples,4-10 there appears to be remarkably little published evidence available to assess the magnitude and prevalence of this effect.

If improvements in sleep disordered breathing in SWS amongst OSA patients are substantiated as being both common and marked it may be a phenomenon worthy of further investigation, for while much has been learned about the risk factors for OSA and OSA pathogenesis, only a relatively small degree of the variance in OSA severity is currently explained by these various mechanisms.11 It seems likely that non-anatomical factors mediating upper airway and respiratory control stability, such as ventilatory chemosensitivity, plant gain control factors, arousal threshold, and the magnitude of post-arousal ventilatory overshoot-undershoot responses,11 would be involved in SWS-mediated improvements in sleep apnea severity. Ultimately, better knowledge of the extent and mechanisms of SWS-mediated improvements in OSA could lead to new therapeutic approaches for this disorder.

Therefore, the purpose of this study was to investigate in detail, the effect of NREM sleep stages on the frequency of respiratory and arousal events in a large cohort of patients referred for the investigation of possible OSA.
### Statistical Analysis

Sleep stage (1-4 and REM) and posture (supine vs lateral) effects in all 3 groups were examined using linear mixed model analysis using an autoregressive covariance structure (SPSS version 16, SPSS Inc, Chicago, IL). In the event of significant mixed model effects, relevant post hoc comparisons were performed using Student t-tests with Dunn-Sidak correction for multiple comparisons. The strength of relationships between respiratory and arousal event rates in NREM sleep in the supine and lateral postures in the OSA and non-OSA groups were examined on a within-subject basis for each individual in which 3 or all 4 NREM stages were available for analysis. Effect sizes for posture and stage effects were estimated from within subject differences in lateral versus supine values in stage 2 sleep and differences between stage 2, SWS and REM sleep in the supine posture respectively. All data are presented as mean ± SEM. P-values < 0.05 were considered significant.

### RESULTS

A total of 253 overnight diagnostic studies were performed during the time period of interest. Fourteen patients had a central apnea index ≥ 5/h; 171 of the remaining patients had an AHI ≥ 15/h, and 68 had an AHI < 15/h. Baseline demographic and sleep study data for the groups are summarized in Table 1. The patient population was typical of diagnostic referrals primarily for evaluation of OSA and was comprised predominantly of males who were middle-aged and overweight to obese. Approximately 70% of patients received a positive diagnosis for OSA. This group was significantly older, comprised relatively more males, and had a higher BMI than the non-OSA group (Table 1).

There was no difference in total sleep time between OSA and non-OSA patients (Table 2). OSA and non-OSA patients spent similar proportions of total sleep time in lateral (60.8 ± 2.1 vs 66.2 ± 3.2%, p = 0.159); and supine sleep (42.3 ± 2.3 vs 35.6 ± 3.6%, p = 0.119) respectively. As expected, OSA patients had significantly more stage 1 and less stage 4 sleep compared to the non-OSA group, both in absolute terms (group × stage effect p = 0.037) and as a proportion of total sleep time (Table 2). OSA patients took significantly longer to attain the first epoch of slow wave (39.3 ± 3.5 vs 25.6 ± 2.6 min, p = 0.005) and REM sleep (147.4 ± 6.1 vs 123.3 ± 6.8 min, p = 0.015) following sleep onset compared to the non-OSA group.

Changes in AHI and AI as a function of sleep stage and OSA diagnosis are shown in Figure 1A and further separated as a function of supine versus lateral postures in Figure 1B. There was a striking NREM sleep stage dependence in the frequency of respiratory (stage effect p < 0.001) and arousal events (p <
0.001), with a progressive reduction in event rates from stage 1-4, with REM sleep at an intermediate level. Compared to stage 2, the REM AHI was ~40% higher (effect size 0.55), while SWS AHI was ~50% less (effect size 0.94). The reduction in respiratory and arousal event rates was noted in all patient groups. Total sleep event rates were weighted towards stage 2 values, consistent with the predominance of stage 2 sleep. The ratio of respiratory events to arousal events also showed strong stage (p < 0.001) and group (p < 0.001) effects. In REM sleep, respiratory events occurred considerably more frequently relative to arousal events (AHI/Al ratio 3.9 ± 0.2, compared to NREM sleep 1.2 ± 0.2, p < 0.001) but remained essentially unchanged within NREM sleep. The frequency of arousals exceeded the frequency of respiratory events in all NREM sleep stages in non-OSA patients, whereas the opposite was true for OSA patients AHI/Al 0.7 ± 0.3 vs 1.7 ± 0.2, p < 0.001. The respiratory event rate was strongly correlated with the arousal index, overall r² = 0.82 ± 0.02.

As shown in Figure 1B posture had substantial effects on respiratory and to a lesser degree arousal event rates in both OSA and non-OSA patient groups. Respiratory event rates in the lateral postures were in the order of 50% to 60% of supine values in both groups (p < 0.001), while arousal event rates were in the order of 60% to 80% of supine values in lateral postures, (p < 0.001). Thus respiratory event frequency in the supine posture was higher, relative to arousal frequency, p = 0.018. However, a similar pattern of decline in respiratory and arousal frequencies were noted from stage 1 to 4 NREM sleep. The CSA group also had a reduced rate of respiratory events in the lateral posture (p = 0.009) and a trend towards reduced arousal frequency in the lateral posture (p = 0.057).

Respiratory event types in the OSA and CSA groups were further differentiated into obstructive, central, mixed, and hypopneas as shown in Figure 2. All types of respiratory events showed a strong sleep stage effect in the OSA group, (p < 0.001). In the CSA group, obstructive and central events showed a stage effect, p = 0.048 and p < 0.001, respectively, whereas hypopneas and mixed apneas did not have a significant stage effect.

Sleep stage effects were large and of similar or greater magnitude when compared to posture effects. In the OSA patient group, the effect size of the difference between stage 2 and SWS (stages 3 and 4 combined) was 1.1 for AHI and 1.4 for Al, while that of the difference between supine and lateral postures in stage 2 sleep was 0.8 for AHI and 0.7 for Al. The corresponding effect sizes in the non-OSA group were: 0.6, 1, 0.6, and 0.3, respectively.

Most patients attained relatively low event rates in SWS. For example, 82% of OSA patients exhibited < 15 respiratory events/h and 57% < 5 events/h in stage 4 sleep.

Table 2 — Time Spent in Each Sleep Stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>non-OSA (AHI &lt; 15)</th>
<th>OSA (AHI ≥ 15)</th>
<th>CSA (CAI ≥ 5/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>min</td>
<td>%</td>
<td>min</td>
</tr>
<tr>
<td>1</td>
<td>33.9 ± 4.2</td>
<td>10.4 ± 1.2</td>
<td>45.4 ± 2.3*</td>
</tr>
<tr>
<td>2</td>
<td>153.6 ± 7.2</td>
<td>47.4 ± 1.5</td>
<td>148.1 ± 3.7</td>
</tr>
<tr>
<td>3</td>
<td>50.3 ± 3.3</td>
<td>16.5 ± 1.1</td>
<td>50.2 ± 2.4</td>
</tr>
<tr>
<td>4</td>
<td>37.0 ± 3.4</td>
<td>11.7 ± 1.1</td>
<td>22.3 ± 2.0*</td>
</tr>
<tr>
<td>REM</td>
<td>54.3 ± 3.6</td>
<td>16.2 ± 0.8</td>
<td>50.6 ± 2.0</td>
</tr>
<tr>
<td>Total Sleep</td>
<td>316.2 ± 10.1</td>
<td>100</td>
<td>310.1 ± 5.7</td>
</tr>
</tbody>
</table>

Values are time (minutes) spent in each sleep stage and percentage of total sleep time, mean ± SEM. *p < 0.05 vs non-OSA group.
This is the first large systematic observational study of the effects of NREM sleep stage on OSA severity. OSA patients demonstrated significantly reduced stage 4 and increased stage 1 sleep, and a significantly longer latency to achieve SWS compared to patients without OSA. There was striking NREM sleep stage dependence in OSA severity in both OSA patients and non-OSA patients, with progressive reductions in respiratory and arousal event rates from stage 1 to stage 4 sleep, that were systematically improved during lateral sleep. Respiratory and arousal event rates were strongly associated throughout NREM sleep. Patients with CSA showed similar patterns.

Previous studies of sleep-stage dependence of OSA severity have generally focussed on REM versus NREM sleep comparisons and shown elevated AHI in REM compared with NREM, while ignoring the changes in AHI within NREM sleep. The present study, conducted in a large clinic patient population, showed a marked reduction in AHI during SWS compared with stages 1 and 2 NREM sleep. These findings are similar to those in previous preliminary reports but extend these earlier observations by showing that the SWS effects are of a similar or greater magnitude than posture effects and that most patients, even those with moderate to severe OSA, can achieve low respiratory event rates in SWS. The magnitude of the improvement we observed amongst OSA patients in AHI during SWS versus stage 2 is similar to the deterioration in AHI observed in REM sleep compared with stage 2 sleep. The improvement in AHI frequency from stage 1 to 4 NREM sleep occurred regardless of the scored event type.

There are several possible reasons for the improvement in OSA during SWS. One possibility is that the upper airway becomes more neuromechanically stable with the onset of SWS. Alternatively, upper airway function could improve for some other reason, allowing patients to progress to deeper sleep. There is some evidence that the upper airway is better able to resist collapse during induced airway occlusion in SWS, but this finding was not replicated when passive airway function was measured by the Pcrit technique. In healthy volunteers, upper airway resistance is thought to be significantly higher during SWS than light sleep, despite genioglossal EMG activity being higher in this state, suggesting that, the upper airway is neuromechanically disadvantaged in SWS.

An alternate reason for OSA improvement with increasing NREM sleep depth may relate to sleep stage modulation of arousal propensity, and potentially to sleep stage modulation of post-arousal ventilatory responses. Poor airway function frequently triggers arousal, and there is emerging evidence that arousal responses themselves promote conditions that predispose the airway to re-collapse. The arousal index in this study was strongly NREM sleep stage dependent with a consistent relationship between arousal and respiratory indexes. Respiratory arousals from NREM sleep are thought to occur when progressively increasing respiratory effort or drive reaches a particular effort threshold. This threshold is significantly higher during SWS than light sleep, Arousal frequency following respiratory loading is reduced during SWS in healthy subjects. Studies have also shown much higher thresholds to non-respiratory stimuli during SWS than stage 2 sleep. Thus, reduced propensity to arouse from sleep during SWS may be an important cause for improvement in OSA.

Although protective upper airway dilatory responses are thought to be impaired during sleep, the upper airway does have the ability to respond to increasingly negative upper airway pressure and chemostimuli such as hypoxia/ hypercapnia, possibly in combination. Reduced arousal propensity during SWS may permit upper airway neuromuscular drive (chemo and/or mechanoreceptor mediated) to achieve sufficient activity to allow steady-state ventilation compatible with sustained sleep. Arousals from sleep may in fact promote ongoing cyclical breathing via post-arousal hyperventilation and a subsequent state of reduced drive, which may favor airway collapse. Theoretical models of OSA predict that a low arousal threshold predisposes to cyclical breathing, although this remains to be shown in OSA patients.

CSA patients were analyzed separately and showed a similar pattern of improvement in overall AHI from stage 1 to 4 NREM sleep. When the event type was analyzed, obstructive and central events improved significantly, whereas mixed events and hypopneas did not show a statistically significant change, unlike the OSA group. This likely reflects the small sample of CSA subjects studied (n = 14). Given the known strong con-
nection between central apneas and arousal, the reduction in AHI and CAI with increasing NREM stage is not surprising. However, this had not been described previously.

There are a number of limitations of this study. Given its observational nature, the causes of improved AHI during slow wave sleep remain speculative. Respiratory and arousal events were scored according to AASM and ASDA criteria respectively. Consequently, subcriterion events, either respiratory or arousal were not considered. However, given that the same criteria were applied across all sleep stages by a single technician within each patient, altered classification criteria and inter-patient scoring differences were unlikely to substantially influence the main within patient findings of this study. Our non-OSA group comprised of clinic referred patients and may not have been a “normal” group. Nevertheless, progressively lower respiratory and arousal event rates across NREM sleep stages, regardless of sleep posture in non-OSA and OSA patients remains consistent with important NREM sleep stage effects on OSA severity. It seems that regardless of the level of underlying anatomical compromise and propensity for upper airway collapse, most people can overcome this in SWS and achieve improved or near normal respiratory and arousal event frequencies.

We conclude that OSA, CSA, and non-OSA subjects demonstrate marked reductions in respiratory and arousal event rates during slow wave compared to light NREM and REM sleep. Further investigation into potential differences in upper airway behaviour and arousal responses to ventilatory challenges in light compared to SWS are warranted, and may lead to an improved understanding of the pathophysiology of OSA and ultimately, to improvements in therapy for this disorder.

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DISCLOSURE STATEMENT

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REFERENCES


