Respiratory Arousal in Mild Obstructive Sleep Apnea Syndrome

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Summary: The objective of the study is to identify patients with mild sleep apnea by counting not only apneas and hypopneas, but also mild respiratory events, which do not fulfill apnea or hypopnea criteria, but result in an arousal (Type-R arousal). Arousals related to body movements (Type-M arousal) were separately counted. The influence of nasal continuous positive airway pressure (nCPAP) on respiratory and movement arousals was analyzed. Daytime sleepiness before and after nCPAP and its relationship to arousal types was investigated using the Multiple Sleep Latency Test (MSLT) and a standardized questionnaire. Twenty-two patients with a mean age of 43.6±9.2 years underwent polysomnographic evaluation on a baseline night, and during three nights with nCPAP. On the baseline night, subjects presented with a mean RDI of 10.5±7.2/h, an apnea index (AI) of 1.2±1.5/h, a hypopnea index (HI) of 9.3±6.6/h, a R index of 5.2±5.9/h, and a M index of 9.7±5.6/h. Use of nCPAP lowered the RDI (p<0.001) and the R index (p<0.01). Mean sleep latency in the MSLT increased with nCPAP (p<0.05) and the patient’s subjective well being improved (p<0.01). Correlation analysis revealed a relationship between Type-R arousals and RDI and HI (r=-0.5, p<0.01) as well as between questionnaire scores and mean sleep latency. The decrease of Type-R indicates the positive effect of nCPAP. Arousal analysis and detection of mild respiratory events associated with arousals are helpful in investigating the sleep structure and in objectifying clinical symptoms and treatment success in patients with mild OSAS.

Key words: Detection and differential diagnosis of arousal; mild OSAS

INTRODUCTION

It is well established, that apneas and hypopneas cause significant sleep fragmentation, resulting in poor sleep quality and impaired daytime vigilance and performance. There is no clear association between the severity of sleep-disordered breathing (SDB), as measured by the number of apneas and hypopneas per hour sleep, and the degree of daytime sleepiness, as measured by the mean sleep latency (MSL) in patients with SDB. However, data from the literature indicates that sleep fragmentation itself can lead to significant impairment of daytime function, especially when caused by brief but frequent arousals.

Patients with mild OSAS or upper airway resistance syndrome (UARS) may present with symptoms similar to those of patients with severe sleep-apnea hypopnea syndrome, especially with regard to excessive daytime sleepiness (EDS). In these patients the number of apneas and hypopneas is relatively low or even negligible. However, several investigations in UARS patients have outlined the significance of obstructive breathing as measured by esophageal pressure changes, respiratory waveform changes, and recording of EEG arousals, for pathologically altered daytime alertness.

Arousals are an important pathophysiological mechanism for daytime sleepiness in UARS, mild and severe OSAS. Despite the fact, that not all respiratory events are accompanied by visible EEG arousals, arousal detection and differentiation have been established as a means for characterization of sleep quality. The less obvious a pathological sleep structure appears in conventional visual inspection of a polysomnogram, the more important this extended method of arousal detection becomes.

Therefore, the aim of this study was to analyze cases of mild sleep apnea by counting EEG arousals and respiratory events including not only apneas and hypopneas, but also mild respiratory events, if associated with EEG arousals. Arousals not related to respiratory events, but to body movements, were also detected.
nCPAP therapy (sufficient to abolish respiratory sleep disturbances) on arousals was evaluated. The MSLT and a standardized questionnaire were used to evaluate the relationship between changes in sleep structure and improvement of clinical symptoms under nCPAP therapy.

**METHODS**

**Characteristics of patient population**

Patients with a tentative diagnosis of SDB were recruited on the basis of overnight monitoring of respiratory activity, using a level III ambulatory sleep apnea monitor (MESAM IV, MAP, Germany). A sleep specialist assessed the associated symptoms such as EDS. Patients with lung disease or other sleep disorders were excluded from the protocol. Forty-seven patients with an oxygen desaturation index (ODI) of 10 or lower were invited for one night of diagnostic polysomnography (PSG#1) in the sleep lab. Patients were labeled as mild sleep apneics and subsequently included in the study, when daytime sleepiness, snoring, and an apnea index (AI) below 5 in PSG#1 occurred. We excluded 25 patients, who demonstrated an RDI>10 due to an AI>5, because they were suspected to suffer from a more severe OSAS. An RDI of 10 is a commonly used criteria for OSAS (RDI>10), and mild OSAS (RDI<10).

The mean age of the 22 remaining patients was 43.6±9.2 years. Mean body mass index (BMI) was 28.1±3.9 kg/m². No other sleep disorders, which could have been a cause for the EDS, were discovered through the history or the PSG.

**Study protocol**

The study protocol consisted of four nights. All 22 patients underwent a second PSG (PSG #2) and three consecutive nights of nasal CPAP therapy. PSG #2 was performed in order to confirm the diagnosis, and was subsequently used as a baseline study. PSG #3 and PSG #4 were nCPAP titration nights to reach the effective nCPAP pressure, and PSG #5 was performed without changing the previously established air pressure. Two titration nights were performed to achieve an optimal CPAP pressure and therefore an effective nCPAP treatment. In the third nCPAP night, according to that practice, therapy proved effective for all patients (i.e., respiratory events, snoring and oxygen desaturations were eliminated).

During daytime hours following nights PSG #2 and #5, a MSLT was performed using standard criteria. Trained personnel continuously monitored patients during the day to prevent them from sleeping outside the allotted periods.

Six months after nCPAP titration, all patients underwent ambulatory control studies by means of a MESAM IV device. The ODI was calculated, and subjective compliance was evaluated.

**Polysomnographic evaluations**

Time in bed (TIB) for all subjects was between seven and eight hours. None of the subjects had a habitual sleep time under seven hours prior to the study. The PSG recording started between 10 and 11 pm and lasted until 6 am. PSG included recording of two EEG leads (C3/A2 and O2/A1 from the 10-20 international electrode placement system), right and left electro-oculogram (EOG), submental electro-myogram (EMG), right and left anterior tibial EMG recording, ECG via modified V-2 lead, oro-nasal airflow using thermistors, snoring sound, abdominal and thoracic effort using uncalibrated inductive plethysmography, and oxygen saturation using pulse oximetry. These data were recorded using the 16-channel polysomnographic system SIDAS-GS (Respironics, Germany).

**Definition and differentiation of breathing disturbances**

**Apneas:** Apneas were scored using standard criteria. Hypopneas: For identification of hypopneas, we applied as criterion a decrease in the respiratory (thoracoabdominal) inductive plethysmography (RIP) signal of at least 50% from the preceding baseline. RIP was used in order to maintain a standard protocol for PSGs, although there is a reported limitation of this indirect measurement especially for detection of hypopneas. No oxygen desaturation was required to achieve scoring as hypopneas.

**Mild respiratory events:** Events that were associated with a visible drop in thoracoabdominal RIP-amplitude of between 20 and 50% from the preceding baseline for at least 10 seconds (effort limitation), and that led to visible arousals, were labeled mild respiratory events and scored as hypopneas. No oxygen desaturation was required for those events. Apnea index (AI), hypopnea index (HI), and RDI were calculated.

In accordance with other studies, the esophageal pressure was not measured because the recording was supposed to be as noninvasive as possible. This was considered especially important since other investigators reported a difference in the number of arousals associated with respiratory events between instrumented and noninstrumented study nights.

**Analysis of sleep and arousals**

Sleep was scored visually in 30-seconds epochs based on the criteria described by Rechtschaffen and Kales. To characterize sleep macrostructure we calculated: sleep period time (SPT), total sleep time (TST), sleep efficiency (SE, as TST/SPT*100%), REM density (percentage of 30-second REM epochs with phasic events), latencies of sleep (Sleep and SWS latency), sleep stage time (SST), percent-
ages of sleep stages in SPT and partial sleep periods (PSP). On the basis of the scored sleep stages, PSP were assigned when containing at least three consecutive epochs of sleep. The end of a sleep period was defined when at least three consecutive wake epochs occurred. The number of such periods and their mean length, as well as the sleep time in all PSP, were included as additional parameters for sleep macrostructure.

Transient events during sleep were scored visually on the basis of ASDA criteria. The duration of arousals was between three and 15 seconds. If an arousal period exceeded 15 s, it was classified as a wake stage, as defined by Rechtschaffen and Kales. Two arousal types (Type-R and Type-M) were separated on the basis of the source of transient events:

1) Type-R arousal: All EEG arousals that were directly associated with the end of apneas or hypopneas (including effort limitations). These arousals could or could not be accompanied with movements or body-position changes.

2) Type-M arousal: All EEG arousals that were not preceded or accompanied by respiratory events (apneas, hypopneas, effort limitations). These arousals were associated with EMG changes caused by body or leg movements or body-position changes.

An arousal was scored as either a Type-R or a Type-M arousal. EEG arousals without EMG- or other changes in cardiovascular or respiratory parameters were not considered since they were infrequent. One sleep physician visually scored arousals in both categories for all subjects independently of respiratory event scoring. Respiratory event classification was performed by a different scorer, who was blinded to EEG waveforms. After completion of respiratory event and arousal scoring, classification correlation between the two scoring sections was performed. Calculation of three different arousal indices followed, with analysis of TST:

1) R index=total number of Type-R arousals/TST [h],
2) M index=total number of Type-M arousals/TST [h],
3) TAI=total number of Type-R + Type-M arousals/TST [h].

The same indices were calculated for each sleep stage (1, 2, SWS, REM).

The MSLT and questionnaires

After night PSG#2 and #5, an MSLT was performed. Five diurnal sleep latency tests were performed at 0800 AM, 1000 AM, 1200 noon, 1400 PM and 1600 PM. We established the mean sleep latency for the complete test (S1mean). The test at 1600 PM was later excluded from the analysis due to dropouts based on poor patient compliance.

Additionally, subjective daytime tiredness and performance were assessed, using two modified standard questionnaires (morning and evening questionnaires) issued by the German Sleep Society. From each questionnaire we used two questions involving individual sleep quality and daytime well-being for analysis. From the morning questionnaire we asked: "How do you feel now?" and "How well did you sleep?" From the evening questionnaire we asked: "How do you feel now?" and "How do you judge your average daytime performance throughout the past day?" For each question there were six different possible answers, ranging from "very bad" to "very good". They were scored over a discrete scale in two-point increments. According to these scales, the score could vary from 4 to 24 for each protocol.

Statistical analysis

The target parameter for the statistical analysis was the R index. The distribution of all parameters was described as mean and standard deviation. For comparison between baseline (PSG#2) and third nCPAP night (PSG#5), we applied the student’s t-test. The effect of nights and sleep stages were assessed using ANOVA. Correlational analysis between PSG parameters and MSLT sleep latencies or questionnaire scores followed, based on the Pearson correlation index. As only one target variable (R index) was chosen and no \(\alpha\) adjustment was performed, the results for all other parameters have to be interpreted on a descriptive level.

The study was approved by the hospital Ethics Committee.

RESULTS

Respiratory parameters

The mean RDI for the population at baseline (PSG#2) was 10.5±7.1/h. We identified 1.2±1.5/h events as apneas and 9.3±6.6/h events as mild respiratory events and hypopneas. All patients were treated with nCPAP. The mean nCPAP pressure of 21 patients was 10.2±2.1/h mbar. One patient was treated with bi-level positive airway pressure (10/6 mbar). The RDI for all patients dropped to 3.1±3/h mbar. The A1 to 0.3±1/h and the HI to 2.9±3.1/h from baseline to the third nCPAP night (PSG#5) (p<0.001). The immediate compliance was very good in all patients.

Sleep macrostructure

Significant differences in sleep structure and arousal activity comparing PSG#1 and PSG#2 could not be detected.

Macrostructural analysis of sleep did not reveal major changes under nCPAP-treatment. Comparing parameters of sleep macrostructure between baseline and two CPAP titration nights, significant changes occurred only in REM den-
Comparing baseline and the three nCPAP nights (ANOVA), there was a decrease of Sleep and SWS latencies as well as REM density (p<0.05). No significant changes could be seen in the analysis of partial sleep periods.

Arousal and respiratory event analysis

Improvement of sleep fragmentation with nCPAP became evident from the results of arousal analysis (Table 2). The R index fell from 5.2±5.9/h in the baseline night to 0.7±1.5/h in the third nCPAP night (p<0.01, ANOVA). Likewise, a slight decrease in TAI from 14.9 ± 8.6/h before therapy to 11.2±11.6/h in PSG #5 was detected. The M index did not change significantly.

Analysis of arousals by sleep stages disclosed that Type-M arousals dominated in all four nights (PSG#2-5) in NREM 1 and 2 (p<0.05). Type-R arousals tended to occur more often during REM 1. Nasal pressure ventilation led to a reduction in the R index in NREM-sleep stages 1 and 2 (p<0.01, ANOVA) (Table 2).

The MSLT and questionnaires

A complete MSLT could be performed in 18 patients. Three patients did not agree to carry out the MSLT protocol completely. The MSLT before (PSG #2) and after therapy (PSG #5) revealed a significant prolongation of mean SL (9.4±4.4 vs. 12.9±5.3, p<0.05) (Table 3).

We were able to analyze morning and evening questionnaires for 16 of the 22 patients. The score from the morning questionnaires increased from 18.2±4.4 in the first protocol (after PSG #2) to 22.8±2.9 at the end of treatment (p<0.01). Scores in the evening questionnaires increased from 21.9±3.2 before PSG #2 to 27.4±3.5 after PSG #5 (p<0.01).

Correlational analysis

We determined a significant correlation between the R index and the HI (r=0.58; p<0.01), as well as between the R index and the RDI (r=0.62; p<0.01). Furthermore, we established a correlation between the change of R index under nCPAP treatment and the change of RDI (r = 0.62, p < 0.01) and HI (r=0.82, p<0.01). No significant relationships were found between TAI and M index, and RDI and HI, respectively.

Concerning MSLT and nocturnal sleep, a correlation between SLmean and ASL could be confirmed (r=0.73, p < 0.01). No other correlation to parameters of sleep macrostructure was detected. Analysis of relationships between latencies in MSLT and nocturnal breathing disturbances before and with nCPAP therapy revealed a slight negative correlation between the SLmean and the HI (r=−0.22). Furthermore, we detected a significant correlation between the scores of the questionnaires and HI and RDI (r...
=-0.5, p<0.01). No correlation was found between either
the sleep latency or questionnaire scores and arousal
indices.

nCPAP follow-up

Six months after titration of nCPAP, ambulatory moni-
toring revealed a RDI of 0.2 ± 0.2/h in the 22 patients with
mild OSAS. All patients reported long-term treatment suc-
cess with loss of EDS. They used their nCPAP machines
continuously throughout every night. No side effects were
documented.

DISCUSSION

The patients with mild OSAS included in our study suf-
fered from non-apneic snoring, daytime tiredness, and
fatigue and demonstrated an apnea index below 5/h, as well
as arousals from sleep. Beside apneas and hypopneas, mild
respiratory events were also counted. These events corre-
spended to visible drops in breathing effort independent of
oxygen desaturations, but associated with arousal. They
were added to the HI.

Comparing with other studies, the total arousal index
(TAI) in the baseline night (14.9±8.6/h) corresponded to
the average amount of arousals in normals, OSA, and mild
OSA patients. Chugh and coworkers27 determined a TAI of
0-15 in 336 OSAS patients with a mean RDI of 4.04/h, and
a TAI of 15-25/h in 448 OSAS patients with a mean RDI of
9.09/h. Mathur and coworkers 24 established a median
arousal index of 21/h in normal subjects. Our findings
appear to be within their physiological range. In contrast to
other studies,28 Marthur et al. 24 reported no differences in
arousal frequency between patients with or without snoring
and daytime sleepiness or witnessed apneas. Our patients
with mild OSAS could well belong to this group.

An analysis of the distribution of the arousals in the dif-
ferent sleep stages showed in the baseline night a clear pre-
dominance in stage 1 and, to a lesser extent, in stage 2,
regardless of the arousal type. It is known, that the arousal
threshold, especially for respiratory events, is lowest in
these stages.6

The indication for nCPAP therapy for patients with mild
SAS is the occurrence of EDS, similar to the EDS found
among OSAS and UARS patients. With nCPAP treatment,
the mild respiratory events, hypopneas and apneas were eliminated. However, when comparing the nCPAP nights with the baseline, our findings disclose only a mild decrease in the overall number of arousals. The TAI seems to be insensitive for measuring the effect of therapy in mild SAS. We found, that the majority of arousals, even in the baseline night, were Type-M arousals. This fact corresponds to other data, which showed a decrease in the proportion between apnea/hypopnea related arousals and arousals not related to respiratory events, when the RDI decreased with treatment. The M index did not change during the treatment nights, as seen in patients with severe OSAS. This arousal fraction seems to be necessary for maintenance of a normal sleep profile, and it also seems to be independent of breathing disorders or nCPAP influence. A treatment effect was observed in the EEG only with respect to respiratory arousals, although the range of changes in the R index was not as high as in OSAS patients. A possible explanation is that not all apneas and hypopneas are associated with a visible arousal. This could be due to their subcortical nature (i.e., autonomic arousal), topological distribution (i.e., frontal arousals) or due to their morphology (i.e., delta bursts).

In consensus with the reduction of respiratory-related arousals, clinical symptoms improved with pressure ventilation, as proven either in the MSLT, in the questionnaire, or in both. In the MSLT, a significant increase in the mean sleep latency with nCPAP treatment became apparent. These results corroborate the importance of nCPAP treatment on daytime alertness in patients with mild SAS.

In contrast to these findings, the patients with mild OSAS demonstrated a fairly normal sleep macrostructure, which did not change with nCPAP treatment, not even when recruiting additional parameters like length of PSP. The only significant increase in Sleep and SWS latencies and REM density occurred in the third nCPAP night. An occurrence of SWS and/or REM rebound, as often encountered during initiation of OSAS treatment, did not become evident. However, in direct night-to-night comparison, SWSL and amount of sleep stage 1 decreased, but only in the two titration nights. The relatively high percentage of stage 1 and the low percentage of stage REM in the third nCPAP night may be due to a “last night effect” (night before discharge), or even a result of the first two CPAP nights.

Since the subjective treatment success in mild SAS cannot be explained by changes in sleep macrostructure alone, we assume that analysis of mild respiratory- events associated with arousals and analysis of all respiratory and movement-related arousals is essential in providing effective treatment in patients with mild OSAS.

According to our scoring criteria, the hypopneas included mild respiratory events associated with transient EEG changes. On the basis of our definition, a correlation between Type-R arousal and the hypopnea index or the RDI should be expected — and was subsequently verified by our results. However, this correlation was not very strong, supposedly because both the RDI and the HI contain events that are not associated with arousals. Although it should be expected that apneas typically provoke an arousal response, no correlation between apnea index and the R index was observed in our patients. This result can be explained by their small fraction of the overall RDI (AI< 5/h). It is more likely that hypopneas and mild respiratory events leading to arousal are the main cause of daytime sleepiness in mild OSAS. This hypothesis is supported by the negative correlation between the hypopnea index and the questionnaire scores and the slightly negative correlation between the HI and the MSLT. A correlation between the arousal indices and the MSLT could not be found. Such a correlation is rare even in patients with severe OSAS, although Roehrs et al. 1989 found that arousal appearing at the end of respiratory events are among the best predictors of daytime sleepiness.

In conclusion, the reduction of respiratory related arousals with nCPAP resulted in an improvement in objective and subjective daytime outcome, whereas the movement related arousals seem to be part of the physiological range. The detection and differentiation of arousals — notably respiratory arousals related to mild respiratory events, hypopneas and apneas — represent a good technique for recognizing mild OSAS. They provide assistance in verifying clinical symptoms and therapy control in patients with mild OSAS.

REFERENCES