Prolonged partial obstruction during sleep is a NREM phenomenon

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Abstract

Objective: Prolonged partial obstruction (PPO) is a common finding in sleep studies. Although not verified, it seems to emerge in deep sleep. We study the effect of PPO on sleep architecture or sleep electroencephalography (EEG) frequency.

Methods: Fifteen OSA patients, 15 PPO+OSA patients and 15 healthy subjects underwent a polysomnography. PPO was detected from Emfit mattress signal. Visual sleep parameters and median NREM sleep frequency of the EEG channels were evaluated.

Results: The amount of deep sleep (N3) did not differ between the PPO+OSA and control groups (medians 11.8% and 13.8%). PPO+OSA-patients' N3 consisted mostly of PPO. PPO+OSA patients had lighter sleep than healthy controls in three brain areas (Fp2-A1, C4-A1, O1-A2, p-values < 0.05).

Conclusion: PPO evolved in NREM sleep and especially in N3 indicating that upper airway obstruction does not always ameliorate in deep sleep but changes the type. Even if PPO+OSA-patients had N3, their NREM sleep was lighter in three EEG locations. This might reflect impaired recovery function of sleep.

Keywords: OSA, partial obstruction, Emfit, sleep EEG, flow limitation, sleep-disordered breathing, breathing effort

Introduction

Phenotyping has opened up new ways of evaluating the pathophysiological processes behind sleep disordered breathing (SDB) and addressing the treatment options. Different methods to phenotype obstructive sleep apnoea (OSA) have been presented. For example, cluster analysis has revealed phenotypes associated with position and sleep stages (Joosten et al., 2012).

OSA, assessed using the apnoea-hypopnea index (AHI), is commonly more severe in supine position than in other postures (Cartwright, 1984, Pevernagie and Shepard, 1992, Cartwright et al., 1991). The pressure at which the pharynx collapses (P_{CRIT}) is found to be higher in supine than side position (Boudewyns et al., 2000, Isono et al., 2004, Ong et al., 2011, Penzel et al., 2001), and the higher AHI in supine position may be related to anatomical features (Isono et al., 2002,Ono et al., 2000,Saigusa et al., 2009), although the findings are not consistent (Jan et al., 1994, Walsh et al., 2008, Pevernagie et al., 1995, Martin et al., 1995).

In general, the AHI is higher in rapid eye movement (REM) sleep than in non-REM (NREM) sleep (Cartwright et al., 1991, Oksenberg et al., 2010). In addition, the AHI diminishes in deep sleep (Ratnavadivel et al., 2009). However, the usefulness of the AHI alone to quantify SDB has been criticised because long periods of prolonged partial obstruction without apnoea or hypopnea are common in SDB patients (Anttalainen et al., 2016, Tenhunen et al., 2013). Prolonged partial obstruction causes flow limitation in the nasal pressure signal (Hernandez et al., 2001) and can be assessed quantitatively by measuring oesophageal pressure (see Bao and Guilleminault, 2004). One feasible way to evaluate prolonged partial obstruction is the Emfit mattress sensor. The sleep mattress signal is usually scored into different breathing categories

in 3-min epochs. Simply, the mattress signal is divided into three different breathing categories: non-obstructive breathing (NOB), periodic obstructive breathing (POB) that comprises periodic apnoea and hypopnea, and prolonged partial obstruction (PPO).

Based on our preliminary finding, it seems that PPO manifests during NREM sleep and also during deep NREM sleep (Rauhala et al., 2007). The aim of the present study is to clarify the appearance of PPO in the sleep stages. In addition, we evaluate whether PPO has an effect on the sleep architecture and frequency of NREM sleep electroencephalography (EEG). Furthermore, we evaluate the impact of sleeping position on PPO.

2. Methods

All patients were referred to the Sleep laboratory of Tampere University Hospital because of possible obstructive sleep apnoea (OSA). The control subjects were healthy volunteers recruited through advertisements. The volunteers received no payment for their participation in the study. Both patients and controls were first interviewed by telephone to make sure they met the eligibility criteria: aged between 20 and 65 years, no (other) sleep disorders, no clinically significant medical disorder (e.g., neurological illness, psychiatric disorder, hypo-/hyperthyroidism and no lung diseases other than currently asymptomatic asthma), no medication affecting the central nervous system and no substance or alcohol abuse. The patients' OSA diagnosis and the controls' healthiness were then confirmed by clinical interview and a diagnostic full-night polysomnography in a sleep laboratory. The OSA diagnosis was based on a clinical picture and subjective complaints of OSA and an AHI of > 10/h. The controls had to be asymptomatic and had an AHI of ≤ 5/h. The study was approved

by the Ethical Committee of the Pirkanmaa Hospital District and all the subjects gave their written informed consent.

Sleep recordings were performed with the Embla N7000 device and Somnologica Studio software (Medcare®, Iceland). The recordings comprised six EEG derivations (Fp1-M2, Fp2-M1, C3-M2, C4-M1, O1-M2, O2-M1), two EOG channels, three electromyogram channels (chin and both legs), airflow measured with a thermistor and a nasal pressure transducer, thoracic and abdominal respiratory movements, pulse oximetry and position. In addition, an Emfit mattress (32 cm x 62 cm x 0.4 cm) was placed under a normal foam mattress below the thoracic area of the sleeping subject. The unfiltered Emfit signal was acquired directly as a separate trace in the Somnologica software. A sampling rate of 2 Hz was used for the pulse oximeter (SpO_2 and pulse rate), 10 Hz for respiratory movements and 200 Hz for all the other signals.

2.1. Visual analysis

Polysomnographies were classified into sleep stages according to standard criteria (Iber et al., 2007). The AHI was calculated as the number of obstructive apnoea and hypopnea per hour of sleep (Berry et al., 2012). In addition to total AHI, the AHI was calculated separately for supine and non-supine positions and for NREM sleep and REM sleep. Arousals were scored according to the criteria of the American Sleep Disorders Association (AASM, 1992).

The Emfit signal was visually scored in 3-min epochs into breathing categories as described in our previous work (Tenhunen et al., 2013). The mattress breathing categories used were non-obstructive breathing (NOB), obstructive periodic breathing (POB), and prolonged partial

obstruction (PPO). PPO in Emfit signal is comprised of continuous respiratory-induced spikes, which are known to appear with increasing breathing effort (Figure 1, Kirjavainen et al., 1996).The Emfit signal was scored visually from a lights off-event to the final awakening by two independent scorers with a scoring agreement of 87.8% (median, range 76.9% to 95.7%). The two independent scorers formed the consensus scoring used in the analyses. The percentage of time (referred to as TST) for NOB, POB and PPO were calculated. In addition, the number and the length of PPO-periods were calculated. Due to the epoch scoring, the minimum length of a PPO-period was 3 min.

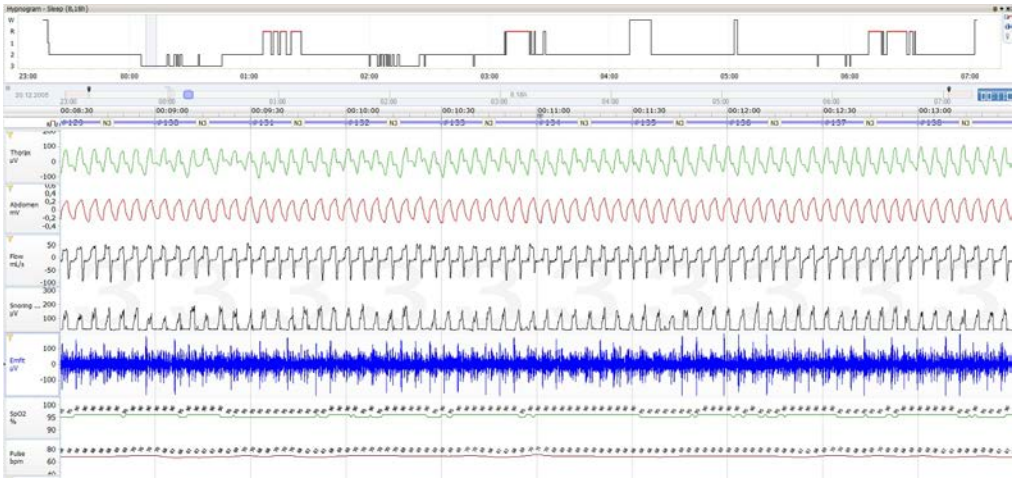

Figure 1. Five minutes epoch of deep sleep (N3) with prolonged partial obstruction. Breathing is stable, nasal flow signal shows mild flow limitation. Patient is snoring. Continuous spikes in the Emfit signal. Oxygen saturation values are normal.
Channels from top: Thorax belt, Abdomen belt, Airflow by nasal prongs, Snoring, Emfit signal, Oxygen saturation, Pulse.

In total, 45 OSA patients and 20 control subjects took part in the study. To evaluate the effect of prolonged partial obstruction (PPO) on sleep architecture, we formed three age-matched groups based on the AHI and amount of PPO-pattern. The OSA group had to have an AHI $\geq$

10, and time with PPO (as percentage of total sleep time) < 5%. The OSA+PPO group had to have an AHI ≥ 10 and PPO ≥ 15%. The subjects in the control group had to have an AHI < 5/h and PPO < 5%. Fifteen control subjects and 30 patients fulfilled the inclusion criteria, and each group comprised 15 male subjects.

2.2 Calculation of EEG median frequency

Mean frequency values were computed from each of the six EEG channels at 1-s time resolution by applying the method described in our previous work (Huupponen et al., 2009, Huupponen et al., 2011). This provided six overnight mean frequency curves with values ranging from 0.5 Hz to 30 Hz. The median of the mean frequency values during the NREM sleep time was extracted from each EEG channel.

2.3. Statistical analysis

Statistical analyses were performed with IBM® SPSS® Statistics version 22 (IBM corp.) with non-parametric tests because some of the parameters were not normally distributed and the sample sizes were small. The Friedman test and Kruskall-Wallis test were used to compare the multiple dependent and independent variables, respectively. The post hoc analyses were made by using the Wilcoxon and Mann-Whitney U-tests and the comparisons were Bonferroni corrected. The probability level of 5% was considered to be significant in the statistical tests.

3. Results

The demographic data and sleep parameters of the subject groups are presented in Table 1. The groups did not differ by age, but the patients in the PPO+OSA group and in the OSA group weighted more than the control subjects. Both patient groups presented more daytime sleepiness than the controls as assessed by Epworth Sleepiness Scale (ESS).

There were no statistical differences between the groups in the sleep efficiency (SEI) or in the amount of N1 or REM sleep. The amount of deep sleep (N3) was diminished in the OSA group when compared with the other groups, and N2 sleep was more abundant in the OSA group than in the control group.

Table 1. Demographic and polysomnographic data of the groups with the statistical comparisons. The statistically significant p-values are bolded.

	PPO+OSA (1)		OSA (2)		Controls (3)		1 vs. 2	1 vs. 3	2 vs. 3
	median	min-max	median	min-max	median	min-max		p-values	
age, years	44	28-65	45	30-63	40	30-63	0.660	0.567	0.193
ESS	12	9-22	9	5-19	4	0-9	0.779	**<0.001**	**<0.001**
BMI, kg/m2	26.5	24.3-36.3	30.4	23.0-41.4	23.8	20.1-30.2	0.168	**0.012**	**<0.001**
TST, min	426.0	347.5-582.0	437.0	330.0-557.0	442.0	358.0-527.0	1.00	1.00	0.617
SEI, %	93.0	86.0-99.5	92.0	65.9-96.1	91.0	79.0-98.0	1.00	1.00	1.00
N1, %	5.9	1.7-10.4	4.9	1.2-18.5	5.4	2.2-16.3	1.00	1.00	0.662
N2, %	62.5	49.5-80.0	74.8	47.6-85.3	59.5	45.4-71.7	0.064	1.00	**0.004**
N3, %	11.8	6.9-22.8	0.6	0.0-15.4	13.8	4.7-25.2	**0.001**	1.00	**0.001**
REM, %	18.0	4.9-26.6	17.4	8.6-21.6	19.4	13.1-27.8	1.00	1.00	0.406
AHI, n/h	34.0	10.8-48.0	50.9	15.8-103.0	3.0	0.0-4.9	0.103	**<0.001**	**<0.001**
AHI REM, n/h	45.0	7.3-67.0	35.0	27.5-87.5	5.2	0.0-14.8	1.00	**<0.001**	**<0.001**
AHI NREM, n/h	31.1	10-54.4	56.2	12.2-106.0	1.7	0.0-4.6	0.079	**<0.001**	**<0.001**
AHI supine, n/h	44.2	11.3-70.1	75.7	19.0-105.5	2.0	0.0-8.2	0.057	**<0.001**	**<0.001**
AHI non-supine, n/h	26.2	0.0-49.3	39.9	0.0-110.0	0.4	0.0-5.8	0.121	**<0.001**	**<0.001**
ARI, n/h	26.6	9.4-38.0	41.1	15.8-95.1	12.2	4.3-22.8	0.114	**0.001**	**<0.001**
ODI4%, n/h	13.0	0.0-41.0	32.0	1.0-88.0	0.4	0.0-3.0	0.266	**<0.001**	**<0.001**
NOB, %	28.1	3.1-68.9	24.9	0.4-87.0	97.5	85.9-99.3	0.330	**<0.001**	**<0.001**
POB, %	48.0	13.5-66.5	75.1	12.3-99.1	2.1	0.0-12.3	0.330	**<0.001**	**<0.001**
PPO, %	23.4	15.4-36.0	0.0	0.0-4.7	0.0	0.0-4.9	**<0.001**	**<0.001**	0.658

Abbreviations: ESS = Epworth Sleepiness Scale; BMI = body mass index; TST = total sleep time; SEI = sleep efficiency of TST; N1%-N3% = percentage of sleep stage 1-3 referred to TST; REM% = percentage of REM sleep referred to TST; AHI = apnea-hypopnea index; ARI = arousal index; ODI4% = oxygen desaturation index; NOB = percentage of time with non-obstructive breathing referred to TST; POB% = percentage of time with periodic obstructive breathing referred to TST; PPO% = percentage of time with prolonged partial obstruction referred to TST.

Median NREM EEG frequency (in Hz) was separately calculated for each EEG channel (Figure 2). The EEG frequency was significantly higher in the OSA group than in the PPO+OSA group and the controls in all EEG-derivations. In addition, EEG frequency was higher in the PPO+OSA group than the controls frontopolarly and centrally in the right hemisphere (Fp2, C4) and occipitally in the left hemisphere (O1).

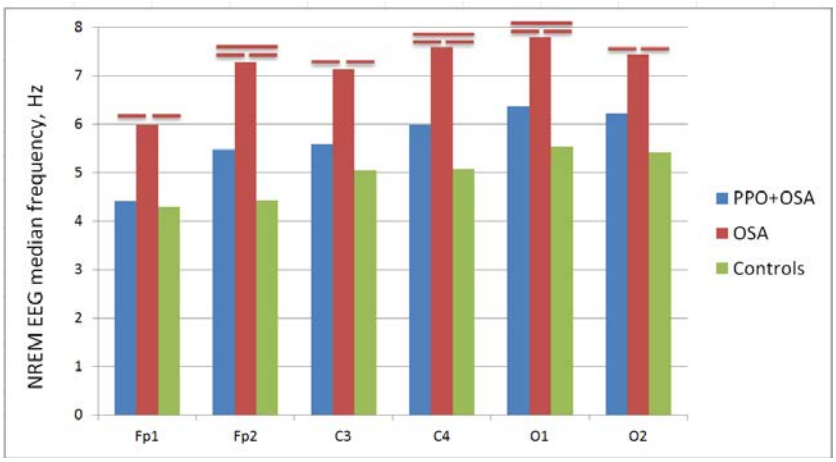

Figure 2. Median NREM EEG frequency in all EEG derivations. The statistically significant differences (Bonferroni corrected p-values < 0.05) are marked with lines.

3.1. AHI, sleep stages and position

As expected, all the calculated AHIs as well as the desaturation index (ODI4) were lower in the control group than in the patient groups (Table 1). In the control group, the AHI in REM

sleep (AHI REM) was higher when compared with the AHI in NREM sleep (AHI NREM, Table 1, p-value 0.005). The median AHI REM seems higher than the AHI NREM in the PPO+OSA group, whereas in the OSA group the median AHI NREM seems higher than the AHI REM. The AHI REM/AHI NREM comparisons within these groups did not, however, reach statistical significance.

In the PPO+OSA group, the AHI in supine position was higher compared with the AHI in non-supine position (p=0.017). No significant differences were found in the OSA group or control group (p-values 0.128 and 0.363, respectively).

3.2. Mattress breathing categories with the effect of position

The control group had more non-obstructive breathing (NOB) than the two patient groups, whereas no statistical difference in NOB% was obtained between the PPO+OSA and OSA groups (Table 1). Both patient groups had more periodic obstructive breathing (POB) than the control group. Due to the inclusion criteria, the PPO+OSA group had clearly more prolonged partial obstruction (PPO) than the other groups. No difference in the amount of PPO was found between the OSA group and the control group.

The total number of PPO-periods in the study sample was 69. PPO+OSA patients had 61 PPO-periods, the OSA group had 6 PPO-periods and healthy controls 2 PPO-periods. The median length of the PPO-periods was 15 min (3 min to 57 min). The PPO-periods of the PPO+OSA patients were in general longer than the periods in the OSA and control groups (medians 18 min, 4.5 min and 6 min, respectively). However, due to the small number of PPO-periods in the OSA and control groups, statistical comparisons could not be performed.

The PPO+OSA group had prolonged partial obstruction in both supine and non-supine positions (Figure 3). POB was more abundant in supine position and NOB in non-supine position. The OSA group had POB more in supine position and more NOB in non-supine position. The control subjects had mostly non-obstructive breathing with no position-dependent differences.

Figure 3. Mattress breathing categories (percentage of time referred to total sleep time) in different sleeping positions. Median values are presented. The statistically significant differences are marked with lines and denoted with the p-values.

3.3. Mattress breathing categories and sleep stages

In N1 sleep, both the PPO+OSA group and the OSA group had more NOB and POB than PPO (Figure 4, Table 2), but there was no statistically significant difference between the amount of NOB and POB. The control group had mostly NOB, and the least common breathing category was PPO.

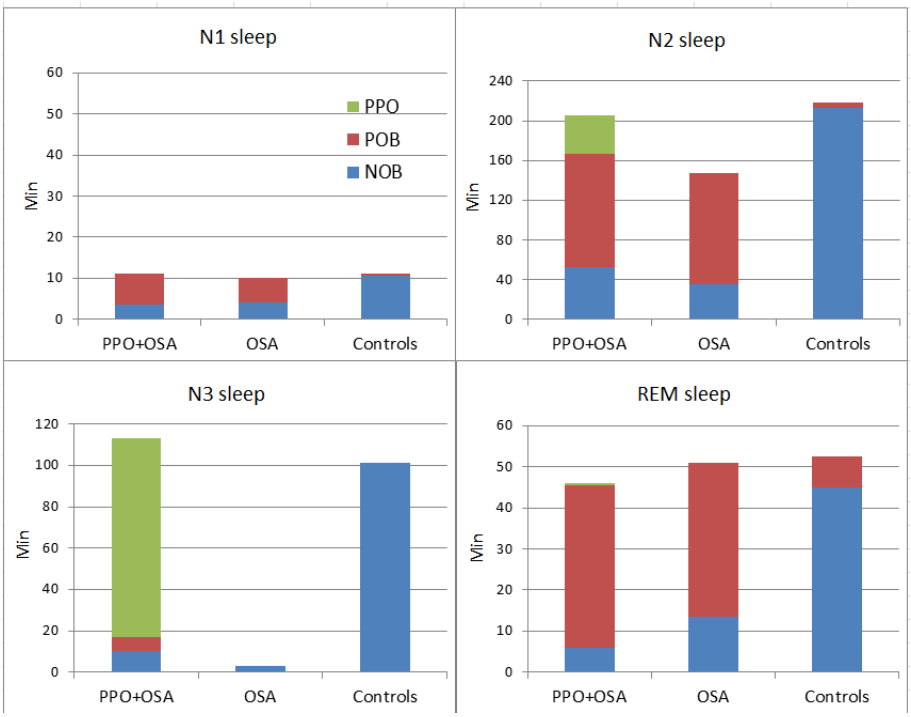

Figure 4. The appearance of mattress breathing categories (in minutes, median values) of the study groups in different sleep stages. Please note the different time scales.

In N2 sleep, the PPO+OSA group had more POB than PPO, with no other significant findings. OSA patients had more NOB and POB than PPO. The control group had mostly normal breathing, and PPO was the least common breathing category.

During N3 sleep, the most common breathing category in the PPO+OSA group was PPO. The OSA group had more NOB than PPO, but the other differences did not reach statistical significance. NOB was the most common breathing category in the control group during N3.

In REM sleep, both the PPO+OSA group and the OSA group had more NOB and POB than PPO, but the amount of NOB did not differ from POB. NOB was the most common breathing category, and PPO was the least common breathing category in the controls.

Table 2. The p-values of the comparisons between the breathing categories in different sleep stages.

		NOB vs POB	NOB vs PPO	POB vs PPO
		p-value	p-value	p-value
N1	OSA+PPO	1.000	0.008	0.003
	OSA	0.473	0.010	0.002
	Controls	0.002	0.002	0.023
N2	OSA+PPO	0.634	0.920	0.006
	OSA	0.768	0.011	0.002
	Controls	0.002	0.002	0.039
N3	OSA+PPO	0.594	0.003	0.002
	OSA	0.181	0.040	1.000
	Controls	<0.001	0.001	0.539
REM	OSA+PPO	0.183	0.028	0.003
	OSA	0.107	0.023	0.002
	Controls	0.002	0.002	0.027

NOB, non-obstructive breathing; POB, periodic obstructive breathing; PPO, prolonged partial obstruction.

4. Discussion

In this study, we evaluated the appearance of prolonged partial obstruction (PPO) in sleep stages and found that in OSA patients with prolonged partial obstruction (PPO+OSA) PPO is solely a NREM sleep phenomenon, emerging especially in deep sleep. The other important finding was that some OSA patients have a lot of deep sleep without apnoea, but with prolonged upper airway obstruction.

In our study, the amount of deep sleep of OSA patients remained low, which is a common finding. In the PPO+OSA group, however, the amount of visually scored slow wave sleep was high and did not differ from the amount of N3 of the normal controls. To the best of our knowledge, the effect of PPO on sleep architecture and sleep EEG in OSA patients has not been previously evaluated. The cumulative increase in transcutaneous carbon dioxide tension during PPO but not during periodic apnoea (Rauhala et al., 2007, Rimpila et al., 2014) might be responsible for the greater share of N3 in PPO+OSA patients, since hypercapnia is known to increase deep sleep (Halpern et al., 2003, Wang et al., 2014, Nguyen et al., 2016). However, PPO+OSA patients had lighter sleep than the control group in three EEG-derivations. Our results suggest that the sleep process might be impaired in PPO+OSA patients even if their visual sleep stage values were within normal ranges. In our study protocol, the effects of OSA hampered the EEG conclusions. Therefore, a future study that includes patients with prolonged partial obstruction without OSA should be conducted.

The PPO+OSA group had a higher AHI in supine position than in non-supine position, but the criteria of positional OSA were not fulfilled. Furthermore, sleeping position had no effect on the amount of PPO in PPO+OSA patients. No clear differences between the AHI in NREM and REM sleep were obtained in the patient groups. This suggests that PPO has no marked association with either the supine predominant or the REM sleep predominant phenotypes of OSA, and there have to be additional factors that account for the building of prolonged partial obstruction during sleep. Eckert (2018) presents SDB phenotypes that take into account several anatomical and non-anatomical features of OSA. The first feature is the stability of respiratory control, which can be estimated using the concept of loop gain. Loop gain denotes the strength of the negative feedback loop, where a disturbance in breathing (for example apnoea with hypoxia/hypercapnia) induces a corrective response (hyperventilation). If loop

gain is high, the correction reaction is excessive leading to oscillating breathing and recurrent apnoea. The association between loop gain and position is not consistent (Joosten et al., 2015), but in some OSA patients high loop gain seems to persist during almost the whole night, as was the case with our OSA-patients who had respiratory events regardless of their position.

Normal loop gain predisposes to stable breathing resulting in eucapnia (Hernandez and Patil, 2016). Hypoventilation with an increase in carbon dioxide tension may occur if loop gain is low (Eckert, 2018). Because prolonged partial obstruction presents with a cumulative increase in carbon dioxide concentration (Rimpila et al., 2014, Rauhala et al., 2007) without oscillating breathing (Tenhunen et al., 2011, Rauhala et al., 2007), it is assumed that in PPO+OSA patients, for some reason, loop gain lowers inducing PPO. In general, our PPO+OSA patients were only mildly obese, and therefore this phenomenon cannot be considered as obesity hypoventilation.

The second feature that Eckert introduced was arousal threshold that reduces in deep sleep (Eckert, 2018), and it has been reported that some OSA patients can achieve deep sleep without apnoea (Ratnavadivel et al., 2009). In fact, our OSA group had non-obstructive deep sleep, even if its amount remained low. Instead, the patients with PPO+OSA had plenty of deep sleep and one of our main findings was that their deep sleep was not free from upper airway obstruction but consisted mostly of prolonged partial obstruction. This means that in these patients SDB did not recover in deep sleep but changed type. It might be that the decrease in arousability during deep sleep predisposes some patients to prolonged partial obstruction, which is in accordance with the finding that arousals are infrequent during prolonged partial obstruction (Tenhunen et al., 2011, Rauhala et al., 2007).

Eckert's third feature (Eckert, 2018) is the neuromuscular function of the upper airway. Genioglossus activity is high during deep sleep compared with other sleep stages (Carberry et al., 2016). This might, in part, explain the occurrence of deep sleep in OSA patients. PPO is common in females, but the findings have not been consistent. However, hormonal regulation might play a role in PPO, since progesterone is known to stimulate respiration and increase genioglossus activity (Porkka-Heiskanen et al., 2014, Popovic and White, 1998). Furthermore, anatomical features might predispose to the emergence of prolonged partial obstruction. For example, micrognathia is found to be more common in women with PPO than in women with OSA (Anttalainen et al., 2013), and patients with PPO+OSA have been found to have narrower airways at the hypopharyngeal level than OSA patients (Polo et al., 1991). Moreover, flow limitation is associated with abnormal nasal structure and voluminous upper airway lateral wall (de Godoy et al., 2015).

Prolonged partial obstruction can last from several minutes up to about an hour, as in our study. During PPO, breathing prevails against a partially closed upper airway, airflow diminishes, snoring is often continuous and breathing effort increases. Evaluating flow limitation measured by nasal pressure transducer signal, which is considered as a marker of partial collapse in upper airways, is a more common method to quantify partial obstruction than the Emfit signal that is used in our study (Hernandez et al., 2001, Bao and Guilleminault, 2004, Johnson et al., 2005, Sabil et al., 2004, Condos et al., 1994). Measuring flow limitation is, however, problematic since nasal prongs may even increase upper airway resistance (Lorino et al., 2000), and obstruction may prevail without flow limitation (Tenhunen et al., 2011). Moreover, flow limitation is not always caused by upper airway obstruction (Condos et al., 1994), but instead may indicate a decrease in breathing effort (Arora et al., 2015). A

simultaneous increase in transcutaneous carbon dioxide with flow limitation confirms its obstructive nature (Rimpila et al., 2014), but carbon dioxide is not always routinely measured in sleep studies. The Emfit mattress measures breathing effort (Tenhunen et al., 2011, Kirjavainen et al., 1996) and provides an additional easy and noninvasive means to quantify different types of sleep disordered breathing.

Prolonged partial obstruction is often considered to be a milder form of SDB than OSA, even if the patients may have severe symptoms, such as fatigue, depressive symptoms, morning headache and decreased quality of life (Anttalainen et al., 2016). Our study cannot address why some patients have PPO. We can, however, show that even if patients with PPO+OSA are as sleepy as OSA patients, they have more N3. They also have deeper sleep than OSA patients in all EEG derivations. Moreover, they present with lighter sleep than healthy controls in the same EEG derivations that show a reduced amount of slow EEG frequencies in OSA patients with six months of CPAP treatment (Saunamaki et al., 2009). Poor quality sleep might explain some of the subjective symptoms of PPO patients. In addition, the increased inspiratory effort related to PPO may induce sleepiness (Pelin et al., 2003). In general, PPO patients present with good adherence to CPAP treatment (Anttalainen et al., 2007, Myllyla et al., 2016).

Phenotyping provides improved understanding of the mechanisms and treatment options for SDB. Prolonged partial obstruction results in different findings than OSA; it emerges in deep sleep, carbon dioxide tension increases cumulatively, and it is not composed of arousals. Medications that reduce the arousal threshold (Eckert et al., 2011) are not expected to be useful in this SDB phenotype with infrequent arousals (Tenhunen et al., 2011). Moreover, reducing the arousal threshold might even be unsafe, as in obesity hypoventilation (Jordan et

al., 2017). Treatments that reduce loop gain, such as oxygen therapy (Wellman et al., 2008,Terrill et al., 2015), do not seem to be the correct choice either. Instead, oropharyngeal exercise (Camacho et al., 2015), drugs that increase muscle activity (Taranto-Montemurro et al., 2016) and upper-airway stimulators (Boon et al., 2018) could be helpful. However, if they only remove respiratory events and prolonged partial obstruction remains, there might be a risk of an excessive increase in carbon dioxide. We therefore suggest that, in addition to common respiratory parameters, the detection of prolonged partial obstruction may be useful in evaluating sleep disordered breathing and in making treatment decisions.

Acknowledgements

The study was financially supported by Tekes (1860), the National Technology Agency of Finland and by the Competitive Research Financing of the Expert Responsibility area of Tampere University Hospital, Grant numbers 9M014 9P013, 9R007, 9S007 and 9T008.

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