Snoozfit Technical Documentation

Controlled Document

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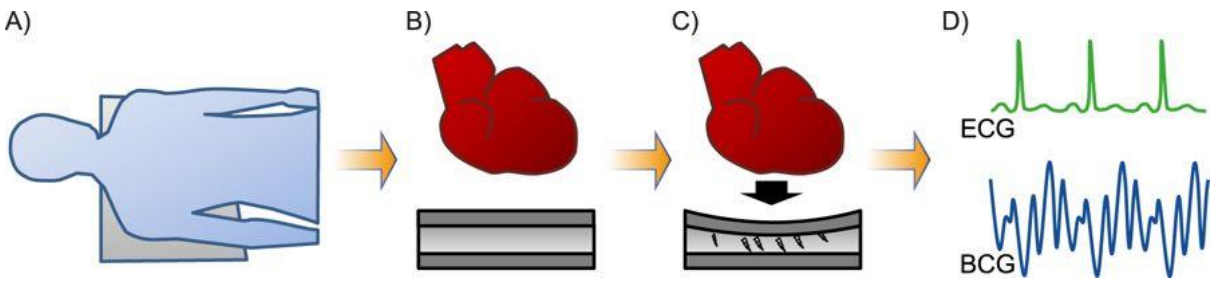
Version 2.0

Snoozfit Confidential

Sensor Measurement Technique

The Snoozfit Sensor uses a technique called Ballistocardiography (BCG) to record breathing patterns, heartrate, respiration rate, and body movement, in a non-invasive manner. BCG relies on recording the mechanical movement of the heart from the ejection of blood into the great vessels with each heartbeat, which is then measured using an electromechanical sensor placed at the Thoracic level of the body. The electrical signals that are generated in the electromechanical sensor are then analysed using signal processing techniques to extract Breathing Patterns, Heartbeat, Respiration Rates and gross body movements.

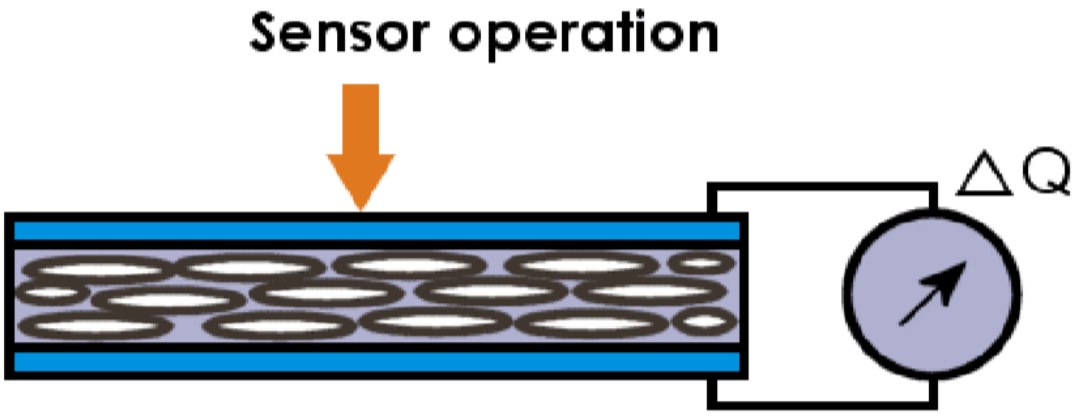


Sleep staging is derived out of the above mentioned parameters by matching measured data with standard models for sleep stages.

The first practical BCG was first developed by Dr. Isaac Starr in 1936. Dr. Starr was an American physician and heart disease specialist, who is also credited as the "Father of Ballistocardiography" for his pioneering work in the field of BCG.

Snoozfit Sensor Technology

The Snoozfit sensor film is an electroactivepolymer (EAP) that has a unique, strong electromechanical response. The film is electrically charged and consists of flat voids separated by thin polyolefin layers. Changes in the thickness of the film due to BCG forces, results in a chance in charge of the film, which is then captured in a signal processing unit for further post processing.



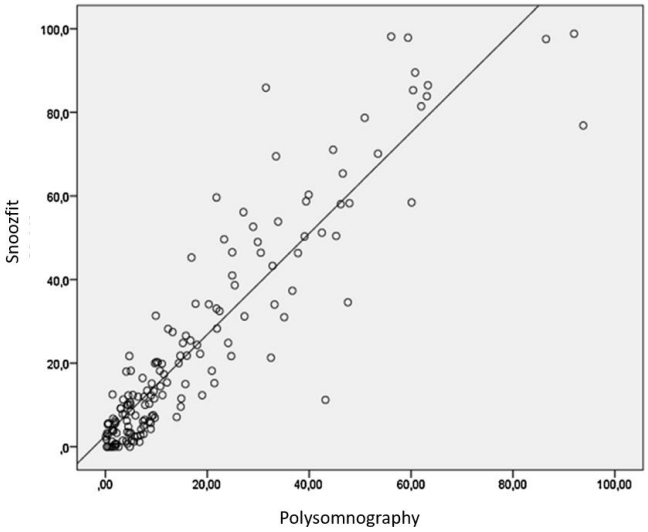
The Snoozfit Sensor is manufactured in Finland per the specifications provided by Snoozfit. The Sensor is validated for medical use and is CE certified.

Validation Studies – For Sleep Apnoea

The validations studies for Snoozfit have been done both in Pune and Finland. Comparative studies were done for both Sleep Staging (REM, NREM, Awake) as well as for Sleep Apnoea Detection (Obstructive Apnoea, Hypopnea, and Central Apnoea). **The correlations from the studies conducted in Finland was 90% for Sleep Apnoea and 80% for Sleep Staging. Whereas that in Pune were 95% for Sleep Apnoea.** The reason for the variation could be from the fact that the Finland studies were done retrospectively, whereas the Pune studies were done synchronously.

In Finland the validation studies were done by retrospectively analysing polysomnograms of adult patients (>18 years) that were recorded in the sleep laboratory of Pirkanmaa Hospital District in Tampere, Finland. The protocol was approved by the medical director of the Tampere University Hospital since the permission of the Ethical Committee of the Pirkanmaa Hospital is not needed for a retrospective analysis of recordings and recordings-related documents only. The total number of polysomnograms was 189. Due to technical problems with the nasal pressure signal or the mattress signal 32 recordings were excluded. One hundred and fifty-seven recordings were of sufficient quality and were further studied.

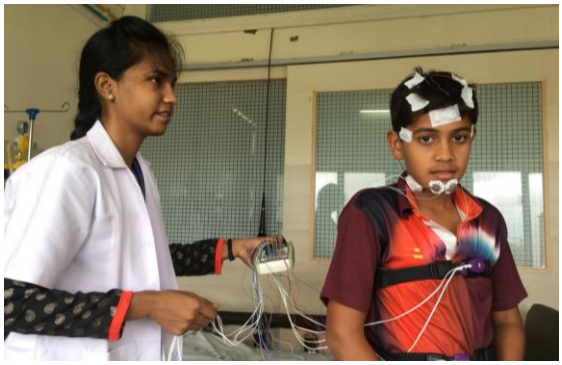
In Pune, the validation studies were done at Deenanath Mangeshkar Hospital, under the guidance of Dr. Sujit Jagtap, MD (Neuro). In Pune, the validation studies were done in parallel with the Polysomnography studies.



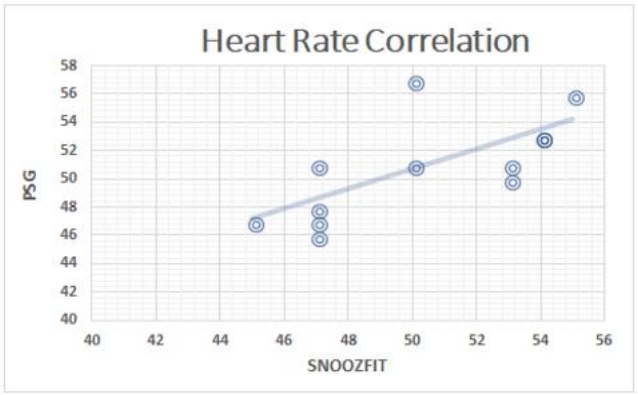
Scatter plot showing the relationship between the Snoozfit Sensor and Polysomnography studies for Sleep Apnoea on 157 studies. The correlation coefficient R^2 was 0.891.

Details of the Validation studies in Finland: The polysomnography recordings were performed with the Embla N7000 and Somnologica Studio 3 software (Embla®, USA) and they consisted of six EEG channels (F3-A2, F4-A1, C3-A2, C4-A1, O1-A2, O2-A1), two electro-oculogram channels, submental and anterior tibialis muscle electromyography, thoracic and abdominal respiratory movements by inductive belts, electrocardiogram, pulse oximetry and position. Airflow was measured with a thermistor and nasal pressure transducer.

Images and analysis of Sleep Studies done in Pune

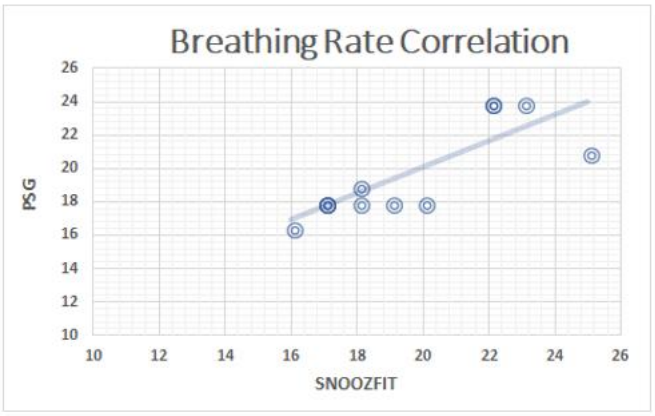


Heart Rate Comparison



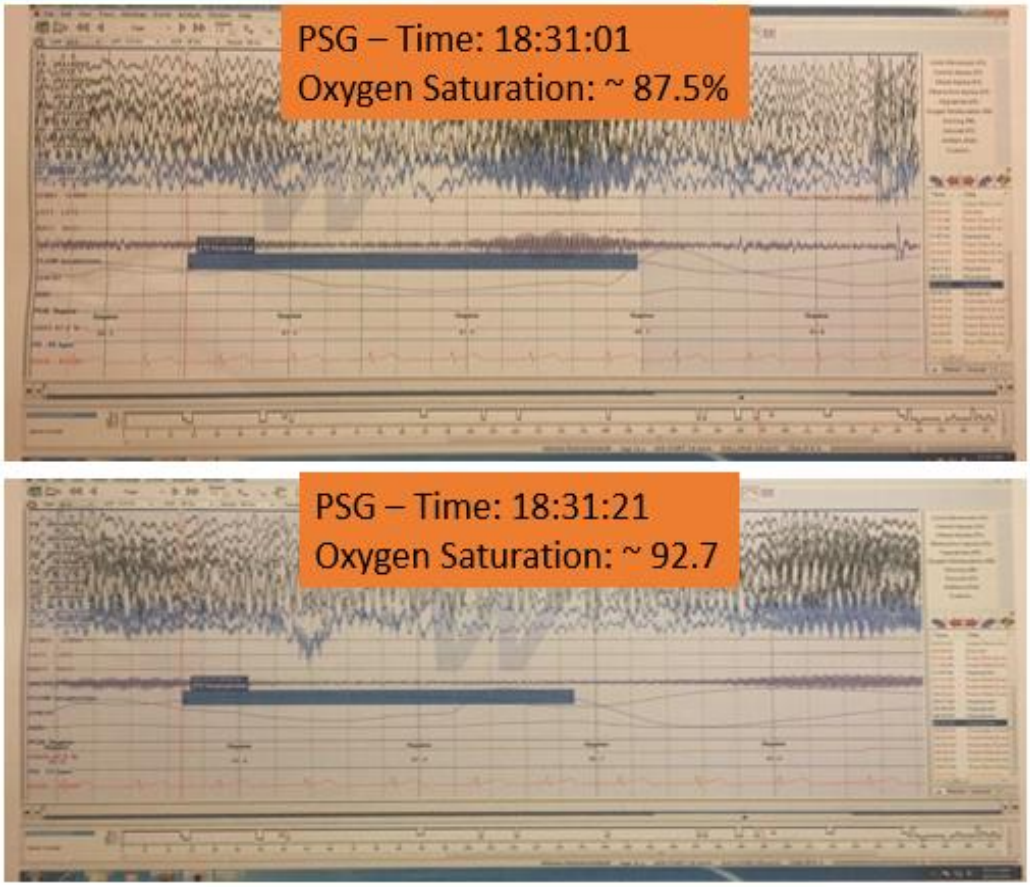
	Heart Rate		Difference
Average	50	51	**1%**
Min	45	46	**2%**
Max	55	57	**4%**

Breathing Rate Comparison



	Breathing Rate		Difference
Average	20	20	**1%**
Min	16	16.5	**3%**
Max	25	24	**-4%**

Apnea Trace Correlation



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Emfit movement sensor in evaluating nocturnal breathing

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ABSTRACT

Obstructive sleep apnea (OSA) diagnostics by the movement sensors static charge-sensitive bed (SCSB) and electromechanical film transducer (Emfit) is based on dividing the signal into different breathing patterns. The usage of non-invasive mattress sensors in diagnosing OSA is particularly tempting if patient has many other non sleep-related monitoring sensors. However, a systematic comparison of the apnea–hypopnea index (AHI) with Emfit-parameters is lacking. In addition to periodic breathing, SCSB and Emfit visualize episodes of sustained negative increases in intrathoracic pressure (increased respiratory resistance, IRR), of which relevance is still ambiguous. Our aim is to compare Emfit-parameters with the AHI and to provide a description of the patients suffering from IRR.

Time percentage with all obstructive periodic Emfit breathing patterns (OPTotal%) showed the best correlation with the AHI. The OPTotal percentage of 21 yielded to excellent accuracy in detecting subjects with an AHI of 15/h or more. Patients with IRR received high scores in GHQ-12-questionnaire.

An Emfit movement sensor might offer additional information in OSA diagnostics especially if nasal pressure transducer cannot be used.

1. Introduction

Usually quantization of nocturnal sleep-disordered breathing (SDB) is based on the apnea–hypopnea index (number of respiratory events per hour of sleep), the arousal index (number of cortical microarousals per hour of sleep) and the oxygen desaturation index calculated from the polysomnography (PSG). The diagnostic sensitivity of the SDB analysis can be improved, for example, by calculating respiratory related arousals (RERAs) as is done when researching the upper airway resistance syndrome (UARS) (Iber et al., 2007). UARS patients have inspiratory flow limitation which leads to progressive increases in respiratory effort terminated by a sudden decrease in negative oesophageal pressure and arousal (Guilleminault et al., 1993). Repetitive respiratory events can also be detected with noninvasive movement sensors such as the static charge-sensitive bed (SCSB) and the Emfit (electromechanical film transducer) sensor, which are widely used in Finland in diagnosing SDB and periodic leg movements (Anttalainen et al., 2007b; Kirjavainen et al., 1996; Rauhala et al., 2009; Tenhunen et al., 2011). The suitability of SCSB movement sensor in sleep apnea diagnostics has been evaluated in many studies and it has been shown to identify obstructive apneas with high sensitivity (Anttalainen et al., 2010; Lojander et al., 1998; Polo et al., 1988; Polo, 1992; Salmi et al., 1989; Svanborg et al., 1990). In mattress scoring episodes of periodic apneas/hypopneas are named as obstructive periodic patterns (OP-patterns) by Polo et al. (1988).

Attention has recently been paid to another type of SDB; prolonged or sustained partial upper airway obstruction (Anttalainen et al., 2007a, 2010; Bao and Guilleminault, 2004). This phenomenon can be assessed either by sustained negative increase in oesophageal pressure or by prolonged flow limitation pattern in the nasal pressure transducer signal (Bao and Guilleminault, 2004; Hernandez et al., 2001). Also the SCSB and the Emfit can serve as non-invasive means to detect prolonged partial obstruction (Kirjavainen et al., 1996; Polo, 1992; Polo et al., 1991; Tenhunen et al., 2011). Increased negative intrathoracic pressure

Abbreviations: AHI, apnea–hypopnea index; AI, apnea index; CPB, central periodic breathing pattern; EDS, excessive daytime sleepiness; EEG, electroencephalography; Emfit, electromechanical film transducer; ESS, Epworth sleepiness scale; GHQ, general health questionnaire; HI, hypopnea index; IRR, increased respiratory resistance pattern; M, movement pattern; NB, normal breathing pattern; NREM sleep, non-rapid eye movement sleep; OP1-3, obstructive periodic breathing patterns, types 1–3; OPTotal%, percentage of time with obstructive periodic breathing patterns (OP1% + OP2% + OP3%); P1, periodic breathing pattern, type 1; PM, periodic movement pattern; PSG, polysomnography; REM sleep, rapid eye movement sleep; RERA, respiratory effort-related arousal; SCSB, static charge-sensitive bed; SDB, sleep-disordered breathing; TIB, time in bed; TST, total sleep time; UARS, upper airway resistance syndrome; W, Emfit wakefulness epoch based on sleep EEG.

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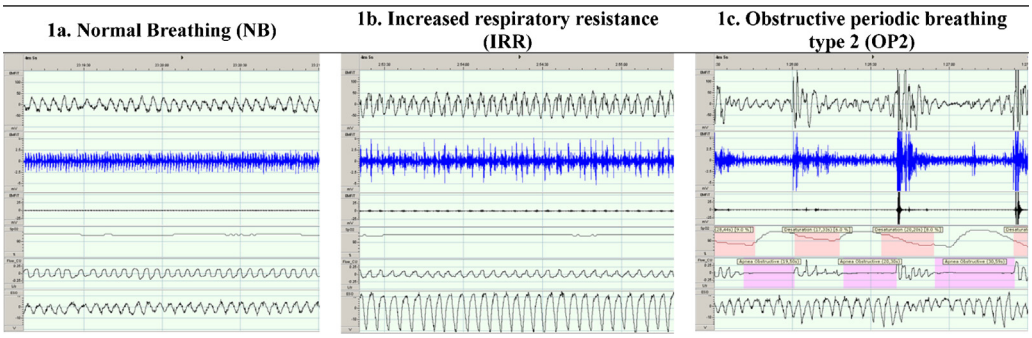

Fig. 1. Three examples of mattress breathing categories. (a) A 2-min period of normal breathing (NB). The uppermost channel represents regular respiratory movements measured by the Emfit. The second channel shows the Emfit high-frequency signal where only heart-related spikes are seen during unobstructed breathing. The third channel records large movements that are not present during normal breathing (raw Emfit signal). The following traces are the oxygen saturation percentage, airflow by the nasal pressure transducer and oesophageal pressure. (b) A 2-min period with increased respiratory resistance (IRR): respiratory-related spikes in the second Emfit channel. Breathing is regular, as assessed by the Emfit (trace 1) and by the nasal pressure transducer (trace 5) but negative oesophageal pressure has clearly increased (trace 6). (c) A 2-min episode of obstructive periodic breathing (OP2). Periodic respiratory amplitude variation in the Emfit (trace 1). In the high-frequency Emfit channel (trace 2), periodic bursts of respiratory-related spikes with large movements are seen. Movements appear also in the third Emfit channel (trace 3). Obstructive apneas in channel 5 (nasal airflow). Oesophageal pressure (trace 6) shows periodic negative swings. Scaling and order of the traces is kept the same in all of the figures.

induces respiratory-related spikes to the SCSB and the Emfit signal (Kirjavainen et al., 1996; Tenhunen et al., 2011), and the sustained partial upper airway obstruction with sustained spiking has been entitled "increased respiratory resistance, IRR" (Alihanka et al., 1981; Alihanka, 1987; Polo, 1992). IRR is clearly distinguishable from the OP-patterns (Fig. 1). In our recent work we discovered that during IRR there is a sustained negative increase in the oesophageal pressure but arousals and apneas/hypopneas are sparse. During OP-patterns oesophageal pressure is also increased, but apneas/hyponeas and arousals are frequent (Tenhunen et al., 2011).

The smaller Emfit bed sensor has replaced the SCSB in many laboratories, and because a systematic comparison between the AHI measured by the PSG and obstructive breathing periods measured with the Emfit has not been done, the main aim of the present study was to evaluate the feasibility of the Emfit-sensor in diagnosing obstructive sleep apnea (OSA) using the PSG with a nasal pressure transducer as a reference method. As there is only little epidemiologic data from prolonged partial obstruction, the other aim was to examine the prevalence of prolonged partial obstruction (IRR) among adult patients who were referred to a full polysomnography. The third aim was to compare polysomnographic and demographic parameters between obstructive sleep apnea syndrome–patients (OSAS) and patients with prolonged partial obstruction.

2. Materials and methods

We analysed retrospectively polysomnograms of adult patients (>18 years) that were recorded between 03/2005 and 03/2006 in the sleep laboratory of Pirkanmaa Hospital District in Tampere, Finland. The protocol was approved by the medical director of the Tampere University Hospital since the permission of the Ethical Committee of the Pirkanmaa Hospital is not needed for a retrospective analysis of recordings and recordings-related documents only. The total number of polysomnograms was 189. Due to technical problems with the nasal pressure signal or the mattress signal 32 recordings were excluded. One hundred and fifty-seven recordings were of sufficient quality and were further studied.

The polysomnography recordings were performed with the Embla N7000 and Somnologica Studio 3 software (Embla®, USA) and they consisted of six EEG channels (F3-A2, F4-A1, C3-A2, C4-A1, O1-A2, O2-A1), two electro-oculogram channels, submental and anterior tibialis muscle electromyography, thoracic and abdominal respiratory movements by inductive belts, electrocardiogram, pulse oximetry and position. Airflow was measured with a thermistor and nasal pressure transducer. In addition Emfit-sensor signal was acquired. The Emfit mattress is a moveable movement sensor, which consists of thin elastic light weight polymer layers separated by air voids and coated with electrically conductive, permanently polarized layers. Changes in the pressure acting on the film generate a charge on its electrically conductive surfaces and this charge can be measured as a current or a voltage signal (Paajanen et al., 2000). An Emfit sensor (32 cm × 62 cm × 0.4 cm) was placed under the thoracic area of the sleeping patient. A sampling rate of 2 Hz was used for pulse oximetry, 10 Hz for respiratory movements, 500 Hz for ECG, and 200 Hz for the Emfit-sensor and all the other signals.

Polysomnographies were classified into the sleep stages according to standard criteria (Iber et al., 2007). The apnea–hypopnea index (AHI) was calculated as the number of obstructive apneas and hypopneas (hypopnea rule 4b in (Iber et al., 2007) per hour of sleep. In addition, the apnea index (AI) and the hypopnea index (HI) were calculated. Arousals were scored according to the criteria of the ASDA (ASDA, 1992).

Conventional sleep parameters were gathered from polysomnographic recordings. Demographic data (age, sex, BMI, reason for sleep study, end-diagnosis, Epworth sleepiness scale (ESS) score (Johns, 1991), GHQ-12 score (Goldberg et al., 1997), subjective time in sleep as well as medications of the patients) were collected from the questionnaires, which are routinely used during sleep studies in our laboratory.

The Emfit signal was filtered into two different frequency bands. These filtered signals and the raw signal were used in visual scoring of the Emfit signal into nine Emfit categories as in our previous work (Tenhunen et al., 2011). Large body movements were analysed from the raw signal channel, the respiratory movements were analysed from the low-frequency channel (LF, 0.3–10 Hz) and the high-frequency channel (HF, 6–16 Hz) was used to visualize heart- and respiratory-related spikes (Alametsa et al., 2006; Kirjavainen et al., 1996). The scoring was performed in 3-min epochs from lights off-event to the final awakening. The mattress signal categories are presented in Table 1, and they were: normal breathing (NB), periodic breathing type 1 (P1), obstructive periodic breathing types 1–3 (OP1–3), central periodic breathing (CPB), increased respiratory resistance (IRR), large movements in the row signal lasting >40s (M), epochs with at least four short periodic movements in the channels without respiratory variation (periodic movements, PM), and wake epochs (W) with EEG-defined wakefulness more than 50% of time. Wake and REM sleep epochs were not included into

Table 1
Characteristics of mattress breathing categories.

	Breathing movements in LF channel	Increased effort in HF channel (=respiratory-related spiking)	Large body movements in the raw Emfit signal
NB	Regular	No	No
P1	Periodic amplitude variation	No	No
OP1	Periodic amplitude variation	Periodic	No
OP2	Periodic amplitude variation	Periodic	Present between apneas/hypopneas
OP3	Periodic amplitude variation	Periodic	Present between apneas/hypopneas
CPB	No movements during apnea, periodic movements between apneas	May be present between apneas	May be present between apneas
IRR	Regular	Sustained	No
M	May vary	Artifact	Prolonged (duration >40 s)
PM	Regular	No	Periodic; more than 3 short (<10 s) movements per epoch

LF = Emfit-signal power band 0.3–10 Hz; HF = Emfit-signal power band 6–16 Hz; NB = normal breathing; P1 = periodic breathing type 1; OP1 = obstructive periodic breathing type 1; OP2 = obstructive periodic breathing type 2; OP3 = obstructive periodic breathing type 3; CPB = central periodic breathing; IRR = increased respiratory resistance; M = movement; PM = periodic movement.

the analyses. Examples of some breathing categories are presented in Fig. 1.

The Emfit signal scoring was performed visually by two independent scorers with a scoring agreement of 86.2% (median, range 67.6–95.3%). The Kappa index was 0.763 ($p < 0.001$), 95% confidence interval (0.716, 0.815), which means a substantial level of agreement. The consensus scoring, which was used in the analyses, was formed by the two independent scorers together. The proportions of different breathing categories were expressed as a median percentage of total sleep time (TST) across the patients.

In the statistical analyses, nonparametric tests were used as all the parameters were not normally distributed. The Spearman's correlation coefficient was used to assess the relationship between the AHI/AI/HI and the Emfit-categories. In addition, the Emfit breathing category that correlates best with the AHI was determined. After that, the linear fit line function was used to estimate the percentage of time with obstructive periodic breathing (OP1% + OP2% + OP3%) corresponding with the AHI values of 5/h, 15/h and 30/h. These percentages were used together with AHI levels 5/h, 15/h and 30/h in computing the sensitivities and specificities for Emfit scoring. Based on these threshold definitions, receiver operating characteristic (ROC) curves were derived and an area under the curve (AUC) was calculated.

In order to compare OSAS-patients with the patients with prolonged partial obstruction we extracted four subject groups from the database: the OSAS-group (OSAS+), the IRR-group (IRR+), patients with both OSAS and IRR-pattern (OSAS+IRR+) and subjects who had neither OSAS nor IRR (OSAS−IRR−). The cut off limits of the AHI 15/h and IRR 15% were selected as we wanted to exclude the mildest breathing disorders from the OSAS+-group and the IRR+-group. The OSAS+-subjects had to have an AHI of at least 15/h but IRR% less than 15. The IRR+-subjects had to have an AHI less than 15/h but IRR% at least 15. The OSAS+IRR+-subjects had an AHI > 15/h and IRR% > 15 whereas the OSAS−IRR−-subjects had an AHI < 15/h and IRR% < 15. The groups were compared with the Kruskall–Wallis test with post hoc analysis by the Mann–Whitney test using an appropriate Bonferroni correction.

3. Results

The demographic data and the PSG-data of the 157 subjects are presented in Table 2.

The referral diagnoses of all the patients are presented in Fig. 2a and the end-diagnoses in Fig. 2b. Sleep apnea (AHI > 5/h) was the major outcome of the recordings. Some subjects had two end-diagnoses (for example insomnia and mild sleep apnea), in those cases only the first (main) diagnosis is presented.

The percentages of time referred to the TST spent in different mattress breathing categories are presented in Table 3. Normal

Table 2
Demographic and polysomnographic data of the subjects.

	Median	Min	Max
Age (years)	47	18	71
BMI[a]	27	16	45
ESS[b]	10	0	22
GHQ-12[c]	3	0	12
SST[d] (h)	6.3	0.0	10.0
TST[e] (h)	6.8	3.1	10.0
TIB[f] (min)	500.0	351.5	644.5
SEI[g] (%)	84.0	39.0	98.0
SL[h] (min)	16.0	0.0	151.5
REMlat[i] (min)	124.0	1.5	543.0
%S1[j]	7.2	0.1	54.4
%S2[j]	66.1	39.8	88.7
%SWS[j]	7.3	0.0	45
%REM[j]	14.4	0.3	31.2
ARI[k] (n/h)	18.3	5.8	97.7
AHI[l] (n/h)	9.7	0.1	93.8
AI[m] (n/h)	1.1	0.0	85.3
ODI4[n] (%)	2.0	0.0	81.0
SaO2minimum[o] (%)	88.0	53.0	96.0
Pulse	60.4	40.1	96.0
PLMI[p] (n/h)	4.5	0.0	145.9

[a] Body mass index.
[b] Epworth sleepiness scale.
[c] 12-Item general health questionnaire.
[d] Subjective sleep time.
[e] Total sleep time.
[f] Time in bed.
[g] Sleep efficiency index.
[h] Sleep latency.
[i] Latency to REM (rapid eye movement) sleep.
[j] Amount of sleep stage referred to TST.
[k] Arousal index.
[l] Apnea–hypopnea index.
[m] Apnea index.
[n] Oxygen desaturation index, number of desaturations ≥4% per hour of TST.
[o] Minimum percentage of oxygen saturation.
[p] Periodic limb movement index.

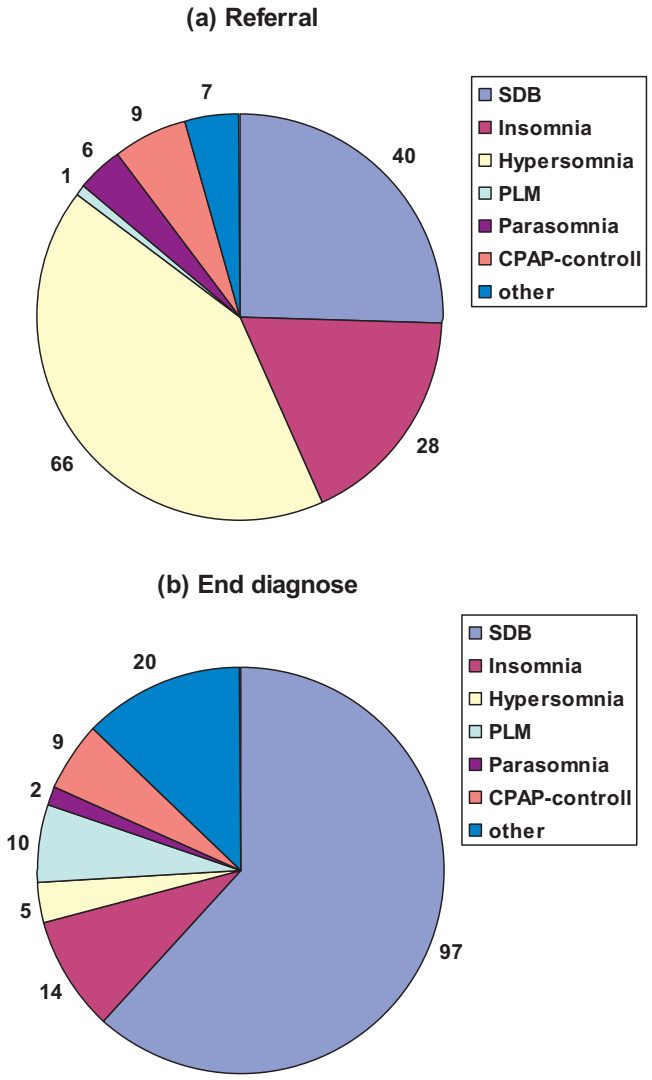

Fig. 2. Referral reasons (a) and end-diagnoses (b) of the 157 subjects.

breathing was abundant and the OP1-pattern quite common, whereas other breathing patterns were more sparse. Central periodic breathing was not detected in any of the subjects.

3.1. Emfit in OSA diagnostics

The correlation coefficients between polysomnographic OSA indices and different Emfit breathing categories are presented in Table 4. NB% presented marked negative correlations to the OSA indices. The best positive correlation was achieved between the AHI and summed OP-patterns (OP1% + OP2% + OP3%, Fig. 3). The correlation weakened if P1% and/or IRR% were added to the OP-patterns.

The correlation results confirmed our previous finding that apneas and hypopneas are present in all OP-categories. Therefore in further analyses we formed an OPTotal-category (OPTotal% = OP1% + OP2% + OP3%) that was used in further analyses. The OPTotal percentages that correspond to the AHI cut-off values of 5/h, 15/h and 30/h were calculated from the fit line function between the AHI and OPTotal%. The resulting OPTotal percentages were 9%, 21% and 39%, respectively. These cut-off values were used in calculating the sensitivities and specificities. The sensitivity of the Emfit OPTotal-time of <9% to detect AHI < 5/h was 0.766 and the specificity was 0.809. These numbers, along with other sensitivities and specificities as well as positive and negative predictive values are presented in Table 5.

Table 3
Percentages of time (referred to TST) spent in different Emfit categories.

	Median	Min	Max
NB%	51.6	0.0	89.4
P1%	5.0	0.0	33.2
OP1%	11.3	0.0	95.9
OP2%	0.7	0.0	43.3
OP3%	0.0	0.0	36.3
CPB%	0.0	0.0	0.0
IRR%	3.5	0.0	55.3
M%	3.0	0.0	19.7
PM%	4.1	0.0	59.0

NB = normal breathing; P1 = periodic breathing type 1;OP1 = obstructive periodic breathing type 1; OP2 = obstructive periodic breathing type 2; OP3 = obstructive periodic breathing type 3; CPB = central periodic breathing; IRR = increased respiratory resistance; M = movement; PM = periodic movement.

Table 4
Spearman's correlation coefficients between PSG respiratory indices and different Emfit breathing combinations. The best Emfit correlations with AI, HI and AHI are bolded.

Emfit breathing category	AI	HI	AHI
NB%	−.672*	−.692*	−.806*
P1%	−.063	−.042	−.105
OP1%	.754*	.761*	.865*
OP2%	.453*	.522*	.558*
OP3%	.443*	.318*	.499*
IRR%	.199*	.286*	.248*
OP1% + OP2%	.774*	.772*	.888*
OP2% + OP3%	.489*	.514*	.596*
OP1% + OP3%	.761*	.764*	.872*
P1% + OP1%	.685*	.671*	.777*
P1% + OP2%	.267*	.288*	.270*
P1% + OP3%	.150	.080	.113
P1% + OP1% + OP2%	.735*	.706*	.828*
P1% + OP2% + OP3%	.699*	.677*	.790*
P1% + OP1% + OP2% + OP3%	.699*	.677*	.790*
OP1% + OP2% + OP3%	**.777***	**.773***	**.891***
OP1% + OP2% + OP3% + IRR%	.728*	.719*	.849*
P1% + OP1% + OP2% + OP3%	.742*	.708*	.835*
P1% + OP1% + OP2% + OP3% + IRR%	.718*	.692*	.824*

Correlations with statistical significance are marked with asterisk. AI = apnea index; HI = Hypopnea index; AHI = apnea–hypopnea index; abbreviations of Emfit breathing categories as in Table 2.

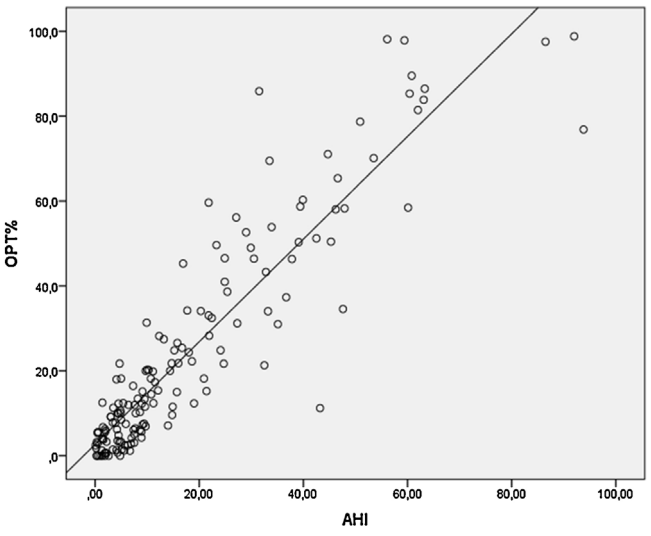

Fig. 3. Scatter plot showing the relationship between the AHI and the percentage of time spent in combined OP-patterns (OP1% + OP2% + OP3%). The correlation coefficient R^2 was 0.891.

Table 5
The sensitivities, specifities, negative predictive values and positive predictive values for the OPTotal-parameter in different AHI cut-off levels.

	AHI 5/h OPTotal 9%	AHI 15/h OPTotal 21%	AHI 30/h OPTotal 39%
Sensitivity	0.766	0.948	0.935
Specificity	0.809	0.918	0.824
Negative predictive value NPV	0.890	0.918	0.778
Positive predictive value PPV	0.632	0.948	0.950

AHI = apnea–hypopnea index; OPTotal% = percentage of combined obstructive periodic breathing categories referred to total sleep time.

Fig. 4 shows the receiver operating characteristic (ROC) curve reflecting the diagnostic capability of the OPTotal-parameter when the AHI threshold was set at AHI < 15/h. The area under curve was 0.978.

3.2. Prevalence of IRR among sleep laboratory patients

There was no marked correlation between the AHI and the IRR% (Fig. 5). Some subjects had a high AHI without a marked amount of IRR, whereas some subjects had a lot of IRR with a low AHI. The subjects were divided into four groups based on the AHI and IRR-percentages. We used the cut off limits of an AHI 15/h and IRR 15% (Fig. 5). The OSAS+-group consisted of 47 subjects, 17% of which were females. The IRR+-group had 17 subjects, of whom 47% were females. The OSAS+IRR+-group had 13 subjects, 23% of whom were females. The OSAS−IRR−-group consisted of 80 subjects and the percentage of females was 51%.

The first end diagnoses of the subjects in the OSAS+-group, the IRR+-group and the OSAS+IRR+-group were all mild to severe SDB but in the OSAS−IRR−-group the end diagnoses varied substantially. Twenty subjects had mild OSAS (AHI 5–14.9/h), 14 had insomnia, five were diagnosed with central hypersomnia, 12 had PLM, two had parasomnia, 9 patients slept with a CPAP-device and 18 patients had other or nonspecific outcomes. As the other than SDB-diagnoses might cause confounding factors to the results, we decided to include only the 20 patients with mild OSAS in further analyses instead of all the subjects in the OSAS−IRR−-group. Ten of the mild OSAS patients (50%) were female.

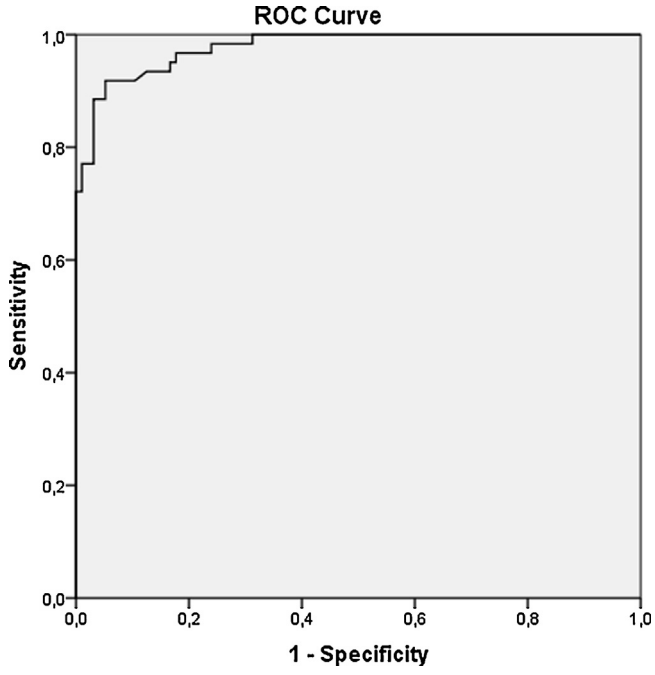

Fig. 4. Receiver operating characteristic (ROC) curve for identifying the Emfit scoring limit (OPTotal%) for threshold AHI < 15.

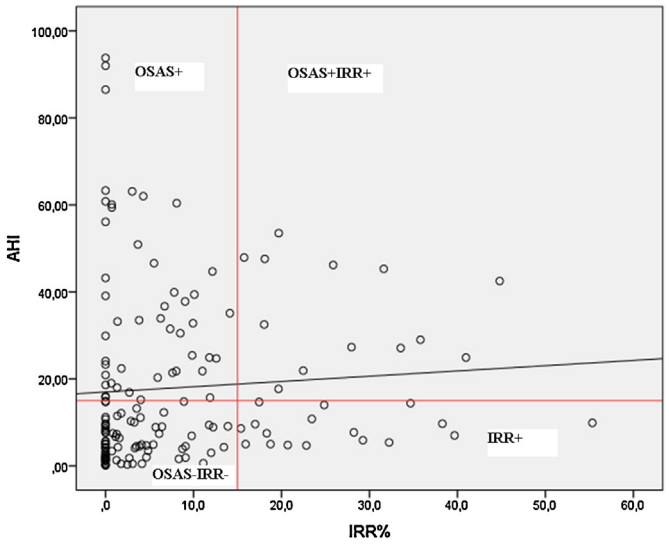

Fig. 5. Scatter plot showing the relationship between the apnea–hypopnea index (AHI) and the time percentage of increased respiratory resistance (IRR%) breathing category. Text boxes show the formation of the patient groups. From the OSAS−IRR−-group, only the 20 patients with mild OSAS were accepted for further analyses.

The sleep parameters of the four groups are presented in Table 6. The IRR+-group differed significantly from the OSAS+-group by several parameters. They had higher scores in the GHQ-12 questionnaire and their objective sleep quality was better as indicated by a higher SWS percentage, a lower arousal index and a lower PLM index. Their sleep apnea and oxygen saturation indices (AI, AHI, ODI4, SaO2minimum percentage) were naturally more normal. The IRR+-group also presented differences as compared to OSAS+IRR+-group. The IRR+-group had higher scores in the GHQ-12, their arousal index was lower, they slept more and their AHI and AI were smaller. There was only one significant difference between the IRR+-group and the Mild OSAS-group; the IRR+-patients had fewer arousals. The OSAS+-group did not differ from the OSAS+IRR+-group. However, the OSAS+-group differed from the Mild OSAS-group by having less slow wave sleep, more arousals, more apneas and hypopneas, more oxygen desaturations and lower SaO2minimum values. The patients in the OSAS+IRR+-group had more arousals and a higher AHI than the Mild OSAS patients and their oxygen saturation values were worse. The use of medications did not differ between the four groups (Table 6).

4. Discussion

SCSBs are used since 1980s in the diagnostics of OSA in Finland. The main aim of the present study was to evaluate the feasibility of the smaller Emfit movement sensor in the diagnosing OSA. The results confirm that the Emfit-mattress is quite suitable for OSA detection. The percentage of time with combined obstructive periodic breathing patterns (OPTotal%) can be used to estimate the AHI, since the OPTotal percentage of 21 (referred to total sleep time) yielded to excellent accuracy in detecting subjects with an AHI 15/h or more. The correlation results show that all OP-categories have an impact on the AHI. Although some previous studies have proposed that P1, OP1 and OP2-categories would represent more hypopneas and OP3 more obstructive apneas, it seems that the differentiation between apneas and hypopneas is not straightforward with OP-classification (Polo et al., 1988, 1989, 1991; Tenhunen et al., 2011) However, as the severity of the OSA is mostly expressed

Table 6
Statistical comparisons of demographic data, polysomnographic and Emfit parameters and medications between the four patient groups.

	OSAS+ (n = 47)	IRR+ (n = 17)	OSAS+IRR+ (n = 13)	MildOSAS (n = 20)	OSAS+ vs IRR+	OSAS+ vs OSAS+IRR+	OSAS+ vs MildOSAS	IRR+ vs OSAS+IRR+	IRR vs MildOSAS	OSAS+IRR+ vs MildOSAS
Age (years)	52	47	51	49	ns	ns	ns	ns	ns	ns
BMI	28.1	30.0	31.0	26.0	ns	ns	ns	ns	ns	ns
ESS	9	8	12	9	ns	ns	ns	ns	ns	ns
GHQ-12	2	8	2	3	0.009	ns	ns	0.029	ns	ns
SST (h)	7.0	7.8	6.0	5.8	ns	ns	ns	ns	ns	ns
TST (h)	6.7	7.4	6.3	7.3	ns	ns	ns	ns	ns	ns
TIB (min)	496.8	510.5	452.0	518.5	ns	ns	ns	0.042	ns	ns
SEI %	83.0	89.3	83.0	82.5	ns	ns	ns	ns	ns	ns
SL	13	15	22	20	ns	ns	ns	ns	ns	ns
REMlat	134.0	125.0	104.0	107.0	ns	ns	ns	ns	ns	ns
%S1	9.3	5.8	5.7	7.7	ns	ns	ns	ns	ns	ns
%S2	72.3	65.8	70.8	65.7	ns	ns	ns	ns	ns	ns
%SWS	3.0	9.1	5.4	9.0	0.005	ns	0.020	ns	ns	ns
%REM	12.5	16.8	14.4	16.5	ns	ns	ns	ns	ns	ns
ARI (n/h)	26.00	11.00	30.00	18.80	3.27E−06	ns	0.004	0.000	0.007	0.005
AHI (n/h)	33.20	7.70	32.50	9.05	0.000	ns	0.000	2.25E−05	ns	1.00E−05
AI (n/h)	10.6	.4	10.3	1.1	1E−05	ns	0.000	1E−03	ns	0.000
ODI4 (%)	14.5	1.0	10.0	2.0	0.000	ns	0.000	ns	ns	2.24E−04
SaO2min (%)	84.0	87.0	82.0	89.0	4E−02	ns	0.000	ns	ns	0.035
Pulse	61.00	60.70	56.30	59.15	ns	ns	ns	ns	ns	ns
PLMI (n/h)	12.8	1.2	6.2	.9	0.002	ns	0.001	ns	ns	ns
IRR%	3.7	23.4	25.9	3.1	0.000	ns	ns	ns	1.15E−06	8.46E−06
OPTotal%	46.5	10.3	50.4	11.7	0.000	ns	.000	4.97E−05	ns	1.73E−05
Short-acting sleeping pill	6.4	17.6	23.1	35.0	ns	ns	ns	ns	ns	ns
Benzodiazepine	8.5	5.9	7.7	10.0	ns	ns	ns	ns	ns	ns
Antihypertensives	36.2	23.5	38.5	20.0	ns	ns	ns	ns	ns	ns
Cholesterol drug	12.8	11.8	23.1	10.0	ns	ns	ns	ns	ns	ns
Antidepressant	19.1	17.6	15.4	25.0	ns	ns	ns	ns	ns	ns

Abbreviations as in Tables 1 and 4.

by the AHI and not by the apnea index or the hypopnea index, the differentiation of apneas from hypopneas might be considered unnecessary in routine clinical work. The other breathing categories did not present marked correlations with the AHI. The NB category obviously represents normal, unobstructive breathing, confirming our previous result (Tenhunen et al., 2011). This time, we found no marked correlation between the AHI and the P1%, but in the past some apneas and hypopneas were found to be present in P1-breathing with normal oesophageal pressure values (Tenhunen et al., 2011). Thus the significance of P1-pattern remains still somewhat ambiguous. The IRR-pattern seems not to comprise of apneas or hypopneas but represents a different entity.

The other aims of the present study were to examine the prevalence of prolonged partial obstruction (IRR) among sleep laboratory patients, as well as to compare the polysomnographic and demographic parameters between OSA patients and patients with prolonged partial obstruction. The IRR is an interesting phenomenon. It does not appear with apneas, hypopneas or arousals, but the partial pressure of transcutaneus carbon dioxide presents a cumulative increase during IRR and oesophageal negativity is increased (Rauhala et al., 2007; Tenhunen et al., 2011).

It seems that prolonged partial obstruction is not a milder form of SDB, but presents its own entity. Clinically IRR has been found to have associations with higher prevalence of asthma and chronic obstructive pulmonary disease in both sexes and a lower prevalence of hypertension in women (Anttalainen et al., 2010). Decreased blood pressure may result from an increased pCO2, causing local endothelial changes and vasodilatation with low sympathetic activity. In that way, IRR might induce harmful physiological effects and we propose that the prolonged obstruction should be taken into account when the severity of SDB is determined.

In one former work, IRR was the most frequent single breathing abnormality in patients with suspected SDB and it was more common among women than among men, representing 50.2% of all breathing abnormalities among females and 37.2% among males (Anttalainen et al., 2007a). We found that IRR without marked OSA is not common, but however, it was present in 16 of our 157 subjects (10.2%). A closer evaluation disclosed that about half of the patients in our IRR+-group and in our Mild OSAS-group were females, whereas most of the subjects in the OSAS+-group were males. It is well known that women may present different subjective symptoms with lower AHI than men (Young, 1996). Unfortunately, we were not able to examine the gender differences of the IRR+-patients as the number of subjects remained too small.

Different atypical subjective symptoms are found to be more common among female than in male SDB patients. These symptoms include, for example, difficulty in falling asleep, frequent awakenings, insomnia and depression (Valipour et al., 2007). We wonder whether IRR would account for the atypical subjective symptoms, since the GHQ-12 score of the IRR-patients was high indicating depressive mood. On the other hand, the polysomnographic parameters of our IRR-patients did not resemble the parameters described in depressive patients. In depression, sleep latency is found to lengthen, arousals and awakenings increase in number, SWS is reduced and REM sleep latencies shorten (Benca et al., 1997). In our study, IRR-patients had less arousals, fewer periodic leg movements, better minimum oxygen saturation values and more SWS than the OSAS-patients indicating better objective sleep. Without detecting prolonged partial obstruction, the SDB would be classified as mild and the patients might be left without treatment, even if the CPAP treatment compliance is found to be fairly good in IRR-patients (Anttalainen et al., 2007a).

Increased inspiratory effort has been found to induce sleepiness (Pelin et al., 2003) so it might be the reason for atypical SDB symptoms with IRR patients. Indeed, poor subjective sleep has been found to predict life dissatisfaction (Paunio et al., 2009). However, despite the fact that some subjects in all groups had medication for depression, perhaps we should not pay too much attention to the GHQ-12 scores in particular, as we did not have a group of healthy

subjects as a control group. In the future, a comparison of sleep and demographic parameters between IRR-patients and healthy volunteers is needed.

Why do some patients present SDB without repetitive patterns but sustain obstruction? Anatomical structures might be of importance as patients with both IRR and OSAS have been found to have narrower airways at the hypopharyngeal (hyoid bone) level than pure OSAS patients (Polo et al., 1991). This might reflect the different kinetic airway properties of the two groups. Anatomical gender differences may also have impact on findings.

Does IRR represent the same phenomenon as UARS? It might be, as partial obstruction is the main pattern in both entities and symptoms of UARS (fatigue, depression, anxiety and somatic complaints) resemble mood symptoms in IRR (Bao and Guilleminault, 2004). On the other hand, respiratory related arousals are usually frequent in UARS but few during IRR, as we have also earlier demonstrated (Rauhala et al., 2007; Tenhunen et al., 2011). In that way there are some differences between the two entities. But if prolonged flow limitation is considered to be one form of UARS as Bao and Guilleminault presented in the figure of their article (Bao and Guilleminault, 2004) it would be easily and noninvasively detected with an Emfit-sensor.

Recently, there have been concerns about the use of the AHI as the only marker of upper airway obstruction during sleep or as the index of its severity. As SCSB and Emfit mattresses disclose increased respiratory effort, not airflow, they have the capability to offer notable additional information to sleep studies. It is not uncommon that young patients with obstructive breathing and flow limitation events have excellent oxygen saturation values often due to markedly increased breathing effort. In such cases the outcome of the sleep study might underestimate the severity of the disorder as oxygen desaturation events are needed in detecting hypopnea. This is a concern especially related to ambulatory polygraphies without an EEG when the arousal rule cannot be used in hypopnea detection.

In the present work we used the Emfit signal alone to classify breathing. Adding pulse oximeter channels to the mattress signal might still improve the sensitivity and specificity, at least if the mattress was used as a stand alone device in OSA diagnostics. In our further study we are going to apply the Emfit with a pulse oximetry when screening for SDB in patients with an ischemic stroke. Patients in stroke units often have many different monitoring devices as well as nasal supplementary oxygen therapy. Measuring nasal pressure can thus be challenging. Therefore it is tempting to perform SDB diagnostics with the non-invasive sensor. The Emfit can be assessed in all patients and there are no contraindications for its usage. The easy and rapid manual scoring procedure in 3-min epochs increases the attraction of using mattress sensors with large patient samples.

Acknowledgements

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Efficacy of Mandibular Advancement Splint for Treatment of OSA, Report at Three Months of a One-Year Follow-Up Study

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INTRODUCTION

Mandibular advancement splint *Silensor-sl* (MAS) can effectively treat mild to moderate obstructive sleep apnea (OSA). It is worn during sleep to maintain the patency of the upper airway by increasing its dimensions and reducing its collapsibility. Although less efficacious than continous positive airway pressure (CPAP) for improving the polysomnographic indexes of OSA, MAS is generally preferred by patients which ensures better compliance and may provide an equivalent health outcome.

MAS have been shown to have a beneficial impact on numerous clinical outcomes, including the polysomnographic indexes of OSA, subjective and objective measures of sleepiness, blood pressure, aspects of neurophysiological functioning, and quality of life.

In this study we sought to evidence the efficacy of specific mandibular advancement splint *Silensor-sl* and the long-term impact on numerous clinical outcomes.

METHODS

- 7 patients with mild to moderate OSA
- patients were initially screened for dental status; inclusion criteria was at least 6 healthy teeth in each dental arch
- dental impressions and lateral cephalometric radiographs were obtained prior to the initiation of the treatment
- arterial stiffness, blood pressure and metabolic blood parameters were measured at baseline and after 3 months of MAS treatment
- treatment outcome was determined by polysomnography

RESULTS

Variables		Total	Male	Female
Patients No.		7 (100)	5 (71)	2 (21)
Age, yr		54.67±6.16	53.8±7.29	52.5±3.54
Height, (cm)		180.3±7.7	184.0±5.3	171.0±0
Weight, (kg)		89.43±7.74	89.6±7.02	89.0±12.73
BMI, (kg/m^2)		27.7±3.61	26.6±3.06	30.4±4.35
ESS score		6.29±3.40	6.6±4.1	5.5±0.71
Neck circumference, (cm)		41.79±2.94	43.3±1.57	38±1.41
STOP questionnaire N (%)	High risk (≥2)	7(100)	5(100)	2(100)
	Low risk (<2)	0(0)	0(0)	0(0)

TABLE 1. DEMOGRAPHIC CHARACTERISTICS OF PATIENTS

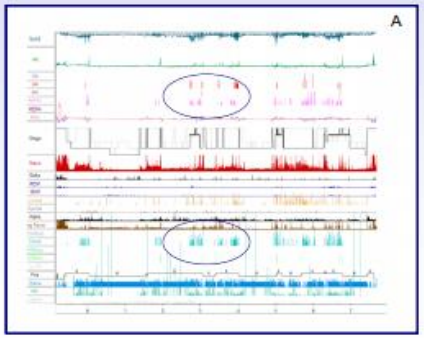
Values are given as No.(%) or mean±SD, unless otherwise indicated. BMI=body mass index; ESS=Epworth Sleepiness Score; STOP=snoring, tiredness, observed apnea, and high blood pressure

Variables	Baseline,before MAS treatment	At 3 months of MAS treatment	*P* value
ESS score	6.29±3.40	6.0±4.30	NS
AHI (events/hr)	21.79±5.78	10.76±3.98	0.0156
Minimum SpO_2	84.0±5.35	86.57±2.94	NS
Mean SpO_2	94.29±1.98	95.14±1.21	NS
Snoring time (min)	264.9±199.48	165.29±182.79	NS
Fibrinogen (g/L)	3.13±0.73	3.46±0.89	NS
Total cholesterol (mmol/L)	5.74±1.08	5.94±1.33	NS
Cortisol (nmol/L)	372.57±83.98	353.37±107.71	NS
FPG (mmol/L)	5.0±0.33	4.86±0.4	NS
FPI (pmol/L)	75.46±80.53	72.27±74.65	NS
HR (beats/min)	68.67±19.82	64.43±12.35	NS
Systolic BP (mmHg)	129.57±20.53	126.43±12.08	NS
Diastolic BP (mmHg)	76.0±11.58	77.14±5.37	NS

TABLE 2. EFFECTS OF MANDIBULAR ADVANCEMENT SPLINT ON SLEEP, RESPIRATION AND METABOLISM

Values are given as mean±SD or No.(%), unless otherwise indicated. NS=not significant; MAS=mandibular advancement splint; ESS=Epworth Sleepiness Score; AHI=apnea/hypopnea index; SpO_2=pulse oxymeter oxygen saturation; FPG=fasting plasma glucose; FPI=fasting plasma insulin; HR=heart rate; BP=blood pressure.

P value<0.05 was considered to be statistically significant.



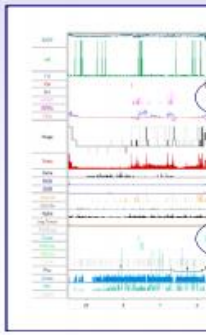


FIGURE 1. Whole night polysomnography data for one patient (Alice 5 d sleep system device; Philips Respironics)

A - Prior to MAS treatment
B - At 3 months of MAS treatment

CONCLUSION

Mandibular advancement splint *Silensor-sl* may be offered treatment with moderate improvement of OSA symptoms in to moderate OSA.

The significant changes in arterial stiffness, blood pressu blood parameters, did not occur in 3 months of treatment be continued to 1-year treatment period.

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The Relationship between Sleep Bruxism and Obstructive Sleep Apnea Based on Polysomnographic Findings

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Abstract: Obstructive sleep apnea (OSA) is the most common sleep disorder. Sleep bruxism (SB) is a masticatory muscle activity during sleep that commonly co-occurs with OSA. The presented study aimed to assess this relationship and to identify factors affecting this co-occurrence. Adult patients (n = 110) were evaluated for OSA and SB in a sleep laboratory using polysomnography. The episodes of bruxism and respiratory events were scored according to the standards of the American Academy of Sleep Medicine. The prevalence of OSA and SB was found to be 86.37% and 50%, respectively. The bruxism episode index (BEI) was increased in the group with mild and moderate OSA (apnea–hypopnea index (AHI) <30) compared to that in the group with severe OSA (AHI ≥ 30) (5.50 ± 4.58 vs. 1.62 ± 1.28, $p < 0.05$). A positive correlation between AHI and BEI was observed in the group with AHI < 30. Regression analysis indicated that higher AHI, male gender, and diabetes were independent predictors for the increased BEI in group with AHI < 30. The relationship between OSA and SB depends on the degree of severity of OSA. OSA is correlated with SB in mild and moderate cases of OSA in the group of patients with increased risk of OSA.

Keywords: sleep bruxism; obstructive sleep apnea; polysomnography; diabetes

1. Introduction

Obstructive sleep apnea (OSA) is a common sleep disorder characterized by a collapse of the upper airways in the setting of continued respiratory effort, leading to airflow cessation and arterial oxygen desaturation, often terminated by arousal. OSA has been independently associated with cardiovascular diseases such as hypertension [1], stroke [2], myocardial ischemia [3], and arrhythmias [4] and mortality [5]. A relationship between OSA and sleep bruxism (SB) has been previously demonstrated [6]. The problem seems to be significant due to the high prevalence of OSA and SB. The prevalence of OSA ranges from 9% to 38% [7], and the prevalence of SB is estimated to occur in 13% of adults [8]. Thus, OSA may be one of the most frequent risk factors for SB in the adult population. SB has been defined as a masticatory muscle activity during sleep that is characterized as rhythmic (phasic) or nonrhythmic (tonic). According to the American Academy of Sleep Medicine (AASM), bruxism is a repetitive jaw-muscle activity characterized by clenching or grinding of the teeth

and/or by bracing or thrusting of the mandible [9]. The International Classification of Sleep Disorders (ICDS-3) indicates the following clinical criteria for the classification of sleep bruxism: (A) the presence of regular or frequent tooth grinding sounds occurring during sleep and (B) the presence of one or more of the following clinical signs: (1) abnormal tooth wear consistent with the above reports of tooth grinding during sleep and (2) transient morning jaw-muscle pain or fatigue; and/or temporal headache; and/or jaw locking upon awakening consistent with the above reports of tooth grinding during sleep [10]. The most recent hypotheses on the etiology of SB support the roles of the central and autonomic nervous systems in the genesis of SB [11]. Most SB episodes occur during cortical arousal associated with an increase in heart rate [12]. Emotional stress; certain groups of drugs; consumption of tobacco, alcohol, or coffee; OSA; and anxiety disorders are recognized as important risk factors of bruxism among adults [13]. Recently, the relationship between SB and OSA has received much attention [14]. OSA has been considered as a new risk factor for SB [15]. However, the data on the association between SB and OSA are contradictory. Although the association between SB and OSA has been discussed in earlier studies [14,16], these studies have failed to confirm this relationship [15,17].

Therefore, in the present study, we aimed to assess the relationship between SB and OSA and to identify factors affecting this relationship.

2. Material and Methods

In this study, 110 adult patients were enrolled between March 2017 and March 2019. All subjects were suspected to have OSA and were hospitalized in the Department and Clinic of Internal Diseases, Occupational Diseases, Hypertension, and Clinical Oncology at the Wroclaw Medical University.

Inclusion criteria were as follows: age between 18 and 90 years, clinical suspicion of OSA, and willingness to participate in this study. Exclusion criteria were as follows: presence of neurological disorders and/or neuropathic pain, respiratory insufficiency, active inflammation, treatment with or addiction to analgesic drugs and/or drugs that affect muscle and breath function, presence of active malignancy and severe mental disorders, and cognitive disability.

All patients underwent overnight diagnostic polysomnography using Nox-A1 (Nox Medical, Reykjavik, Iceland) in the Sleep Laboratory of the Department and Clinic of Internal Medicine, Occupational Diseases, Hypertension, and Clinical Oncology at the Wroclaw Medical University, Poland. Polysomnograms were assessed in 30 s epochs in accordance with the AASM standard criteria for sleep scoring. Polysomnography (PSG) outcome variables included sleep latency, total sleep time (TST); sleep efficiency (%); and the percentages of N1, N2, N3, and rapid eye movement (REM) sleep. Abnormal respiratory events were scored from the pressure airflow signal evaluated in accordance with the standard criteria of the AASM Task Force [18]. Apneas were defined as the absence of airflow for ≥10 s. Hypopnea was defined as a reduction in the amplitude of breathing by ≥30% for ≥10 s with a ≥3% decline in blood oxygen saturation or arousal. The arterial oxygen saturation (SpO_2) was measured with finger pulse oximetry.

SB was assessed by bilateral masseter electromyography (EMG), and the audio and video evaluation bruxism episodes were scored according to the standards of the AASM in three forms: phasic, tonic, and mixed. For the consideration of SB, EMG bursts should not be separated by >3 s to be considered part of the same episode, and EMG activity had to be at least twice the amplitude of the background EMG [19]. The scoring and manual analysis of the collected data were performed by a qualified physician (HM) from the Sleep Laboratory of the Wroclaw Medical University, Poland.

Statistical analysis was performed using the "Dell Statistica 13" software (Dell Inc., Round Rock, TX, USA). Quantitative data are presented as mean and standard deviation. Qualitative variables are expressed as percentage values. Significant statistical differences between arithmetic means were determined by the Mann–Whitney U test and between percentage values by the chi-square test. To determine the relationship between the analyzed variables, a correlation and regression analysis was performed. Parameters of the model obtained in the regression analysis were estimated using the least

squares method. Moreover, the test accuracy was assessed based on receiver operating characteristic (ROC) analysis. Statistical significance was set at $p < 0.05$.

This study was approved by the Ethical Committee of the Wroclaw Medical University (ID KB-195/2017) and was conducted in accordance with the Declaration of Helsinki. All patients signed an informed consent form for participating in this study. Clinical Trial Registration: www.ClinicalTrials.gov, identifier NCT03083405.

3. Results

The mean age of all participants was 51.02 ± 14.19 years. Women constituted 40% ($n = 44$) of all the participants. The mean BMI was 28.93 ± 5.52 kg/m2. Diabetes and ischemic heart disease were diagnosed in 11% ($n = 12$) and 7.27% ($n = 8$) of the study patients, respectively. Hypertension was diagnosed in 45% ($n = 50$) patients.

The mean AHI and mean BEI were 23.28 ± 19.98 and 3.70 ± 4.27, respectively. The polysomnographic parameters in the studied group are presented in Table 1.

Table 1. Polysomnographic indices in the studied group ($n = 110$).

Parameter	Mean ± SD	Minimum	Maximum
SE (%)	80.48 ± 10.37	52.40	96.80
SL (min)	21.92 ± 20.70	0.00	112.60
WASO (min)	55.88 ± 38.96	3.00	172.50
N1 (% of TST)	5.93 ± 4.99	0.20	21.20
N2 (% of TST)	47.72 ± 9.79	26.20	72.90
N3 (% of TST)	24.61 ± 9.65	2.60	52.70
REM (% of TST)	21.75 ± 7.72	4.10	48.90
BEI (n/hour)	3.70 ± 4.27	0.0	24.70
Phasic BEI (n/hour)	1.93 ± 3.13	0.0	19.30
Tonic BEI (n/hour)	1.13 ± 1.30	0.0	6.90
Mixed BEI (n/hour)	0.66 ± 0.79	0.0	4.00
AHI (n/hour)	23.28 ± 19.98	0.0	100.10
ODI (n/hour)	22.92 ± 19.60	0.0	83.40
Mean $SatO_2$ (%)	92.68 ± 2.19	83.30	96.80
Minimal $SatO_2$(%)	81.76± 7.39	54.00	93.00
Cheyne-Stokes (% of TST)	0.69 ± 2.41	0.0	18.20
Mean desaturation (%)	4.78± 2.28	3.0	19.80

SE: sleep efficiency, SL: sleep latency, WASO: wake after sleep onset, REM: rapid eye movement, BEI: bruxism episode index, AHI: apnea–hypopnea index, ODI: oxygen desaturation index, $SatO_2$: oxygen saturation.

The prevalence of OSA (AHI ≥ 5) was 86.37% ($n = 85$) in the studied group. SB (BEI ≥ 2) was diagnosed in 50% ($n = 55$) of the studied patients. The prevalence of mild, moderate, and severe OSA and of mild/moderate and severe SB is presented in Table 2.

Table 2. The prevalence of obstructive sleep apnea and sleep bruxism in the studied group.

Parameter	%	*n*	
AHI (n/hour)	<5	13.63	15
	≥5<15	30.0	33
	≥15<30	25.44	28
	≥30	30.90	34
BEI (n/hour)	<2	50	55
	≥2<4	20	22
	≥4	30	33

BEI: bruxism episode index, AHI: apnea–hypopnea index.

SB (BEI ≥ 2) occurred significantly more frequently in the group with OSA (AHI ≥ 5) than in the group without OSA (AHI < 5) (53.7% vs. 26.7%, $p < 0.05$). The incidence of SB in groups with mild, moderate, and severe OSA was: 61.6%, 64.3% and 35.3%.

No statistically significant correlation was found between AHI and BEI in the entire group (r = −0.05, $p > 0.05$, Figure 1). A positive linear correlation was observed between BEI and arousal index (r = 0.21, $p < 0.05$) and between phasic bruxism and arousal index (r = 029, $p < 0.05$) in the entire group. We also found a positive linear correlation between AHI and BEI (r = 0.24, $p < 0.05$, Figure 1) and between AHI and phasic bruxism (r = 0.27, $p < 0.05$) in the group with mild and moderate OSA (AHI < 30). No such correlations were observed in the group with severe OSA (AHI ≥ 30; r = −0.21, $p > 0.05$, Figure 1). Furthermore, no correlations were observed between AHI and tonic or mixed bruxism in both studied groups. In the group with AHI < 30, BEI was increased compared to that in the group with AHI ≥ 30 (5.50 ± 4.58 vs. 1.62 ± 1.28, $p < 0.05$). BEI was also increased in the group with OSA (AHI ≥ 5) compared to that in healthy subjects (AHI < 5) (4.03 ± 4.48 vs. 1.62 ± 1.28).

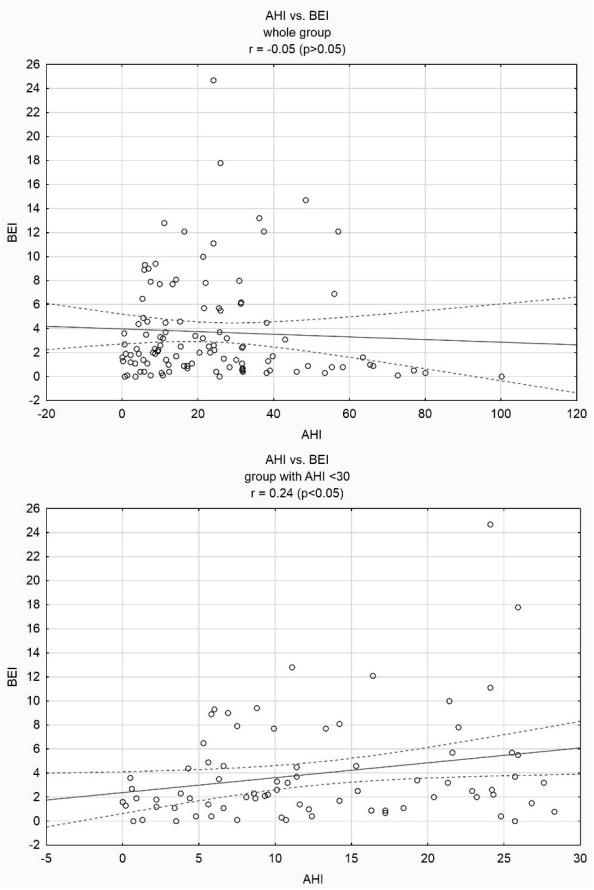

Figure 1. *Cont.*

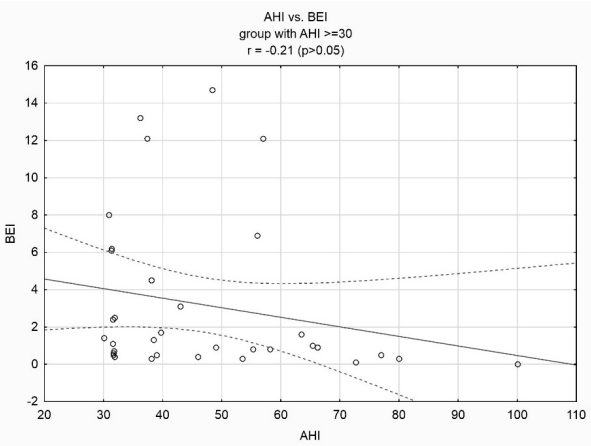

Figure 1. Correlation scatter plots between apnea–hypopnea index (AHI) and bruxism episode index (BEI) in the whole group, in the group with AHI < 30 and in the group with AHI ≥ 30.

A positive linear correlation was observed between phasic bruxism and oxygen desaturation index (ODI) and between phasic bruxism and minimal oxygen saturation in the group with AHI < 30 (Table 3).

Table 3. The correlations between polysomnographic indices and BEI in the group with mild and moderate OSA (AHI < 30).

Parameter	BEI (n/hour)	Phasic BEI (n/hour)	Tonic BEI (n/hour)	Mixed BEI (n/hour)
AHI (n/hour)	**0.24**	**0.27**	0.03	0.15
SL (min)	−0.11	−0.08	−0.07	−0.16
WASO (min)	−0.06	−0.01	−0.15	−0.08
SE (%)	0.17	0.16	0.14	0.07
N1 (% of TST)	0.10	0.10	−0.07	0.19
N2 (% of TST)	−0.01	−0.01	−0.00	−0.01
N3 (% of TST)	0.08	0.06	0.10	0.05
REM (% of TST)	−0.15	−0.12	−0.09	−0.17
Arousal index (n/hour)	**0.45**	**0.52**	−0.08	**0.34**
Cheyne-Stokes (% of TST)	0.09	0.07	−0.13	−0.05
ODI (n/hour)	0.20	**0.23**	0.02	0.14
$SatO_2$ (%)	−0.02	−0.06	0.09	0.02
Min $SatO_2$ (%)	−0.20	**−0.26**	0.08	−0.11
Mean desaturation (%)	−0.04	0.03	−0.07	0.0

SE: sleep efficiency, SL: sleep latency, WASO: wake after sleep onset, REM: rapid eye movement, BEI: bruxism episode index, AHI: apnea–hypopnea index, ODI: oxygen desaturation index, $SatO_2$: oxygen saturation; statistically significant differences are marked as bold ($p < 0.05$).

BEI was increased in patients with diabetes compared to that in patients without diabetes (5.78 ± 5.27 vs. 2.59 ± 4.17, $p < 0.05$).

The cut-off point for AHI to predict bruxism (BEI ≥ 2) in the group with AHI < 30 was determined on the basis of the ROC curve (Figure 2). According to the ROC curve, the cutoff point was set at AHI = 5.3. In this group, the criterion AHI > 5.3 indicates bruxism with sensitivity and specificity of 0.533 and 0.907, respectively, which gives a prediction accuracy of 0.658.

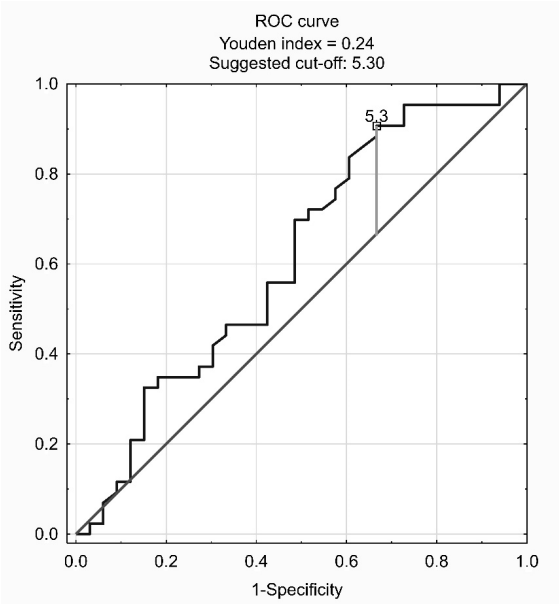

Figure 2. Receiver operating characteristic curve (ROC) suggesting the optimal apnea–hypopnea index (AHI) cutoff point for indicating its suitability to recognize bruxism (BEI ≥ 2) in the group with AHI < 30.

Subsequently, to determine the factors that were independently associated with BEI in the studied patients, a regression analysis was made. In the group with AHI < 30, using a multivariate regression analysis and considering all potentially independent variables that were statistically significant in univariate models (male gender, age, diabetes, coronary artery diseases, AHI and arousal index), model 1 was obtained. Then, stepwise (in each step by removing the variable with the highest *p* value from the model), models 2–4 were obtained (Table 4). The highest determination coefficient R^2 (0.488) was shown for model 1: BEI = 0.92 + 0.12 AHI + 1.73 male gender + 1.59 diabetes ± 3.82. On the basis of the obtained model, it can be stated that higher AHI, male gender, and diabetes were independent predictors for increased BEI in the studied patients.

Table 4. The results of estimation for the models obtained with multivariate regression analysis in group with AHI < 30.

Parameter	Models for BEI			
	Model 1			
	Rc	SEM of RC	*p*	R^2
intercept	**0.92**	**0.69**	**0.024**	
AHI	**0.12**	**0.03**	**0.029**	
Arousal index	0.23	0.17	0.076	
Male gender	**1.73**	**0.72**	**0.034**	**0.488**
Age	0.03	0.03	0.115	
Diabetes	**1.59**	**1.21**	**0.039**	
Coronary artery disease	1.25	1.66	0.201	
	Model 2			
	Rc	SEM of RC	*p*	R^2
intercept	**1.28**	**0.68**	**0.013**	
AHI	**0.09**	**0.03**	**0.030**	
Arousal index	0.24	0.15	0.071	**0.471**
Male gender	**1.80**	**0.82**	**0.045**	
Age	0.04	0.03	0.285	
Diabetes	**1.43**	**1.07**	**0.036**	

Table 4. *Cont.*

Parameter	Models for BEI			
		Model 3		
	Rc	SEM of RC	*p*	R^2
intercept	**1.65**	**1.03**	**0.007**	
AHI	**0.08**	**0.03**	**0.034**	
Arousal index	0.25	0.17	0.070	**0.458**
Male gender	**1.97**	**0.91**	**0.035**	
Diabetes	**1.47**	**0.94**	**0.040**	
		Model 4		
	Rc	SEM of RC	*p*	R^2
intercept	**1.83**	**1.06**	**0.004**	
AHI	**0.10**	**0.04**	**0.044**	**0.423**
Male gender	**2.22**	**0.96**	**0.024**	
Diabetes	**1.47**	**1.06**	**0.047**	

AHI: apnea–hypopnea index, Rc: regression coefficient, SEM: standard error of mean; statistically significant differences are marked as bold ($p < 0.05$).

4. Discussion

The most important result of this study is the positive correlation between BEI and AHI in the group with mild and moderate OSA. This result indicates the effect of the severity of OSA on the occurrence of correlation between AHI and BEI. The correlation was also observed in the group with AHI < 30. However, no such correlation was observed in patients with a severe form of OSA (AHI ≥ 30). One of the hypotheses linking SB and OSA is that SB activity protects against OSA by protruding the mandible and restoring airway patency [20,21]. However, this mechanism may not be adequate to prevent the airway from collapsing in severe OSA. In severe OSA, more effective mechanisms may be involved, e.g., excessive respiratory effort and/or increased respiratory rate, leading to a reduction in bruxism episodes. Thus, the probable explanation of this phenomenon is the limited role of bruxism as a protective factor in severe OSA. In this study, we did not investigate other protective mechanisms against OSA events.

The results of our study may explain the contradicting results of studies that investigated the correlation between OSA and SB. This correlation may depend on the studied population. The correlation may be observed if mild or moderate OSA is predominant in the studied population. However, if severe OSA prevails in the studied population, then the attempt to find a correlation may fail. It is worth noting that in many studies on the association between SB and OSA, insufficient research methods have been used, e.g., a telephone survey was used to diagnose SB [22], or self-administered questionnaire and clinical examination were conducted [23]. Studies that used polysomnography to diagnose SB in the studied groups are few [16,17,24,25]; hence, the results of these studies should be interpreted with caution. Recently, a correlation between OSA and bruxism was found in polysomnographic studies [26].

In the present study, we demonstrated that OSA (AHI ≥ 5), male gender, and diabetes are the independent risk factors for increased BEI. Numerous risk factors for SB in the general population have been reported. Caffeine, smoking, stress, alcohol, and anxiety are well-known risk factors for SB [13,22]. Reflux esophagitis [27], depression [28], and nocturnal frontal lobe epilepsy [29] were also described as a risk factor for bruxism. Few studies indicate OSA as a risk factor for bruxism [14,26,30]. Thus, the results of our study are in agreement with the findings of these studies.

In the present study, we found diabetes as a new potential risk factor for bruxism. Data on the association between diabetes and bruxism are very limited. Diabetes is associated with cardiovascular neuropathy, which results in a decrease in parasympathetic tone and sympathetic overactivity, similar to that occurring in bruxism [31]. Bruxism is considered as a protective factor in impaired salivation. Decreased salivary flow also occurs in diabetes [32]; thus, these findings may explain the increased risk for SB in diabetes.

Transient hypoxia commonly occurs in OSA, which is considered as a risk factor for bruxism. Moreover, hypoxia was previously described as a factor potentially associated with the onset of bruxism episodes [26,33]. The present study also showed a positive correlation between phasic bruxism and minimal $SatO_2$ and between phasic bruxism and ODI; these findings confirm the association between hypoxia and SB.

It is worth noting that the prevalence of bruxism was quite high in the studied group with clinician suspicion of sleep apnea. SB was diagnosed in 50% of the studied subjects. A recent study by Tan et al. showed an SB prevalence of 33% in patients with OSA. Interestingly, the prevalence of SB is estimated at 12% in the general population [8,34] thus, the prevalence of SB in patients with OSA is higher than that in the general population.

The present study has some limitations. First, there is no adequate explanation for the decline in correlation between AHI and BEI in a more severe form of OSA. Second, the enrolled patient had increased risk of OSA, and thus, risk of SB was assessed in the cohort of sleep-disturbing breathing, not in general population. Third, the study group included a few patients with diabetes; hence, further studies in a group with more patients with diabetes are needed to confirm these new risk factor for SB.

5. Conclusions

The relationship between OSA and SB depends on the degree of severity of OSA. From the results of the present study, mild-to-moderate OSA is associated with SB in the group of patients with increased risk of OSA. Diabetes could be a new risk factor for SB.

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Comorbid insomnia in sleep-related breathing disorders: An under-recognized association

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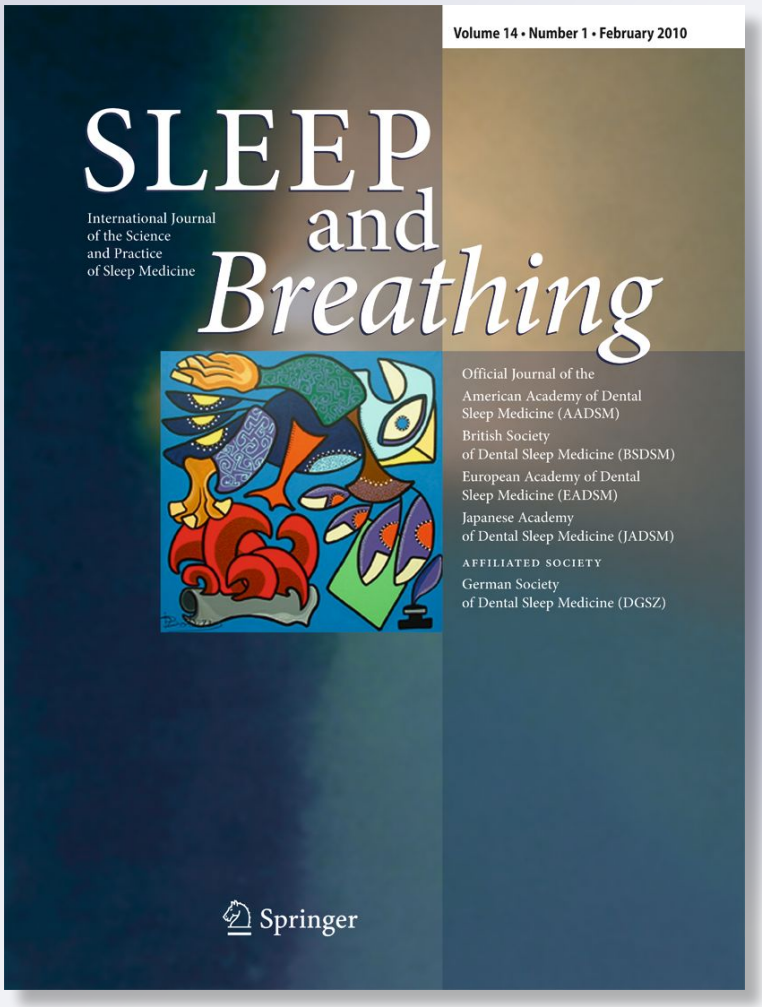

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REVIEW

Comorbid insomnia in sleep-related breathing disorders: an under-recognized association

Suhaila E. Al-Jawder · Ahmed S. BaHammam

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Abstract
Background In the clinical practice of sleep medicine, the coexistence of common sleep disorders is not uncommon. Patients with sleep disordered breathing (SDB) may present with insomnia, and studies have shown that SDB is common among insomnia patients. Little is known about the pathophysiological mechanisms underlying this coexistence, and limited information is available regarding the impact of each disorder on the other. It is essential to consider the effect of each disorder on the other and to understand the clinical consequences anticipated when treating each disorder in isolation. The management plan should be directed toward both disorders in a systematic and evidence-based approach. Unfortunately, a consensus standard approach for the management of comorbid insomnia and SDB is not yet available.
Methods Therefore, we have reviewed published studies that investigated insomnia in patients with different types of SBD; obstructive sleep apnea, central sleep apnea, and hypoventilation syndromes, as well as studies that assessed SBD in patients with insomnia. In addition, we reviewed the effects of SBD treatment modalities on insomnia and the effects of insomnia treatments on SBD.

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Keywords Insomnia · Sleep disordered breathing · Obstructive sleep apnea · Central sleep apnea · Hypoventilation · CPAP · Hypnotics

Introduction

In the clinical practice of sleep medicine, sleep disorders frequently overlap or coexist with each other. Sleep-related breathing disorders (SBD) are the most common disorders evaluated and managed in sleep clinics [1, 2]. Insomnia, on the other hand, represents the other bulk of cases in sleep medicine. Recent data suggest that the coexistence of these two major disorders in one individual is not uncommon, and hence, modification of the management plan might be required. The literature supports a high prevalence of insomnia complaints in SBD patients and vice versa. However, the interaction between the two disorders remains to be defined. Insomnia and its subtypes (sleep-initiation, sleep-maintenance, and early-morning awakenings) are characterized by a state of physiological and cognitive hyperarousal that is persistent in nighttime and daytime [3, 4]. In SBD, complaints of excessive daytime sleepiness are usually present in addition to insomnia complaints. It is essential to consider the effects anticipated with the treatment provided for each disorder on the other disorder in the management plan of patients with both disorders. Therefore, an integrated approach is required to achieve proper control of both coexisting disorders.

In this review, we present studies that investigated insomnia in patients with all types of SBD, obstructive sleep apnea (OSA), central sleep apnea (CSA), and hypoventilation syndromes, as well as studies that assessed SBD in patients with insomnia. In addition, we review the

effects of SBD treatment modalities on insomnia and the effects of insomnia treatments on SBD.

The references included in this article were obtained from journals listed in MEDLINE, EMBASE, and PsycINFO. Original studies that explored insomnia in SBD patients or SBD in insomnia patients were included (Tables 1 and 2). Studies addressing the effect of hypnotics on patients with SBD were retrieved as well.

Sleep-related breathing disorders

Sleep-related breathing disorders include OSA, CSA, and hypoventilation syndromes. In addition to discussing the relationship between OSA and insomnia, we tried to explore the relationship between insomnia and other SBDs.

1. Obstructive sleep apnea

   This is the most common SBD. The usual presentation is complaints of unintentional daytime sleepiness, un-refreshing sleep, fatigue or insomnia, and nocturnal awakenings with breath holding, gasping, or choking. The bed partner might also report breathing interruptions, loud snoring or both during the patient's sleep [5]. OSA (apnea hypopnea index (AHI)>5/h) is a prevalent problem, affecting 24% of men and 9% of women; 4% of men and 2% of women suffer from obstructive sleep apnea syndrome (AHI>5/h and excessive daytime sleepiness) [6].
2. Central sleep apnea

   CSA is defined as intermittently diminished or absent respiratory effort. CSA can be physiological related to high altitude, idiopathic, or caused by cardiac dysfunction, brain stem lesions, drugs, or other substances. Cheyne-Stokes respiration (CSR), frequently seen in association with cardiac dysfunction, is the most common and widely studied phenotype associated with central sleep apnea.
3. Hypoventilation syndromes

   These are a variable group of disorders of central and peripheral origin that result in progressive accumulation of arterial carbon-dioxide tension ($PaCO_2$) above 45 mmHg. Such syndromes include obesity-hypoventilation syndrome (OHS), neuromuscular and chest wall disorders, and diseases of the lower airways such as chronic obstructive pulmonary disease (COPD), bronchiectasis, and cystic fibrosis.

Comorbid insomnia and SBD

Insomnia and OSA

The first description of the comorbidity of insomnia and OSA was published in 1973 by Guilleminault. The report described the comorbidity of insomnia and OSA as a new clinical syndrome of insomnia that should be ruled in/out by PSG [7]. This association was further evaluated in 2001, when the prevalence of insomnia in patients objectively diagnosed with OSA and upper airway resistance syndrome (UARS) was retrospectively evaluated and found to be as high as 50% [8]. Subsequent studies reported a prevalence ranging from 22% to 54.9% [8–14]. This wide range of prevalence is primarily attributed to the variable insomnia definitions used by different studies. The OSA patients who suffered from insomnia were found to have twice as many

Table 1 Prevalence of comorbid insomnia in OSA patients

Study	Population	Prevalence	Onset insomnia	Maintenance insomnia	Early-morning awakening insomnia
Krakow et al. [8]	231 patients with SBD	50%	NA	NA	NA
Krell et al. [11]	228 OSA patients	54.9%	33.4%	38.8%	31.4%
Smith et al. [12]	105 OSA patients	39%	NA	NA	NA
Chung et al. [10]	157 OSA patients	42%	6%	26%	19%
Lavie et al. [14]	358 OSA patients	27.9% in women 21.9% in men	NA	NA	NA
Gold et al. [19]	220 OSA, 137 UARS	–	UARS: 33.4% AHI>60, 15.6% AHI>30, 18.2% AHI>10, 20.9%	UARS: 59.9% AHI>60, 73.9% AHI>30, 62.9% AHI>10, 58.2%	
Wickwire et al. [13]	232 OSA patients	37%	16.6%	23.7%	20.6%
Chung et al. [15]	119 OSA patients	–	9%	33%	21%
Al otair and BaHammam [9]	384 OSA patients	39.8% in women 25.9% in men	NA	NA	NA

UARS upper airway resistance syndrome

Table 2 Prevalence of comorbid OSA in insomnia patients

Study	Population	Insomnia/inclusion criteria	SBD criteria	Prevalence
Lichstein et al. [20]	80	SOL>30 min or WASO>30 min, 6-min duration	AHI>5 or AHI>15	29% or 43% OSA
BaHammam [22]	67	Difficulty initiating or maintaining sleep or non-restorative sleep, lasting>3 months	AHI>5	25.4% OSA+1 case CSA/CSR
Stone et al. [21]	45	TST<6.5 h, SOL>30 min, WASO>30 min, 6-min duration	RDI>10 or RDI>5	40% or 64.4%
Krakow et al. [111]	44	Weekly episodes of insomnia	RDI≥15	50% OSA 40.9% UARS
Guilleminault et al. [23]	394	SOL>30 min or WASO>20 min, 1-min duration	AHI>5	67% OSA 15.7% UARS
Gooneratne et al. [112]	100	Difficulty initiating or maintaining sleep or early-morning awakening≥3 nights/week and for≥3 weeks	AHI≥15	29.3% OSA
Krakow et al. [25]	137	Patients using prescription sleep medication nightly for at least 6 months	AHI≥5	71% OSA
Krakow et al. [24]	218	Use of hypnotic medication for≥6 months	AHI≥5	75% OSA

SOL sleep-onset latency, *WASO* wakefulness after sleep onset, *TST* total sleep time

mental symptoms and psychiatric disorders and twice as much use of psychotropic and sedating medication than OSA patients without insomnia [8]. Of the insomnia subtypes, sleep-maintenance insomnia is the most common comorbid insomnia in OSA patients and is typically associated with daytime sleepiness followed by early-morning awakening insomnia [10, 11, 13, 15]. However, 42% of OSA patients present with more than one subtype of insomnia [10]. Comorbid insomnia is more common in women than men with sleep-onset insomnia being the predominant subtype [9, 14]. This comorbid insomnia is frequently the presenting complaint among women [9, 16–18].

The severity of OSA can influence the type of insomnia complaints and causes increased sleep-maintenance difficulty [10]. In a study by Gold et al., sleep-maintenance insomnia was reported by 73.9% of patients with an apnea hypopnea index (AHI)>60/h, by 62.9% of patients with an AHI>30/h and by 58.2% of patients with an AHI>10/h [19]. On the other hand, sleep-onset insomnia was associated with a lower AHI, 15.6% in patients with an AHI>60/h, 18.2% of patients with an AHI>30/h, and 20.9% of patients with an AHI>10/h [19]. Table 1 presents a summary of the studies of comorbid insomnia prevalence in OSA patients.

Individuals with insomnia complaints were also found to have a high prevalence of OSA (Table 2). The prevalence varies with the criteria used to define OSA. In a study of older adults with insomnia complaints, OSA prevalences of 43% (AHI>5/h) and 29% (AHI>15/h) were reported [20]. Another study reported a higher prevalence of OSA in insomnia patients with a prevalence of 64.4% for respiratory disturbance index (RDI)>5/h and 40% for RDI>10/h [21]. A third study conducted on middle-aged patients with chronic insomnia reported an OSA (defined as AHI>5/h) prevalence of 25.4% [22]. The highest prevalence of SBD, 83% (67% OSA and 15.7% UARS), was reported in a cohort of postmenopausal women with chronic insomnia [23]. For patients with drug-resistant insomnia who suffered insomnia symptoms for more than a decade and were on hypnotics for an average of 4.5 years, OSA with an average AHI of 19.5/h was objectively diagnosed in 75% of patients [24]. In another similar study of drug-resistant insomnia among patients with an average insomnia chronicity of 13 years and medication use for 3.81 years, OSA was diagnosed in 71% of patients [25]. Such findings highlight the importance of diagnostic PSG for patients with chronic insomnia, particularly if they fail drug therapy.

Interaction between Insomnia and OSA

OSA can be associated with repeated nocturnal awakenings and difficulty in maintaining sleep for several reasons. Sequential apnea/hypopnea events and post-event arousals can result in sleep fragmentation and frequent awakenings. Nocturia is another factor, which results from an increase in the transmural pressure and left ventricle afterload and subsequent release of atrial natriuretic peptide. Treating OSA usually improves nocturia [26]. Therefore, the presence of OSA can be a precipitating and perpetuating factor for insomnia. On the other hand, sleep deprivation adversely affects the tone of the pharyngeal muscles, particularly the genioglossus muscle, which in turn contributes to the generation of OSA and increases its severity [27, 28]. Sleep fragmentation has more profound effects on the genioglossus muscle than does sleep deprivation [29]. Therefore, sleep-maintenance insomnia with frequent sleep

fragmentation can lead to higher collapsibility of the upper airway and worsening OSA [29].

Primary insomnia represents a state of physiological and cognitive hyperarousal [4]. The multiple sleep latency test (MSLT) showed that insomniacs are not sleepier than normal controls and that the scored sleep latency was prolonged, indicating the existence of a persistent state of hyperarousal [30, 31]. However, in the case of comorbid insomnia and OSA, the MSLT and Epworth Sleepiness Scores (ESS) show different results, as the extent of daytime sleepiness is influenced by the predominant subtype of comorbid insomnia. Sleep latency on MSLT is longer, and the ESS is lower in sleep-initiation insomnia as compared to those with sleep-maintenance insomnia, which is associated with more daytime sleepiness [10].

Insomnia in central sleep apnea

Very few, if any, studies have described the coexistence of insomnia and CSA, despite the frequent complaints of sleep disturbances among CSA patients. As in OSA, the first description was more than three decades ago, in 1976, when CSA was first reported as an unusual cause of insomnia in non-obese apneic patients [32]. In heart failure patients, where the Cheyne-Stokes respiration (CSA-CSR) prevalence is 25–40%, the most commonly reported insomnia complaints are difficulty maintaining sleep followed by difficulty initiating sleep [33, 34]. In a study that assessed sleep difficulties among patients with chronic heart failure, 24% of women with heart failure reported sleep-maintenance insomnia, compared to 10% of normal women. Sleep-maintenance insomnia was reported by 23% of men with heart failure, compared to 8.5% of normal men [35]. The presence of sleep complaints in patients with heart failure was associated with poor health-related quality of life [35]. Although the presence or absence of CSA or other SBD was not documented in this study, it highlighted the frequent insomnia complaints among patients who have experienced heart failure [35].

Insomnia in hypoventilation syndrome

Hypoventilation syndromes are variable disorders that are frequently associated with sleep dysfunction. Sleep difficulties are usually related to the underlying disease. In the case of neuromuscular disorders, insomnia can be secondary to muscular pain, cramps, contractures, joint pain, anxiety, and depression [36, 37].

Insomnia is the third most common morbidity, reported by 50% of patients with chronic obstructive airway disease (COPD) [38–40]. The presence of COPD symptoms (coughs, wheezing, etc.) can precipitate insomnia; insomnia will further worsen the quality of life and pulmonary function [41]. Deteriorated pulmonary function and attenuation of the ventilatory response to hypercapnia can be induced by sleep deprivation [41]. As with OSA, sleep-maintenance insomnia (44%) is the predominant subtype, followed by early-morning awakenings (30%) and sleep-initiation insomnia (26%) [41, 42].

Treatment

Treatment of comorbid insomnia in patients with SBD

Both pharmacological and non-pharmacological options are effective in treating insomnia. It is essential to understand the effect of either type of intervention on the coexisting SBD.

Pharmacological therapy

a. Benzodiazepine receptor agonist

BzRAs bind to the benzodiazepine receptors on neurons that also express gamma-aminobutyric acid (GABA) type A receptors, which facilitates GABA inhibition and induces sedative, hypnotic, anxiolytic, anticonvulsant, myorelaxant, and amnesic effects. These effects are divided to short-, intermediate-, or long-term effects and are effective in treating various insomnia-associated symptoms [43].

Due to the negative impact induced by BzRAs on respiratory mechanics, caution is needed when using BzRAs in SBD patients. In normal subjects, BzRAs increase end-tidal CO_2 and reduce minute ventilation, tidal volume, respiratory rate, ventilator response to hypercapnia, and genioglossus electromyography (EMG) activity [44–47].

BzRA in OSA patients

Studies performed in OSA patients are not very consistent with regard to the negative adverse effects on respiratory mechanics. Such controversy may be due to variability in the drugs used (dose and duration of action) and to the severity of the underlying OSA. In a case report of a young man with severe OSA, administration of 15 mg of midazolam caused a life-threatening apnea that was eliminated by continuous positive airway pressure (CPAP); however, marked central hypoventilation persisted [48]. Long-acting BzRA flurazepam was shown to increase the frequency of apnea episodes, the total duration of apnea and the degree of oxygen desaturation in OSA patients, but long-acting nitrazepam did not affect AHI or oxygen desaturation in patients with mild to moderate OSA [49, 50]. Intermediate-acting

temazepam in mild OSA patients also did not worsen the AHI [51].

BzRAs in CSA patients

In contrast to OSA, the use of BzRAs in CSA patients can be beneficial. Suppressing arousals reduces the oscillation in PCO_2 levels and minimizes the frequency of central apnea events. Clonazepam and temazepam are effective in suppressing CSA, and temazepam reduces the periodic breathing induced by high altitude [52, 53].

BzRAs in hypoventilation syndrome

Caution is required when using BzRAs in patients with hypoventilation syndromes, as the suppression of respiratory mechanics can be profound and life threatening. With regard to COPD, some studies have assessed the effect of hypnotics in patients with stable mild to moderate COPD; none has explored related effects during COPD exacerbation. Clinical studies did not support the use of BzRAs in stable mild to moderate COPD, as the results were variable and the studied population was small [54–56]. For safety reasons, a small dose of short-acting or intermediate-acting BzRAs can be used when necessary, provided that the patient is on NIPPV, to avoid any severe respiratory suppression.

b. Non-benzodiazepine receptor agonists

Non-BzRAs, such as zolpidem, eszopiclone, and zaleplon, bind to the alpha-1 subunit of the GABA receptor, which is known to mediate sedation and amnesia but not anxiolytic or myorelaxant effects. Therefore, the impact on respiration control mechanisms is less potent than that of BzRAs [57].

i. Non-BzRAs in OSA patients:

In mild to moderate OSA, eszopiclone improves sleep duration and efficiency but has no significant effect on AHI, total arousals, respiratory-related arousals, duration of apnea/hypopnea episodes, or oxygen saturation [58]. As premedication for PSG, eszopiclone improves sleep duration and continuity without worsening the AHI. This drug also facilitates performance of the CPAP titration, achieving better sleep efficiency than is observed in the placebo group [59]. Eszopiclone also significantly improved short-term compliance with CPAP therapy [60]. The other non-BzRA, zolpidem, was also an effective premedication for PSG; treatment with this drug resulted in more successful diagnostic and CPAP titration studies without worsening the AHI [61]. The acute administration of zolpidem (10 mg) was not associated with impairment of the effective level of CPAP in patients with severe OSA (no change in AHI, oxygen desaturation index, or minimum SaO_2 [62].

ii. Non-BzRAs in CSA patients:

Zolpidem and zaleplon were safe when used in hypoxemic environments of simulated altitude. These drugs stabilize sleep architecture, respiratory patterns, and performance [63, 64]. As is observed when the drug is used to treat idiopathic CSA, zolpidem decreased central apneas and hypopneas and improved sleep architecture [65]. Although no randomized controlled trials have been performed to assess the efficacy of non-BzRAs in treating CSA, non-BzRAs represent a promising option, particularly for high-altitude and idiopathic forms of CSA.

iii. Non-BzRAs in hypoventilation syndromes

COPD is the only hypoventilation syndrome in which the effect of non-BzRAs has been studied. Repeated doses of zolpidem (10 mg) for 8 days did not impair nocturnal respiratory and sleep architecture parameters, diurnal pulmonary function tests, central control of breathing, or physical performance in patients with stable COPD [56, 66]. In mild to severe COPD, zolpidem use was not associated with significant respiratory disturbances, as was the use of BzRAs [56, 67].

c. Sedating antidepressants

The serotonin system could play an important role in the pathophysiology of sleep apnea, as it provides tonic excitatory input to the genioglossus and other upper airway-dilating muscles [68, 69]. The fact that sedating antidepressants are able to increase levels of serotonin in the brain encouraged investigators to assess the efficacy of this drug type in patients with SBD.

In an animal model of OSA, trazodone significantly reduced respiratory events in both non-REM and REM sleep [70]. However, in moderate to severe OSA patients, trazodone increased the respiratory effort-related arousal threshold in response to hypercapnia, allowing for a higher level of CO_2 tolerance without arousal [71]. Mirtazapine at low doses (4.5 to 15 mg) significantly reduced the AHI in OSA patients [72, 73]. Higher doses of mirtazapine (up to 45 mg) in another study were not associated with improvement in sleep apnea parameters, and the withdrawal rate was higher in the mirtazapine group due to undesirable side effects [74]. The long-term effects of mirtazapine are not yet known, as weight gain is an important side effect that might worsen OSA.

d. Other pharmacological drugs:

Ramelteon is a selective melatonin receptor agonist with the ability to reduce sleep latency and increase

total sleep time in patients with chronic primary insomnia [75–77]. In mild to moderate OSA, ramelteon is well-tolerated and does not worsen AHI or oxygen saturation [78]. Ramelteon remains a safe drug for use in mild, moderate, and severe COPD patients [79, 80]. Over-the-counter medications (antihistamines, tryptophan, etc.) are frequently used to treat insomnia symptoms; however, data about the efficacy and safety of these drugs are limited. Therefore, the use of over-the-counter drugs is not recommended to treat comorbid insomnia [81].

Non-pharmacological therapy

Cognitive-behavioral therapy (CBT) targets the cognitive hyperarousal factors that precipitate and perpetuate insomnia. CBT usually consists of stimulus control, sleep restriction, relaxation training, cognitive therapy, and sleep hygiene education [82–85]. Cognitive-behavioral therapy is currently recommended as the first-line treatment for chronic insomnia by both the National Institutes of Health and the American Academy of Sleep Medicine (AASM) [81, 86, 87].

In the setting of OSA and comorbid refractory insomnia, combining CBT with OSA treatment (CPAP, oral appliances, or surgery) was associated with more clinical cures or near-cures on the validated measures of insomnia, sleep quality, and sleep impairment, as compared to treatment with CBT alone [88]. In another study, providing surgical intervention for patients with insomnia and mild OSA improved both subjective and objective outcome measures, as compared to treatment with CBT alone [89]. However, the addition of CBT to the surgical arm had an additional benefit of increasing total sleep time and controlling sleep-onset difficulties [89]. In summary, CBT is effective as an add-on therapy to treat comorbid insomnia and OSA.

Treatment of SBD in patients with insomnia

OSA therapy

CPAP therapy is considered to be the "gold standard" therapy for OSA. Its use has been associated with a reduction in daytime sleepiness, improvements in the quality of sleep and life, enhanced cognitive function, and improvement in cardiovascular morbidities and mortalities [90–93]. The initiation of CPAP therapy is opposed by poor acceptance and adherence in up to 46–83% of patients [94–96]. Several approaches have been studied to enhance CPAP adherence. The use of behavioral therapy, hypnotic medications, desensitization to CPAP, and use of the appropriate interface were all successful in improving CPAP adherence. Eszopiclone and zolpidem were used as premedications for both diagnostic and CPAP titration sleep studies. These drugs are able to provide high-quality sleep on the first night of CPAP therapy, which is vital in improving long-term adherence [59, 61, 62, 97]. Notably, early acceptance of and compliance with CPAP therapy are essential and predict long-term compliance [98].

The coexistence of insomnia symptoms, especially sleep-maintenance insomnia, can worsen CPAP adherence, thereby identifying and reducing comorbid insomnia symptoms in patients who have been prescribed CPAP is therefore essential to achieve proper CPAP adherence [13]. When accompanied by other psychological comorbidities such as anxiety, insomnia can predispose patients to claustrophobia, a known factor for poor compliance with CPAP therapy [99]. A recent study reported no impact of insomnia (measured by the insomnia severity index) on CPAP rejection and long-term compliance [100]. However, these findings need to be interpreted with caution as 50% of the studied population had moderate to severe insomnia and were on hypnotic and psychotropic medications, which could mask CPAP compliance problems [100]. Incorporating behavioral sleep medicine into the management of CPAP adherence and comorbid insomnia could potentially be of great value. An integrated CBT could manage coexisting sleep disorders [101, 102]. A new protocol to enhance CPAP adherence in insomnia patients with OSA involves a daytime nap to optimize mask fit, mask and pressure desensitization, and cognitive therapy that addresses the concerns and anxiety associated with CPAP therapy (PAP-NAP). The initial results showed an increase in CPAP adherence compared to historical control patients who did not undergo these additional steps [103].

CSA treatment

Central sleep apnea still has no proven standardized treatment. The treatment options can be as simple as supplemental oxygen or as sophisticated as adaptive servo-ventilation (ASV) [104]. One treatment might be successful in one case but not with other cases. Although these treatment modalities can improve sleep parameters in CSA patients, none of the studies published previously has addressed the impact on coexisting insomnia complaints.

Hypoventilation syndrome treatment

In general, sleep disturbances (mainly insomnia) are common complaints among patients with some of the hypoventilation syndromes. Insomnia is usually precipitated and perpetuated by the severity of the underlying condition. Therefore, the first step in patient management is to achieve better control of the underlying diseases. Thereafter, insomnia-specific treatments can be considered. Cognitive-

behavioral therapy sessions can be initiated first; subsequent integration of a CBT protocol for insomnia, pain control, and stress can achieve a higher level of disease control. The use of hypnotic drugs in the setting of hypoventilation syndromes is not encouraged, especially if the patient has severe hypoventilation and has not yet been started on any noninvasive or invasive type of ventilation.

The use of noninvasive bi-level positive pressure ventilation (BPAP) is proven to increase survival and quality of life among patients with neuromuscular diseases [105–107], in addition to improving sleep efficiency and sleep architecture [108]. The control of muscular cramps, contractures, and pain in neuromuscular disorder patients is also vital in improving sleep and reducing insomnia. In obesity-hypoventilation syndrome, the use of both BPAP and CPAP has improved sleep parameters [109].

Treating COPD symptoms will help reduce insomnia complaints, as such symptoms are closely related to the severity of the COPD symptoms. The treatment of COPD involves a combination of bronchodilators and steroids. Of the bronchodilator agents used to treat COPD, the anticholinergic agent ipratropium bromide is proven to improve total sleep time, sleep quality, nocturnal awakenings and number of arousals [110].

Conclusion

In the clinical practice of sleep medicine, the coexistence of common sleep disorders is not uncommon, and the identification of these disorders is the first step in patient management. In comorbid insomnia in patients with SBDs, the main obstacle is in initiating the proper treatment for one disorder without worsening the other. Based on the available literature, it is recommended to first initiate treatment of the underlying SBD (OSA, CSA, or hypoventilation). Subsequently, residual insomnia symptoms can be managed with integrated CBT protocols and, if required, small doses of short-acting hypnotics. There will always be challenging cases that remain refractory to either therapy arm, which will motivate further research.

Future research

1. Determine the prevalence of insomnia in patients with different subtypes of CSA and hypoventilation syndromes.
2. Assess the long-term effects of CPAP/BPAP/ASV therapies on the resolution of comorbid insomnia.
3. Identify the resistant insomnia subtypes and alternative management pathways.
4. Identify other measures to enhance compliance with CPAP/BPAP in those patients with comorbid insomnia.

Conflict of interest The authors declare that they have no conflict of interest.

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SLEEP APNEA- A PREVENTABLE RISK FACTOR FOR STROKE

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Sleep apnea

- A common, yet underestimated, chronic disorder with a major impact on morbidity and mortality in the general population.

Sleep apnea

- **The condition affects more that 20 million adults in the U.S. and is associated with a number of serious health consequences and early death.**

- **Women are much less likely to be diagnosed than men as symptoms are more subtle, but long term implications same in both.**

What is Sleep Apnea

- A disorder that occurs when a person's breathing is **repeatedly interrupted** during sleep.

- **Due to repetitive collapse of the airway during sleep resulting** in apneas and hypopneas

- Each time, the oxygen level in the blood drops, eventually resulting in **damage to many cells in the body**.

A picture is worth a thousand words

Stroke

- Stroke is the 3rd leading cause of death in US and second world wide.
- Leading cause of long term disability.
- OSA is a potentially modifiable risk factor of stroke.

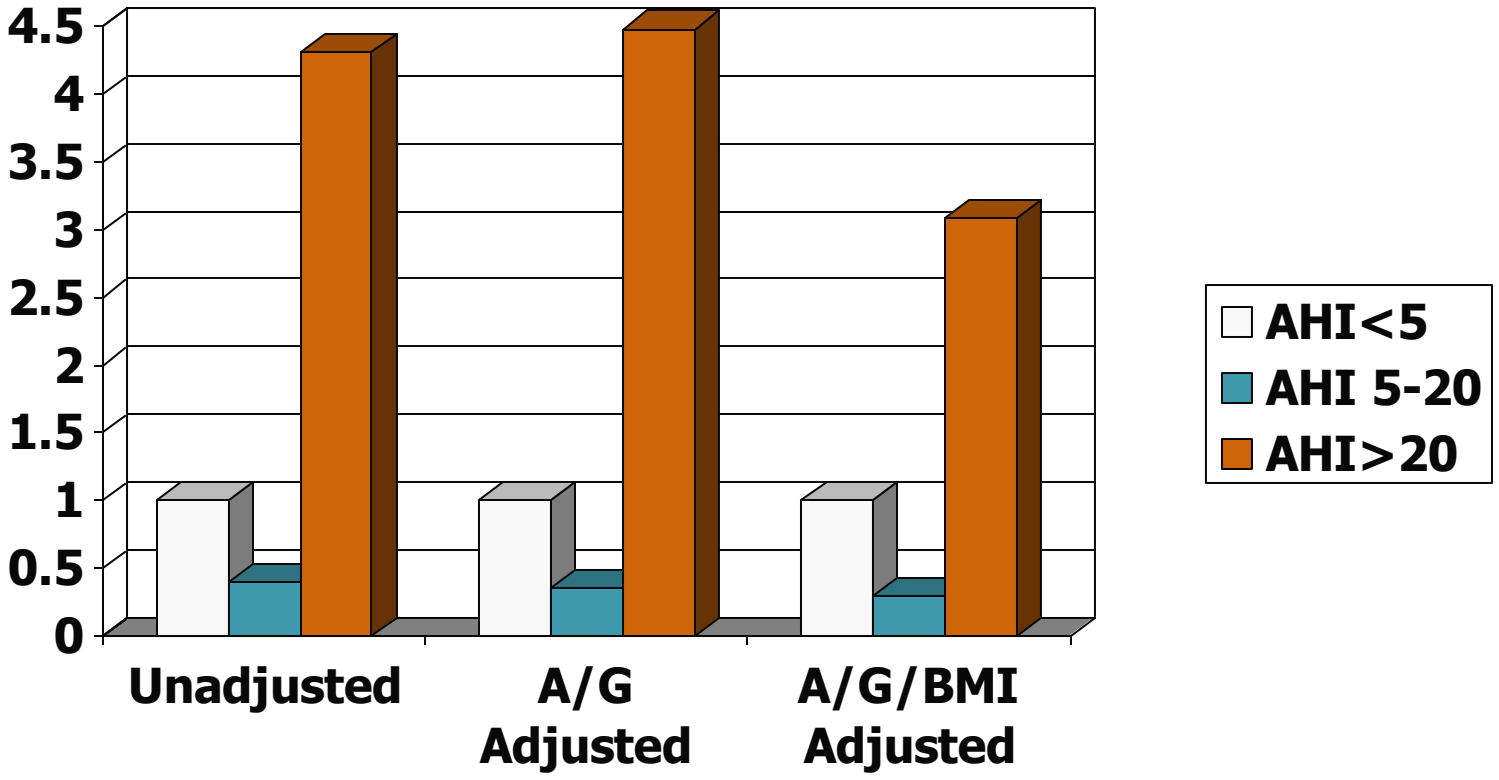
Stroke and OSA

- About 25% of strokes occur in sleep.
- Wake up strokes occur close to awakening.
- Afib , OSA and stroke are closely linked.
- They are a cause and effect for each other.

Potential mechanisms

- **Intermittent hypoxia**
- **Nocturnal sympathetic activation**
- **Sleep loss and metabolic dysregulation**

OSA and Stroke – from AASM 2009- Wisconsin Cohort Study – OSA and Stroke risk



OSA and Stroke

- **Wisconsin Sleep Cohort Study**
- **In a cross-sectional analysis, subjects with an AHI > 20 had increased odds of having prevalent stroke compared to subjects without OSAS (AHI < 5) after correcting for confounding factors.**
- 1200 subjects from the cohort were followed for 4 years after their initial sleep study.
- **These indicate that OSA is associated with prevalent stroke and may precede and contribute to the development of the stroke.**
- **Arzt M, Young T, Finn L, Skatrud JB, Bradley TD. Association of sleep-disordered breathing and the occurrence of stroke. Am J Respir Crit Care Med 2005;172(11):1447-51.**

Sleep apnea and lacunar infarcts

- **The prevalence of silent cerebrovascular lesions in patients with obstructive sleep apnea (OSA) and the correlation between OSA severity and prevalence of silent cerebrovascular lesions in Japanese patients.**

- Study subjects were 192 polysomnography (PSG)-confirmed patients who visited the sleep disorders clinic in our university hospital. None had a history of cerebrovascular disease (CVD). A cross-sectional study on OSA severity and the prevalence of silent cerebrovascular lesions detected by brain MRI analysis.

- CONCLUSION:
- **Results indicate that patients with moderate to severe (AHI > or = 15/h) OSA have a higher prevalence of silent cerebrovascular lesion(lacunar infarcts) than those with less severe OSA.**

- **Ref. Journal of Clinical Sleep MedicineJ Clin Sleep Med 2008; 4(3)Correlation between severity of obstructive sleep apnea and prevalence of silent cerebrovascular lesions.Momoka Nishibayashi, Masayuki Miyamoto, Tomoyuki Miyamoto, Keisuke Suzuki, Koichi Hirata**

Wake up TIA and Stroke

- **Long obstructive sleep apneas (LOSAs) can cause brain ischemia** through **paradoxical embolism since they can lead to right to left shunting (RLSh**)

- There were significantly more wake-up strokes/TIAs in subjects with RLSh plus LOSA than those without this association (27/69 vs 70/266; OR 1.91, controlled for age, sex, hypertension, diabetes, atrial fibrillation, antithrombotic therapy; 95% CI 1.08 to 3.38; p=0.03).
- No other risk factor was associated with an increase in the incidence of events on waking.
- **The study suggests that the combination of LOSA and RLSh could be a new major, potentially treatable risk factor for cerebrovascular ischemic events**.

- *Thorax 2013; 68(1)* **Wake-up stroke and TIA due to paradoxical embolism during long obstructive sleep apnoeas: a cross-sectional study.**

CVA, CAD and Sleep Apnea

- **Tstudy whether sleep apnea is related to stroke, death, or myocardial infarction in patients with symptomatic coronary artery disease.**
- *Methods and Results*— A total of 392 men and women with coronary artery disease referred for coronary angiography were examined by use of overnight sleep apnea recordings.
- All patients were followed up prospectively for 10 years, and no one was lost to follow-up.
- Stroke occurred in 47 (12%) of 392 patients during follow-up. Sleep apnea was associated with an increased risk of stroke,
- Thus with an adjusted hazard ratio of 2.89 (95% confidence interval 1.37 to 6.09, *P*=0.005), independent of age, body mass index, left ventricular function, diabetes mellitus, gender, intervention, hypertension, atrial fibrillation, a previous stroke or transient ischemic attack, and smoking. Patients with an apnea-hypopnea index of 5 to 15 and patients with an apnea-hypopnea index ≥15 had a 2.44 (95% confidence interval 1.08 to 5.52) and 3.56 (95% confidence interval 1.56 to 8.16) times increased risk of stroke, respectively, than patients without sleep apnea, independent of confounders (*P* for trend=0.011).
- Intervention in the form of coronary artery bypass grafting or percutaneous coronary intervention was related to a longer survival but did not affect the incidence of stroke.
- ***Conclusions*— Sleep apnea is significantly associated with the risk of stroke among patients with coronary artery disease who are being evaluated for coronary intervention.**
- **Ref. Circulation 2008; 118(9). Increased risk of stroke in patients with coronary artery disease and sleep apnea: a 10-year follow-up.**

OSA and Acute CVA

- Sleep-disordered breathing (SDB) is a disease of increasing importance and it is frequent in stroke patients. SDB is being recognized as an independent risk factor for several clinical consequences, including cardiovascular and cerebrovascular disease.

- **METHODS:**
- The present review summarizes the current evidence for an independent association between SDB and stroke, defining SDB subgroups, mechanisms, confounding factors and other epidemiological aspects. We analyze stroke outcome and prognosis in SDB patients. A search for recent data on this issue was made in several population-based studies and reference lists of articles.

- **RESULTS:**
- Many recent studies have shown an association between SDB and stroke. Moreover, there is a high prevalence of sleep apnea in patients with stroke. The pathogenesis of stroke in obstructive sleep apnea syndrome is not completely understood and likely to be multifactorial. Several mechanisms like hemodynamic disturbances and inflammatory or endothelial dysfunction could be involved.

- The presence of SDB in stroke patients may lead to a poor outcome and recurrence. Noninvasive treatments such as continuous positive airway pressure may decrease the risk of stroke in terms of secondary, and possibly, primary prevention.

- **CONCLUSIONS:**
- **SDB is associated with cerebrovascular morbidity and an unfavorable clinical course**. The presence of **SDB should be systematically screened in patients with acute stroke**.

- Ref Cerebrovasc Dis. 2009;27 Suppl 1:104-10. doi: 10.1159/000200447. Epub 2009 Apr 3. **Sleep-disordered breathing and acute stroke.**
- Portela PC, Fumadó JC, García HQ, Borrego FR.

OSA and CVA

- **More than 50% of stroke patients have sleep-disordered breathing (SDB), mostly in the form of obstructive sleep apnea (OSA**).
- SDB represents both a risk factor and a consequence of stroke.
- The presence of SDB has been linked with poorer long-term outcome and increased long-term stroke mortality.
- Continuous positive airway pressure is the treatment of choice for OSA. Oxygen and other forms of ventilation may be helpful in other (e.g., central) forms of SDB. SDB can improve spontaneously after stroke. About 20 to 40% of stroke patients have sleep-wake disorders (SWD), mostly in form of insomnia, excessive daytime sleepiness/fatigue, or hypersomnia (increased sleep needs).
- Depression, anxiety, SDB, stroke complications, and medications may contribute to SWD and should be addressed first therapeutically. Brain damage per se, often at thalamic or brainstem level, can be also a cause of persisting SWD.

- **Ref Semin Neurol. 2005 Mar;25(1):19-32. Sleep and stroke. Bassetti CL.**

Stroke and OSA

- **Sleep-disordered breathing (SDB) is more probably the cause rather than the consequence of stroke because:** apneas are essentially obstructive rather than central, the frequency of SDB is not different between transient ischemic attack and cerebral infarction; and previous excessive daytime sleepiness is significantly more frequent among stroke patients with SDB than those without.

- The presence of SDB in stroke patients could lead to a poor outcome.

- Experimental and clinical studies have shown that both short- and long-term factors may play a role in increasing the susceptibility to stroke in patients with obstructive sleep apnea syndrome.

- **Ref Clin Exp Hypertens. 2006 Apr-May;28(3-4):225-31. Cerebrovascular diseases and sleep-disordered breathing. Ferini-Strambi L, Fantini ML.**

Osa and CVA

- Due to changes in cerebral hemodynamics, hematologic alterations, and cardiocirculatory dysfunctions that typically and repeatedly occur during apnea episodes and also may persist during wakefulness.
- Regarding long-term factors, some changes in the anatomical characteristics of carotid arteries wall have been recognized in SDB patients.
- This finding seems to suggest that the link between SDB and cerebrovascular disease might be explained, at least in part, **by an increase in the progression of the atherosclerosis process involving cerebral vessels**.
- There are several practical implications from the demonstrated significant role of sleep apnea in increasing the predisposition to developing stroke.
- Specific treatment of SDB may reduce the possibility of further cerebrovascular disturbances.
- Ref Clin Exp Hypertens. 2006 Apr-May;28(3-4):225-31. **Cerebrovascular diseases and sleep-disordered breathing.** Ferini-Strambi L, Fantini ML.

Sleep apnea risk factors

- Obesity
- Increasing age
- Male gender
- Anatomic abnormalities of upper airway
- Family history
- Alcohol or sedative use
- Smoking
- Associated conditions

Diagnosis/what are symptoms?

- Snoring (loud, chronic)
- Nocturnal gasping and choking
  - Ask bed partner (witnessed apneas)
- Automobile or work related accidents
- Personality changes or cognitive problems
- Risk factors
- Excessive daytime sleepiness(under recognized due to caffeine and other stimulant use and under reporting by patient)

How to diagnose?

- Signs and symptoms poorly predict disease severity
- Sleep Study is gold standard
- Appropriate therapy dependent on severity
- Failure to treat leads to:
  - Increased morbidity
  - Accident and Injury/Motor vehicle crashes
  - Mortality
- Rule out other causes of daytime sleepiness

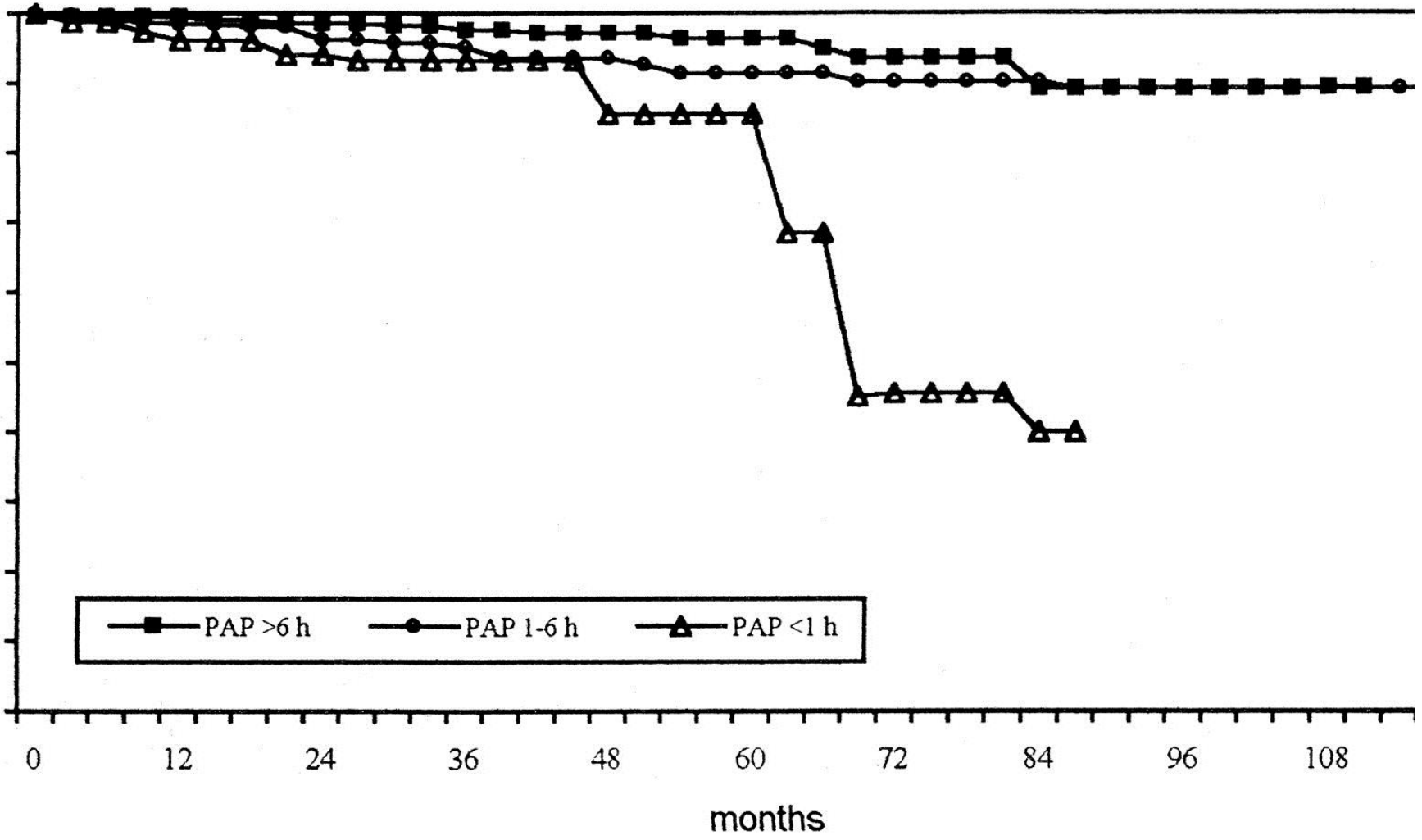
What are tests available

- Home sleep testing
- Diagnostic PSG
- Split night study
- Titration study

Treatment goals

- Reduce morbidity and mortality
  - Reduce sleepiness
  - Decrease cardiovascular/CVA consequences
- Improve quality of life

Treatment-CPAP- provides mortality benefit



Mortality decreased

- Several observational cohort studies have shown that treatment with continuous positive airway pressure (CPAP) reduces **mortality**.
- Data from a historical cohort study performed in Spain in which 871 patients diagnosed with OSAS between 1994 and 2000 were followed through 2001.
- The cohort was divided into 3 groups based upon their compliance with CPAP: > 6 hr per night, 1-6 hr per night and < 1 hr per night.
-
- **At 5 years of follow-up, the group using their CPAP < 1 hr/night had a significantly decreased survival (86%) compared to the group using their CPAP > 6hr (96%) and 1-6 hr (91%) per night**.[61]

Campos-Rodriguez F, Pena-Grinan N, Reyes-Nunez N, et al. Mortality in obstructive sleep apnea-hypopnea patients treated with positive airway pressure. Chest 2005;128(2):624-33.

Summary

- **Why find and treat Sleep apnea?**

- Common
- Dangerous
- Under recognized
- 100% Treatable
- If treated can prevent morbidity and mortality – including that from stroke
- If Untreated → leads to→
- Wake up Strokes/TIAs, Afib, Alzeihmers, Cancer, CKD, CAD, Obesity

Conclusions

- OSA is associated with cerebrovascular vascular events.
- Treatment improves mortality and morbidity

Questions??

- Thank You !!!
- My references are quoted at the bottom of pertinent slides

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Leptin and ghrelin levels in patients with obstructive sleep apnoea: effect of CPAP treatment

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ABSTRACT: Serum leptin and ghrelin levels were investigated in patients with obstructive sleep apnoea (OSA) syndrome before and during continuous positive airways pressure (CPAP) treatment and compared with body mass index (BMI)-matched controls without OSA.

Male patients (n=30) with OSA (apnoea/hypopnoea index=58±16, BMI=32.6±5.3 kg·m^{-2}) underwent CPAP treatment. Fasting leptin and ghrelin were measured at baseline and 2 days, and in the case of leptin 2 months after initiation of treatment.

Baseline plasma ghrelin levels were significantly higher in OSA patients than in controls. After 2 days of CPAP treatment, plasma ghrelin decreased in almost all OSA patients (n=9) to levels that were only slightly higher than those of controls (n=9). Leptin levels did not change significantly from baseline after 2 days of CPAP treatment, but were higher than in the control group. After 8 weeks, leptin levels decreased significantly, although the BMI of the patients showed no change. The decrease in leptin levels was more pronounced in patients with a BMI <30 kg·m^{-2}.

These data indicate that the elevated leptin and ghrelin levels are not determined by obesity alone, since they rapidly decreased during continuous positive airways pressure therapy.

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Obstructive sleep apnoea (OSA) is a common disorder affecting 2–4% of the adult population [1]. OSA is strongly associated with obesity. In a recent study involving 773 patients with OSA, only 6.5% had a normal body mass index (BMI), while 75.2% were obese (BMI $\geqslant$ 30 kg·m^{-2}) [2]. Patients with OSA appear to be more likely to put on weight than equally obese subjects without OSA [3]. The mechanisms underlying this phenomenon remain obscure. Recently, a number of authors have speculated that changes in serum leptin levels or leptin-receptor insensitivity may be involved in the pathogenesis of progressive obesity in patients with OSA [4]. Leptin has been found to reduce appetite and simultaneously to increase respiratory drive in an animal model [5, 6]. In humans, the situation may be expected to be more complicated. In recent studies, fasting leptin levels in patients with OSA decreased after initiation of continuous positive airways pressure (CPAP) treatment [7, 8]. However, those leptin measurements were performed on awake individuals in the morning, when the respiratory situation was normalised, so that any linkage between leptin levels and respiratory effects is difficult in this setting. Furthermore, leptin levels are influenced by a multitude of factors, such as sex, body weight [9, 10], the presence of hypertension, or specific medications impacting on leptin levels. Diurnal and ultradian variations in serum leptin levels are further factors complicating profound insights concerning significant respiratory effects [11–13].

However, the finding that a hormone like leptin is able to cover a variety of biological functions, beyond its well-investigated role for the regulation of body weight and energy expenditure, also prompted the present authors to investigate ghrelin in OSA. Ghrelin is a more recently discovered hormone [14] that also influences appetite and energy homeostasis. Since its initial description in 1999, there is a growing body of evidence, that this 28 amino acid gut-brain peptide has a strong effect on appetite, food utilisation, body weight and body composition in both animals and humans [15]. It stimulates hunger and food intake, when administered intravenously in healthy humans [16]. Human obesity is associated with decreased ghrelin levels that increase after weight reduction [17]. Such findings identify ghrelin, to some extent, as an antagonist of leptin. In analogy with leptin, with its multitude of effects beyond feeding behaviour and energy homeostasis discovered in recent years, it seems reasonable to assume additional effects of ghrelin beyond those already known. Hints on other functions have been the demonstration of growth hormone (GH) secretagogue-binding sites in peripheral tissues, such as the brain and the lung [18, 19], and the observation that ghrelin promotes slow-wave sleep in males [20].

Against this background, the authors decided to measure the plasma ghrelin and leptin levels of patients with OSA before and during CPAP treatment in comparison with equally obese controls without OSA, and to investigate whether those hormones are influenced by a normalisation of sleep and nocturnal respiration during CPAP treatment.

Patients and methods

Subjects

Thirty untreated obese male patients with severe OSA and 30 healthy controls were studied. The OSA group was recruited from a population of patients referred to the sleep laboratory for initiation of CPAP therapy. To confirm the diagnosis, all patients in the OSA group underwent standard polysomnography in the sleep laboratory as well as standard pulmonary function testing. Male patients aged $\geqslant$35 yrs, with a BMI $\geqslant$25 kg·m^{-2} and an apnoea/hypopnoea index (AHI) of at least 30 h·sleep^{-1} were included. Individuals with central sleep apnoea or Cheyne Stokes' respiration, clinically manifest nasal obstruction, severe chronic obstructive pulmonary disease (COPD) or asthma (forced expiratory volume in one second FEV1 <70% predicted) were excluded. Additional characteristics of the patients and the controls are shown in tables 1 and 2.

For the control group, 30 healthy, age- and BMI-matched male volunteers were examined with an ambulatory screening device (Somnocheck®; Weinmann, Hamburg, Germany) [21]. Only male subjects aged $\geqslant$35 yrs, with a BMI $\geqslant$25 kg·m^{-2}, and an AHI <5 h·sleep^{-1} were included. An all-male group was investigated to rule out the potential confounding factor of sex due to higher leptin levels in females [10, 22]. Of the 37 individuals initially screened for the control group, seven had an AHI $\geqslant$5, and had to be excluded, leaving 30 as controls.

Individuals with any other condition that may possibly influence leptin or ghrelin levels, such as chronic inflammatory intestinal diseases or rheumatoid disorders, other chronic inflammatory diseases, malignant tumours, dysfunction of the thyroid gland, diabetes mellitus and cardiac disease (New York Heart Association Functional Class $\geqslant$II), as well as treatment with corticosteroids [23–25], sex hormones [26] and β-blockers [27] were excluded from both groups, as were long-term fasting individuals [28]. Since ghrelin is a stomach-derived hormone, patients with gastric disease or prior gastric surgery were excluded from the study. Nine patients in the OSA group were hypertensive and receiving calcium antagonists (n=5), angiotensin-converting enzyme (ACE) inhibitors (n=4) or angiotensin-II antagonists (n=1). Only one patient within the control group was hypertensive and was receiving a calcium antagonist and an ACE inhibitor.

Sleep studies

Diagnostic polysomnographies were performed in the sleep laboratory by trained sleep laboratory technicians as described

Table 1. – Parameters of the nine obstructive sleep apnoea (OSA) patients and nine controls (ghrelin group)

	OSA patients		Controls	p-value	
	Baseline	2 Days of therapy		At baseline#	At 2 days#
Age yrs	54±2		49±2	0.140	
BMI kg·m^{-2}	33.0±1.4		33.9±1.3	0.644	
Body fat %	34.5±1.6		35.2±1.4	0.730	
AHI·h sleep^{-1}	55±10	5±2	3±1	<0.001	0.102
ODI·h^{-1}	55±4	7±2	7±2	<0.001	0.867
Basal O_2 saturation %	92±1	96±1	95±1	0.018	0.349
Minimal O_2 saturation %	67±3	85±2	85±2	<0.001	0.953
Average O_2 saturation %	85±2	91±1	89±1	0.025	0.047
Arousals n	61±5	18±1			
ESS	12.2±0.7	5.0±0.3	5.6±0.4	<0.001	0.310
Plasma insulin μE·mL^{-1}	11.1±1.5	11.1±1.1	14.7±1.6	0.129	0.090
Somatomedin C ng·mL^{-1}	131±16	146±17	148±15	0.465	0.924
Plasma leptin ng·mL^{-1}	9.2 (7.3–11.5)	10.1 (8.0–12.9)	8.5 (6.7–10.8)	0.824	0.611
Plasma ghrelin pg·μL^{-1}	57.9 (46.0–72.9)	19.7 (15.0–26.6)	10.8 (7.6–15.3)	0.001	0.204

Data are presented as mean±SEM or geometrical mean (geometrical SEM) unless otherwise stated. BMI: body mass index; AHI: apnoea/hypopnoea index; ODI: oxygen desaturation index; O_2: oxygen; ESS: Epworth Sleepiness Scale. #: controls *versus* OSA.

Table 2. – Parameters of obstructive sleep apnoea (OSA) patients and healthy controls (n=30)

	Controls	OSA patients			p-value		
		Baseline	2 Days	8 Weeks	At baseline#	At 2 days#	At 8 weeks#
Subjects n	30	30	30	13			
Age yrs	51±1	52±2			0.540		
BMI kg·m^{-2}	30.6±0.6	32.6±1.0	32.6±1.0	32.4±1.8	0.096	0.096	0.383
Body fat %	30.6±0.6	33.5±1.1	33.5±1.1	32.6±2.2	0.135	0.135	0.583
AHI·h sleep^{-1}	2±1	58±16	6±1	4±1	<0.001	0.003	0.333
ODI·h^{-1}	4±1	58±3	7±2	4±2	<0.001	0.210	0.904
Basal O_2 saturation %	95±1	92±1	96±1	97±1	0.003	0.060	0.003
Minimal O_2 saturation %	87±1	68±2	87±2	88±2	<0.001	0.993	0.666
Average O_2 saturation %	90±1	85±1	92±1	93±1	0.003	0.003	0.003
Arousals n		62±3	21±1	19±1			
ESS	5.1±0.3	11.0±0.4	5.1±0.2	5.1±0.2	<0.001	0.927	0.785
Plasma leptin ng·mL^{-1}	4.4 (3.6–5.4)	12.7 (10.7–14.9)	13.1 (11.1–15.5)	6.8 (4.7–9.7)	<0.001	<0.001	0.660

Data are presented as mean±SEM or geometrical mean (geometrical SEM) unless otherwise stated. BMI: body mass index; AHI: apnoea/hypopnoea index; ODI: oxygen desaturation index; O_2: oxygen; ESS: Epworth Sleepiness Scale. #: controls *versus* OSA patients.

previously [29]. All variables were recorded on a computer (SleepLab, Jaeger and Toennies, Hoechburg, Germany), and included electroencephalography (C4/A1, C3/A2), bilateral electrooculography, submental electromyography, nasal airflow measured by oronasal thermistors, snoring detected by microphone, electrocardiography, thoracic and abdominal movements measured by uncalibrated inductive plethysmography, and oxyhaemoglobin saturation using a finger oxymeter (Microspan® 3040G; Jaeger and Toennies).

Obstructive apnoeas were defined as the absence of oronasal airflow for $\geqslant$10 s. Hypopnoeas were defined as a reduction in thoracoabdominal movement amplitude to $\leqslant$60% of the preceding stable baseline for $\geqslant$10 s [30] together with a drop in oxygen (O_2) saturation of $\geqslant$4%. The mean number of apnoeas and hypopnoeas per hour of sleep was calculated as the AHI. Sleep parameters were determined using the criteria of RECHTSCHAFFEN and KAHLES [31], and arousals were defined in accordance with the guidelines of the American Sleep Disorders Association [32]. The data were analysed manually by one of the authors.

All individuals in the control group underwent polygraphy at home with an ambulatory screening device (Somnocheck®; Weinmann). This unit is provided with a belt that is applied round the patient's chest. A combined airflow/snoring sensor is applied to the patient's upper lip. This sensor picks up the airflow as a summed signal derived from three thermistors, and also the sounds of snoring *via* an integrated microphone. A pulse oxymeter for recording O_2 saturation and pulse rate is attached to a finger. A body position sensor is integrated within the basic unit. The unit was attached to the volunteers by a trained sleep laboratory technician in their homes before they retired. This device has recently been validated and showed a very high sensitivity when used as a screening device for OSA [21]. The data were analysed manually by the same sleep lab technician who read the polysomnography recordings of the study group. For this purpose the data were entered into a computer using the Somnocheck® software (version 1.02). Apnoeas were defined as an absence of oronasal flow for $\geqslant$10 s. Hypopnoeas were defined as a discernible reduction in respiratory airflow accompanied by a decrease in O_2 saturation $\geqslant$4%. For the calculation of the AHI the total number of respiratory events was related to the overall duration of the measurement.

Continuous positive airways pressure therapy

For CPAP treatment a standard CPAP device Somnotron 4® (Weinmann) was used. Manual titration of the CPAP pressure was performed in the sleep laboratory under polysomnographic control by a trained sleep laboratory technician. For each patient, the minimum effective pressure at which most of the apnoeas, hypopnoeas and snoring were abolished in all body postures and all stages of sleep was established. Starting from an initial 0.4 kPa (4 mbars), the pressure was increased in steps of 0.1 kPa (1 mbar) at intervals of $\geqslant$5 min when obstructive events (apnoeas, hypopnoeas or snoring) occurred. If no further events occurred during the next 30 min, the pressure was then reduced every 10 min in steps of 0.1 kPa (1 mbar) until they re-occurred, whereupon the pressure was increased once more in the manner described above [29]. On the second night of CPAP, the patients were treated with the minimum effective pressure established during the previous night.

Serum leptin measurements

Blood samples for leptin measurements were taken at 07:15 h after an overnight fast. The samples were collected in ethylendiamine tetraacetic acid (EDTA)-coated polypropylene tubes kept on ice, centrifuged immediately at 1,800×*g* for 20 min at 0°C, and the clear plasma supernatant was then stored until plasma leptin levels were measured using an enzyme-linked immunosorbent assay (ELISA) kit (IBL ELISA kit™; IBL Inc., Hamburg, Germany). All plasma samples were analysed in duplicate and in the same batch.

Serum ghrelin measurements

Blood samples for ghrelin measurements were collected in vacutainers with EDTA at the same time and under the same conditions as for leptin. Collection and processing were performed as described for leptin. A generic plasma extraction procedure was performed using the elution solvents 1% trifluoroacetic acid (buffer A) and 60% acetonotrile (buffer B). After the extraction procedure, ghrelin was measured using a radioimmunoassay (RIA) kit (Peninsula Laboratories, Inc., San Carlos, CA, USA). Lipaemic sera showing implausible ghrelin values in a preliminary analysis were excluded. The intra- and interassay coefficients of variation were <10%.

Study design

In both OSA patients and controls, baseline blood samples for the measurement of serum leptin and ghrelin, insulin and somatomedin C (also known as insulin-like growth factor-1), were obtained at 07:15 h on the morning after the diagnostic night. At this time, the patients had been awake for ~1 h. All patients, as well as the controls, had had a standard evening meal of ~500 kcal at 19:00 h before the diagnostic nights and the treatment nights. After the evening meal, they were only allowed to drink mineral water. Total body fat was estimated using the formula of GARROW and WEBSTER [33]. In the OSA group, a CPAP titration was performed as described and during the second treatment night CPAP was applied at the effective pressure level. On the morning following the second night of CPAP treatment, another blood sample of leptin and ghrelin was taken at 07:15 h. A further blood sample of leptin was obtained after 8 weeks of effective and regular CPAP treatment at 07:15 h. At all time points, the Epworth Sleepiness Scale (ESS) was assessed [34]. The built-in data stores of the CPAP devices were read out, the number of days of use within the past 42-day period established, and the mean duration of use per night calculated. CPAP treatment was considered "regular" if the device had been used on $\geqslant$35 of 45 nights for a minimum of 3 h each night.

The study protocol was examined and approved by the Ethics Committee of the Friedrich-Alexander University, Erlangen-Nuremberg. All patients gave their written informed consent.

Data collection and statistical analysis

All data are presented as mean±SEM to illustrate differences between groups. To normalise the distribution, plasma leptin and ghrelin levels were log-transformed and are shown as geometric means and with geometric SE. Baseline characteristics were compared using pooled or separate variances t-test or separate-variances t-tests for equality of means where applicable. Homogeneity of variances was tested by Levene's Test for Equality of Variances.

Plasma leptin levels after log transformation and differences during therapy were compared by analysis of covariance with and without repeated measurement design with simultaneous adjustment for BMI. All potentially confounding variables

(age, AHI, oxygen desaturation index (ODI), hypertension, ESS, adherence to CPAP therapy) were tested in preliminary models, and on the basis of these results only BMI and ESS remained in the final models. In analysis of variance models estimating effects on differences in plasma leptin concentrations during therapy, ESS score and the presence of hypertension remained in the final models. In addition, patients were divided into two groups in accordance with the World Health Organization criteria for overweight patients: a BMI $\leqslant 29.99$ kg·m^{-2} (grade I overweight) were compared with patients with a BMI >30 kg·m^{-2} (overweight grades II and III).

The linear relationships between plasma ghrelin, as a dependent variable, and its potential predictors, as independent variables, were estimated using multiple linear regression analysis with backward elimination of independent variables. Removal criteria were a significance level >0.15 and a tolerance level <0.3.

Results

Fasting ghrelin levels were analysed in a subgroup of OSA patients (n=9) before and 2 days after initiation of CPAP treatment and compared with those of nine BMI-matched controls. Parameters of the OSA patients and the control groups, together with leptin and ghrelin levels are shown in table 1. Basal, minimal and average minimal O_2 saturation were significantly lower in OSA patients than in controls. After 2 days of treatment, basal and minimal O_2 saturation were similar to those of controls, the average minimal O_2 saturation was slightly higher in OSA patients. The individual course of ghrelin levels in the nine OSA patients compared with the nine controls is shown in figure 1. The means of ghrelin are given in comparison with the 13 patients with leptin measured before, 2 days and 8 weeks after onset of CPAP treatment in figure 2. Fasting plasma insulin did not change after 2 days of CPAP therapy but were slightly lower in OSA patients than in controls (table 1). In contrast, somatomedin C levels increased significantly after 2 days of treatment (p=0.014).

Baseline plasma ghrelin levels differed significantly between OSA patients and controls (p=0.001). After 2 days of treatment, plasma ghrelin levels decreased in all OSA patients except one and were only slightly higher than those of controls.

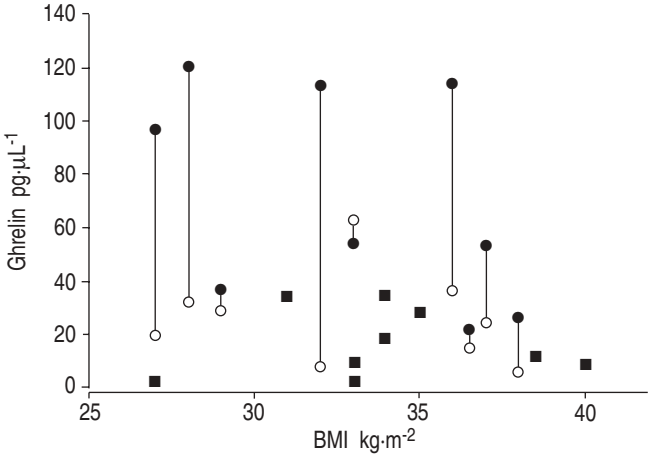

Fig. 1. – Individual fasting ghrelin levels (n=9) in comparison with nine body mass index (BMI)-matched controls. After 2 days of treatment, plasma ghrelin levels decreased in all obstructive sleep anoea (OSA) patients except one and are only slightly higher than those of the controls. ■: control; ●: OSA (untreated); ○: OSA (2 days of continuous positive airways pressure).

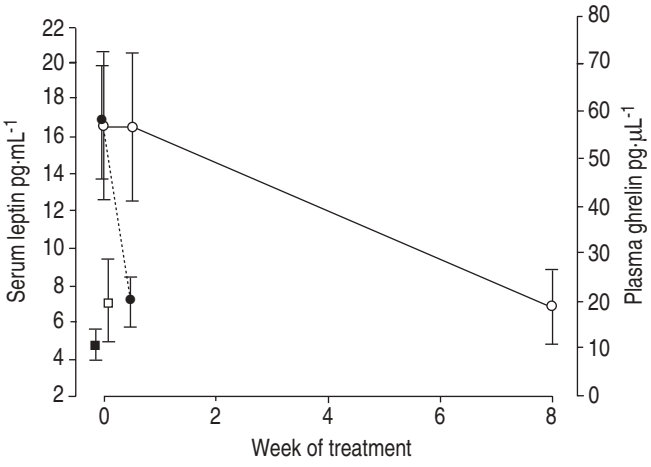

Fig. 2. – Fasting leptin levels (○) in obstructive sleep apnoea (OSA) patients (n=13) before, 2 days and 8 weeks after initiation of continuous positive airway pressure (CPAP) treatment. The leptin values (given as geometric means and geometric SEM) before and after 2 days of CPAP treatment differ significantly in comparison with controls (□) and the leptin values after 8 weeks of CPAP treatment. Fasting ghrelin levels in nine OSA patients (●) and controls (■) are also shown. The baseline ghrelin levels differ significantly between OSA patients (baseline *versus* 2 days of CPAP treatment) and controls.

In a multivariate regression analysis, BMI and total body fat were shown as predictors of ghrelin levels in both OSA patients and controls (table 3). The explanatory power of average minimal and minimal O_2 saturation, serum leptin, presence of hypertension, ESS score and fasting plasma insulin differed between OSA patients and controls. The minimal O_2 saturation was a significant predictor in OSA patients but not in controls. In OSA patients ghrelin levels were higher in the presence of hypertension. They also increased with increasing plasma insulin. In controls plasma ghrelin was predicted by plasma leptin levels and ESS score (table 3).

In a multivariate regression analysis the change of plasma ghrelin after 2 days of treatment was positively related to baseline ghrelin levels (p=0.043), presence of hypertension (p=0.005), minimal O_2 saturation (p=0.023) and ESS score (p=0.001) at baseline. No relationship could be found between changes of plasma ghrelin and BMI, body fat, baseline leptin levels, somatomedin C or fasting plasma insulin.

Parameters of the initial 30 patients with OSA and the 30 controls are shown in table 2. The plasma leptin concentrations were higher in OSA patients before therapy than in controls (p<0.001), even after adjustment for BMI (p<0.001) and ESS (p=0.080). Plasma leptin concentrations were further analysed after 2 days in all patients and after 8 weeks of treatment in a smaller subgroup of 13 patients. This subgroup did not differ from the overall group in any of the baseline parameters, *e.g.* age, BMI, plasma leptin, AHI, ESS. After 2 days of CPAP, plasma leptin concentrations in OSA patients remained unchanged, but after 8 weeks of treatment a significant decrease in plasma leptin was observed (p=0.004) after adjusting for hypertension (p=0.013) and ESS (p=0.029) simultaneously. After 8 weeks of therapy, plasma leptin concentrations in OSA patients were not significantly different from plasma leptin concentrations in a subgroup of 13 healthy controls matched for BMI (p=0.660).

In the 13 patients studied after 8 weeks of CPAP treatment, no significant differences were found between initial and the 8 week BMI (p=0.290). The treatment-associated decrease in

Table 3. – Multivariate relationships between characteristics of the obstructive sleep apnoea (OSA) patients and plasma ghrelin concentrations in all subjects

Independent variable[#]	Dependent variable log plasma ghrelin[¶] for OSA patients			Dependent variable log plasma ghrelin[¶] for controls		
	β	SEE	p-value	β	SEE	p-value
Intercept	8.525	1.576	0.012	-4.342	1.977	0.116
BMI $kg \cdot m^{-2}$	-0.742	0.229	0.048	-0.504	0.070	0.006
Total body fat %	0.591	0.199	0.059	0.395	0.060	0.007
Hypertension	0.609	0.160	0.032			
Log plasma leptin $pg \cdot mL^{-1}$				1.860	0.209	0.003
Average minimal O_2 saturation %				0.065	0.025	0.076
Minimal O_2 saturation %	0.037	0.010	0.031			
ESS				0.175	0.055	0.050
Plasma insulin $\mu E \cdot mL^{-1}$	0.030	0.012	0.056			

BMI: body mass index; O_2: oxygen; ESS: Epworth Sleepiness Scale. [#]: variables excluded from the model were age, basal O_2 saturation, apnoea/hypopnoea index, oxygen desaturation index, somatomedin C; [¶]: β-coefficients of multiple linear regression analysis and standard error of the estimate (SEE). R^2 was 0.764 for OSA patients and 0.946 for control subjects.

serum leptin was affected by the initial weight and degree of hypertension (data not shown). The decrease in plasma leptin concentrations between baseline and treatment day 2 was similar in OSA patients with a BMI <30 $kg \cdot m^{-2}$ and OSA patients with a BMI >30 $kg \cdot m^{-2}$. After 8 weeks of treatment the decrease in plasma leptin was more pronounced in OSA patients with a BMI <30 $kg \cdot m^{-2}$ than in those with a BMI >30 $kg \cdot m^{-2}$ (p=0.021). The decrease in plasma leptin was slightly greater in hypertensive than in normotensive OSA patients (p=0.053). The adherence to CPAP therapy of OSA patients was 5.1 ± 0.2 $h \cdot night^{-1}$. Due to the small range of adherence no effect of adherence to CPAP therapy on the decrease in plasma leptin during therapy could be observed.

Baseline leptin correlated significantly with BMI (r=0.744, p<0.001) and body fat content (r=0.729, p<0.001). Only weak correlations with AHI (r=0.421), ODI (r=0.527), arousal index (r=0.462) and the average minimal O_2 saturation (r=-0.287) were found. After adjustment for BMI, these correlations were even weaker (r=0.082, 0.199, 0.154 and 0.004; p=0.673, 0.291, 0.423 and 0.984, respectively).

Discussion

Ghrelin and leptin are both hormones with well-investigated functions concerning body composition, energy homeostasis and feeding behaviour in animal models and humans. A central role of leptin as a neurohumoral modulator of central respiratory mechanisms and lung function has furthermore been established in animal models [35].

Ghrelin is the natural ligand of the GH secretagogue receptor and to some extent a hormone with leptin-antagonistic properties. Possible interactions between ghrelin and respiratory mechanisms have not been investigated as yet. Ghrelin levels were investigated in a subgroup of patients and baseline plasma ghrelin levels were found to be significantly higher in OSA patients than in BMI-matched controls, but decreased to levels similar to those of obese patients without OSA after 2 days of treatment. This decrease occurs within a period of time too short for any significant changes of body fat mass or visceral fat accumulation (VFA). This finding is surprising, since ghrelin and leptin seem to exhibit a similar behaviour under the circumstances described, although they have antagonistic properties in terms of energy balance at least. Furthermore, since insulin is a physiological modulator of plasma ghrelin [36] and insulin resistance is a typical finding in obese patients with OSA [37], an increase in ghrelin may have been expected. Direct interactions could not be established between plasma ghrelin and plasma insulin or somatomedin C, the latter an important mediator of GH action.

Multivariate analysis revealed plasma ghrelin to be correlated with minimal O_2 saturation in the patient group. However, the patient number is low and the study was not designed to investigate interactions between ghrelin and indices of sleep-disordered breathing. Several interactions between OSA and hormonal factors, such as insulin resistance [38] and disturbances of the hypothalamic-pituitary-adrenal axis [39], are known. Thus, further studies are mandatory to clarify whether the decrease of ghrelin under CPAP treatment is due to interactions with respiration physiology, or whether the normalisation of ghrelin is merely the expression of a reconstitution of the complex neurohumoral network regulating sleep and respiratory function caused by the normalisation of nocturnal sympathetic drive and hypoxia. One further unsolved question is whether changes in total ghrelin do reflect changes in the biologically active or inactive peptide, since commercially available ghrelin RIA kits detect both octanoylated and nonoctanoylated ghrelin

Growing insight into the functions of leptin also indicates a possible role of elevated leptin as a homeostatic response to the pathophysiological situation (*e.g.* nocturnal arousals, nocturnal hypoventilation) induced by OSA, which decreases with the control of OSA by CPAP therapy [7, 8]. No significant changes in fasting leptin 2 days after initiation of CPAP treatment were found, but a significant decrease in leptin levels after 2 months of CPAP treatment with no significant changes in body weight were confirmed.

Computed tomographies were not conducted to differentiate between VFA and subcutaneous fat. VFA is regarded as a better predictor of coronary heart disease than the BMI [40]. CHIN *et al.* [8] demonstrated significant decreases in VFA after 6 months of CPAP treatment, even in OSA patients with no loss of body weight. They furthermore demonstrated a significant decrease of leptin after 3–4 days of CPAP treatment, which is too short a time interval to have significant effects on body fat or its distribution. Such a decrease may be more readily explained, for example, by effects of CPAP on sympathetic activation [41].

A number of authors have tried to establish a direct relationship between serum leptin and the severity of OSA, usually determined *via* the AHI [42, 43]. In a recent study, serum leptin concentrations (log-transformed) were found to be significantly correlated with the AHI (r=0.39), but failed to reach significance after correction for BMI and body fat in a group with numerous comorbidities [44]. The latter finding is in accordance with the present results showing a positive

correlation between serum leptin and the AHI (r=0.4), which is lost after correction for the BMI. The frequency of arterial hypertension in the current patient group was high in comparison with the nonhypertensive patients in the studies from PHILLIPS *et al.* [42] and MANZELLA *et al.* [43] and a possible explanation may be that the present patient group and those of SCHÄFER *et al.* [44] are too different in terms of comorbidities, also possibly confounding the relationship between AHI and serum leptin levels.

The AHI, reflecting the mean number of apnoeas and hypopnoeas per hour of sleep, cannot be considered a parameter that adequately reflects the severity of all aspects of OSA. For instance, vigilance, daytime performance and cardiovascular effects of OSA are known to be only weakly correlated with AHI. One further problem has to be addressed; indices of sleep-disordered breathing are measured in sleeping patients, whereas the leptin and ghrelin studies were determined in patients already awake. This bias was also present concerning leptin in preceeding studies, thus, making further investigations with nocturnal profiles of leptin and ghrelin mandatory.

In conclusion, these data support findings suggesting that leptin is a hormonal factor affected by continuous positive airways pressure treatment in obstructive sleep apnoea patients independently of changes in body weight. Plasma ghrelin levels are also significantly higher in obstructive sleep apnoea patients than in body mass index-matched controls, and decreased significantly during continuous positive airways pressure treatment. With reservations dictated by the small number, it may be speculated that ghrelin, as well as leptin, is influenced by continuous positive airways pressure treatment due to effects unknown as yet, which should be investigated in further studies.

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Obstructive sleep apnea syndrome (OSAS) in mouth breathing children

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polysomnography,
prevalence,
mouth breathing,
snoring.

Abstract

It is well known that mouth breathing is associated with adenotonsillar hypertrophy - which is the main cause of obstructive sleep apnea among children. Despite the importance of this matter, there are only a handful of studies showing the relationship between OSAS and mouth breathing.

Aim: to determine the prevalence of obstructive sleep disorders in mouth breathing children and study its correlation with otorhinolaryngological findings.

Study design: Retrospective cohort study.

Method: Data analysis from 248 medical charts of mouth breathing children seen at the Pediatric Otolaryngologic Division of a large medical institution between the years of 2000 and 2006. All patients had nasofibroscopy and or Cavum radiographs and polysomnographic exams. According to the Apnea index, patients were classified as primary snorers (AI<1); and as OSAS (≥1).

Results: From 248 patients included in the study, 144 (58%) were primary snorers and 104 (42%) had OSAS. The most prevalent otorhinolaryngological findings were adenotonsillar hypertrophy (n=152; 61.2%), tonsilar hypertrophy (n=17; 6.8%), adenoid hypertrophy (n=37; 14.9%), rhinitis (n=155; 62.5%) and secretory otitis (n=36; 14.5%).

Conclusions: primary snoring and OSAS are frequent findings in mouth breathing children. The most frequent otorhinolaryngological disorder in children with OSAS is adenotonsillar hypertrophy with or without rhinitis.

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INTRODUCTION

Snoring and oral breathing are frequent complaints which make the parents of children with these symptoms to take them to otorhinolaryngologists. The prevalence of habitual snoring in children between 3 and 13 years varies between 5.2 and 34.45%[1-4], while the prevalence of oral breathing is of 26.8% according to a large study with 661 children aged between 6 and 12 years[5].

Chronic mouth breathing in children is usually associated with palatine and pharyngeal tonsils hypertrophy,[4] with or without allergic rhinitis. Its incidence peak happens in pre-school aged children[6,7]. At this stage, besides the natural growth of the soft palate and pharyngeal tonsils, there are repetition infections which cause tonsillar lymphoid tissue hypertrophy, changing the breathing of children to a chronic obstructive pattern. A consequence of this in the long run has been craniofacial changes8 which maintain the mouth breathing pattern, besides causing postural[9] and hearing[10] disorders. Among mouth breathers, it is also common to find the Obstructive Sleep Apnea Syndrome (OSAS)[11,12], a potentially severe clinical situation, as well as primary snoring.

Primary snoring is noise produced by breathing, caused when air passes through the upper airway without, however, causing changes to sleep, alveolar ventilation and oxygenated hemoglobin saturation. It is common during childhood, happening from 7 to 10% of the children between 1 and 10 years[17] . Obstructive Sleep Apnea Syndrome (OSAS) in children is a disease characterized by partial prolonged and/or complete obstruction of the upper airways, impairing normal ventilation. The signs and symptoms of this syndrome include the common snoring, interrupted sleep, neurocognitive and behavioral disorders such as learning disorders[13,14], behavioral changes, attention deficit and hyperactivity[13,14]. The major complications of the OSAS include growth and development delays[15], mental retardation[15] and cor pulmonale[16] . The gold standard test used to diagnose OSAS is Polysomnography[18], since it enables us to differentiate OSAS from primary snoring[19]. Its high cost and difficulty in performance in children are, however, important limitations and also reasons to explain why only a few centers can count on this exam for most of its patients.

Given the importance of OSAS in children and the scarcity of studies correlating this disease to mouth breathing in children, we designed this study with the goal of determining OSAS prevalence in mouth breathing children and check its correlation with otorhinolaryngological findings.

METHOD

The data was obtained from the charts of patients who visited the pediatric otorhinolaryngology ward of a teaching hospital between 2000 and 2006. In the study we included children with ages ranging between 0 and 13 years, diagnosed by an multidisciplinary team (otorhinolaryngologists, allergists, speech and hearing therapists, orthodontists, physical therapists) as mouth breathers, using the criteria of preferentially oral breathing for more than 6 months and physical exam showing two or more signs of oral breathing (nasal obstruction, deep hard palate, maxillary atresia, open mouth, mouth muscle laxity, bite changes, posture changes and anterior flexion of the head).

Children diagnosed as mouth breathers were submitted to sleep disorder investigation by means of nocturnal polysomnography under the following protocol: in a dark and silent room and with the child's guardian present. The electrophysiological and cardio-respiratory parameters were recorded in a computerized system (Alice 3 Healthdyne/respironics, Marrieta, GA), using EEG data (C3/A2, C4/A2, O1/A2, O2A1), submentonian and tibial electromyogram, right and left side electro-oculogram, oronasal airflow, chest and abdominal movement, laryngeal microphone (snoring), oxyhemoglobin saturation (SaO2) and position on the bed. The test was analyzed by a physician with experience with the pediatric population and it is classified according to criteria from the American Thoracic Society (1995).

We excluded those children with genetic syndromes, metabolic disorders, neurologic diseases or congenital malformations.

From each chart we analyzed the following information: gender, age at the time of the polysomnography, ENT diagnosis and polysomnographic diagnosis, hypopnea/apnea ratio (HAR) and the rate of oxygen saturation ($satO_2$).

According to the "American Thoracic Society"[19], we consider the following:

- Hypopnea/apnea index (HAI): number of obstructive and mixed apnea episodes in a minimum time span of two respiratory cycles (expressed in episodes/hour). OSAS is diagnosed in children with AI >1 / hour.

- O_2 Saturation Nadir: minimum oxygen saturation during the sleep study. Values below 90% are associated with central or obstructive sleep ventilatory disorders.

The otorhinolaryngological diagnoses of each child were based on the initial otorhinolaryngological evaluation, including nasal-fibroscopy.

The data was grouped according to the results from polysomnography tests and all classifications were based on the HAI and O_2 Saturation Nadir values.

The individuals were broken down into primary snorers when they had HAI < 1, and those with OSAS, when the AI was ≥ 1. The children with OSAS were further divided into mild (1 ≤ HAI< 5), moderate (5 ≤ HAI < 10) and severe (HAI ≥ 10)[20]OSAS. Within each subgroup, there was also one more division, according to the degree of O_2 desaturation, considering the nadir (minimum level

of O2 saturation). Thus, we considered four subgroups: Nadir = 80; 80 < Nadir = 85; 85 < Nadir =90 e Nadir = 90. The data obtained was associated with patient age and gender and the findings from the evaluation and otorhinolaryngological exams.

The patients signed the free and informed consent form approved by the Ethics in Research Committee of the Federal University of São Paulo Medical School - Unifesp-EPM, protocol 171/06 approved on February 10, 2006.

For the statistical analysis we used the Chi-squared[28] test.

RESULTS

The final sample comprised 248 patients. Among them, 144 (58%) had primary snoring and 104 (42%) had OSAS. The peak occurrence of sleep disorder happened between 4 and 7 years. The prevalence of OSAS among males was 60% (62) and among females was 42% (42). Chart 1 shows the distribution of sleep respiratory disorders according to gender in the different age ranges.

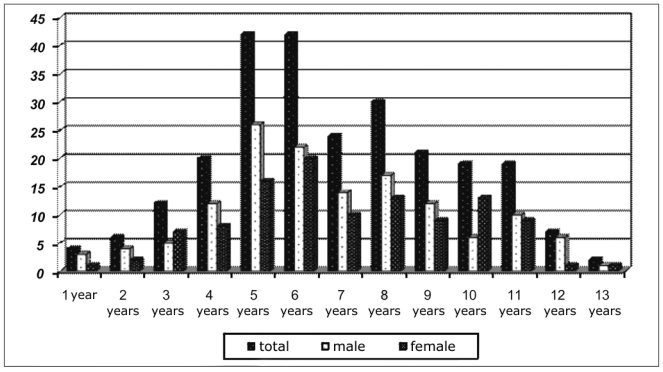

Chart 1. Distribution of sleep respiratory disorders according to gender and age.

Among the 104 patients with OSAS, 69.67% had the mild type; 16.15%, had the moderate type and 19.18% had severe OSAS. Chart 2 shows that the same ratios were obtained when we break down respiratory sleep disorders according to gender.

The level of O_2 desaturation varied as depicted on Chart 3. The lower nadir values were found among severe and moderate OSAS.

Otorhinolaryngological findings are listed on Charts 4, 5, 6 and 7, which show the distributions of the most commonly found Otorhinolaryngological disorders, according to the types and levels of sleep respiratory disorders.

In general, the most frequently found ENT alterations are: adenoid and tonsil hypertrophy (n=152; 61.2%), palatine tonsil hypertrophy (n=17; 6.8%); pharyngeal tonsil hypertrophy (n=37; 14.9%), allergic rhinitis (155; 62.5%) and secretory otitis media (36; 14.5%).

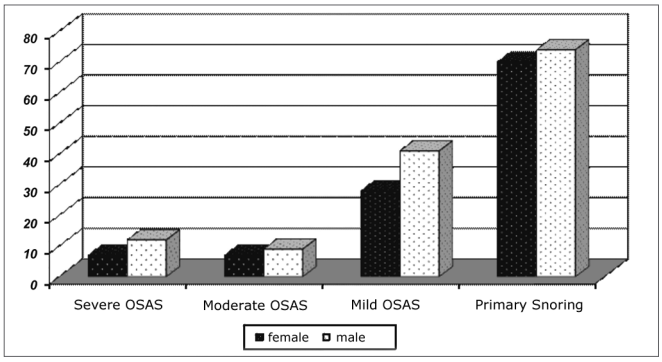

Chart 2. Distribution of sleep respiratory disorders according to age and gender.

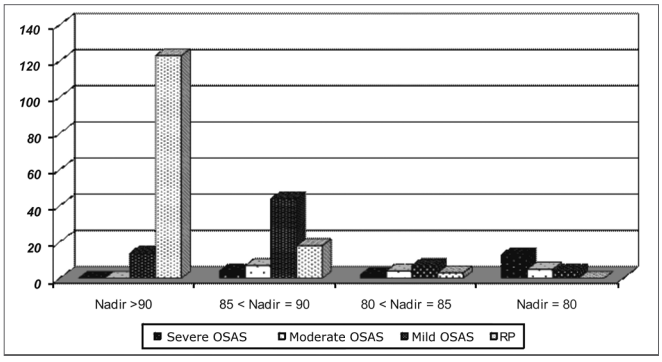

Chart 3. O_2 saturation Nadir in sleep respiratory disorder.

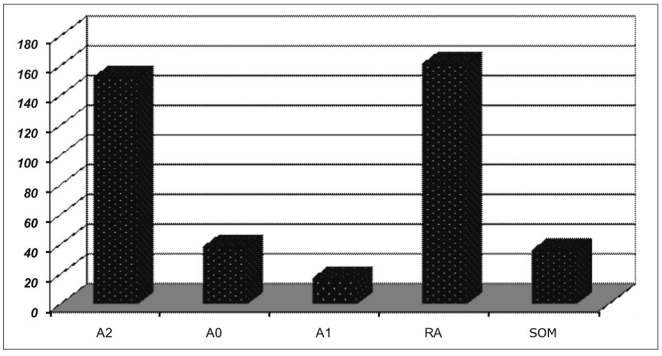

Chart 4. ENT findings in patients with sleep respiratory disorders.

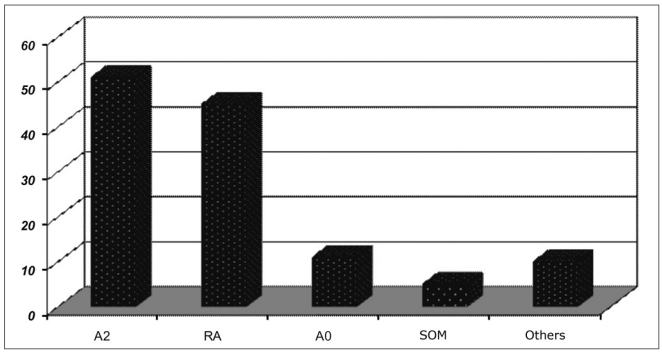

Chart 5. ENT findings in patients with mild OSAS.

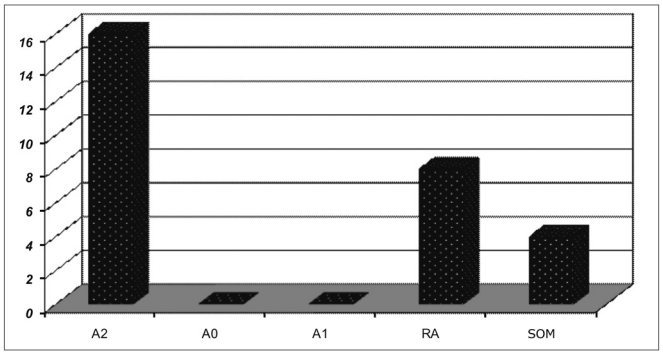

Chart 6. ENT findings in patients with moderate OSAS.

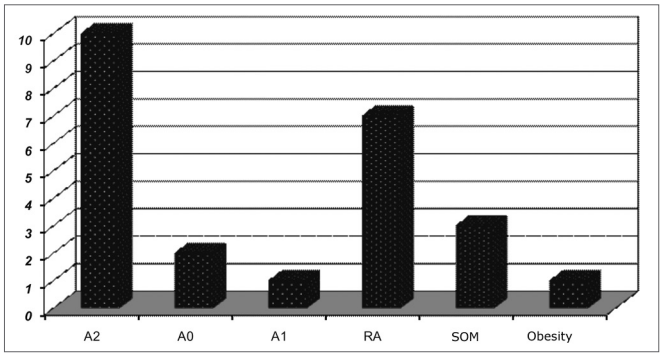

Chart 7. Clinical and ENT findings n patients with severe OSAS.

In all groups, adenoid and tonsil hypertrophy associated with allergic rhinitis were the most common finding.

The correlation between mouth breathing and OSAS was significant for adenoid and tonsil hypertrophy (p=0.001), and there were no significant differences concerning children with allergic rhinitis, tonsil hypertrophy, adenoid hypertrophy and nasal septum deviation.

DISCUSSION

Despite the huge attention the medical community has been paying to sleep respiratory disorders lately, the literature is still relatively poor as far as the pediatric population is concerned.

Our study was carried out with mouth breathing children whom, based on epidemiological studies, can vary between 20 and 40%7,8 of the general pediatric population. We have noticed that the frequency of these disorders, especially primary snoring and OSAS, is very significant in this particular population.

In this study, the prevalence of OSAS was higher among boys, which was not reported by prior epidemiological studies[7,21-24]. Nonetheless, in the adult population, males are more often affected[25,26]. This happens because of the influence of male sex hormones in respiratory control and/or body fat distribution.

We should bear in mind that our institution has a huge backlog of patients waiting for adenotonsillar surgery (as it happens in other large institutions). In some cases, the patients wait for more than three years. It is likely that mothers, concerned with their daughters (female snoring is more disruptive than in males) went to other institutions, and for that reason we lost follow up in our ward.

The peak of prevalence in both genders happened between 4 and 7 years, an age in which adenoid and the tonsils naturally grow. Moreover, it is possible that with children going to day-care centers and schools, a factor known to predispose children to repetitious upper airway infection, may also represent a worsening factor in the induction of adenotonsillar hypertrophy, worsening even further the respiratory condition of the children in this age range.

Although moderate and severe OSAS have been less frequent in relation to other sleep disorders, they were present in 35 (14%) children and, as expected, these were the ones who had the highest saturation drops. It is also interesting to stress that it was only in the group of severe OSAS that children were obese, although obesity is not an associated factor. This data matches sleep studies in obese children[27].

The most commonly found otorhinolaryngological disorder in patients with sleep respiratory disorder was palatine and pharyngeal tonsil hypertrophy, either with or without allergic rhinitis. Such finding coincides with data from prior studies published in the literature on OSAS etiology pointing to adenoid and tonsil hypertrophy as the main causes of OSAS in children[3,5]. Chronic secretory otitis media (SOM), was also a very frequent ENT disorder found in our patients. This fact is probably associated with mouth breathing[10] and the presence of pharyngeal tonsil hypertrophy, a major cause of mouth breathing and Eustachian Tube dysfunction in children.

The results from our study show the importance of sleep respiratory disorders in the pediatric population by its frequency. Nonetheless, it is important to stress the major clinical relevance of such disorders which, as shown in prior studies[6,7,13-16], made the children more prone to hyperactivity and attention deficit, besides impairing learning. Therefore, in regards of the child's development, the knowledge about the real incidence of apnea in the pediatric population complaining of mouth breathing is very important, because of the need for an early intervention which can prevent carriers from developing school problems and, consequently, social and psychological ones. Since the otolaryngologist and the pediatrician are the first to have contact with this type of patient, it is very important that these professionals have an eye open for the diagnosis of sleep disorders, thus making the intervention early and correct.

The follow up of these patients after clinical or surgical treatment of the associated disorders, including

polysomnography, may contribute to the knowledge of the natural history of these disorders and its physiopathology.

CONCLUSIONS

1. The incidence of OSAS occurrence in the mouth breathing children of our study was 42%.

2. In these children, the OSAS prevalence peak happened between 4 and 7 years of age.

3. The most frequently found ENT disorder in OSAS children was adenoid and tonsil hypertrophy with or without allergic rhinitis.

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AFIP

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Association of pediatric obstructive sleep apnea with poor academic performance: A school-based study from India

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Abstract

Background:

Pediatric obstructive sleep apnea (OSA) is a highly prevalent but often neglected disorder. There is paucity of reports on the prevalence of pediatric OSA from India. This study was done to estimate the prevalence of OSA in school children aged 5–10 years and its association with academic performance.

Methodology:

This school-based cross-sectional epidemiological study was conducted from July 2015 to November 2015. A questionnaire seeking information on sociodemographic variables, school performance, sleeping pattern, and a validated 22-item pediatrics sleep-related breathing disorder (SRBD) scale was distributed to 1820 pupils in three primary schools. The prevalence of OSA (defined as SRBD score >33%) was reported as proportion and its 95% confidence interval (CI).

Results:

We received 1520 questionnaires out of 1820 distributed and of which 1346 were complete and were analyzed. The prevalence of OSA among children in our study was 9.6% (95% CI: 8.1%–11.7%). On multivariate analysis, working mother (adjusted odds ratio [OR]: 1.8; 95% CI: 1.2–2.7), sleep bruxism (adjusted OR: 1.7; 95% CI: 1.1–2.6), and sleep talking (adjusted OR: 3.0; 95% CI: 1.9–4.7) were found to be independently associated with OSA. Students with positive SRBD were more prone to nocturnal enuresis (NE) (OR 3.48; 95% CI 2.27–5.26) and poor academic performance in all subjects.

Conclusion:

OSA is highly prevalent (9.6%) in Indian children. OSA is associated with NE and poor academic performance in all subjects. This study found association of maternal occupation and OSA which needs to be confirmed in larger studies.

KEY WORDS: Academic grade, nocturnal enuresis, pediatric obstructive sleep apnea, sleep-related breathing disorder

INTRODUCTION

Pediatric obstructive sleep apnea (OSA) is a highly prevalent but often neglected disorder due to ignorance among general physicians and pediatricians. The prevalence in children is estimated in the range of 2%–4% from western countries but data from India are lacking.[1] The prevalence is increasing and is probably underrepresented in view of pediatric obesity epidemic. Pediatric OSA is usually due to combination of anatomic factors such as adenotonsillar hypertrophy, decreased oropharyngeal dimensions, and/or obesity. Pediatric OSA has different presentation from adult OSA; it can present with hyperactivity, attention deficit, fatigability, growth retardation, enuresis, obesity, hypertension, impaired fasting glucose, and even metabolic syndrome.[2] Recently, pediatric OSA has been associated with poor academic grades.[3]

Till date, no study has been done from Indian subcontinent for prevalence and complications of OSA in children. Hence, we devised this study to find the prevalence of pediatric OSA and its association with enuresis, obesity, socioeconomic factors, and school grades in schoolgoing children of Central India, aged 5–10 years.

METHODOLOGY

Study type and setup

This study is part of a primary study conducted to investigate prevalence of nocturnal enuresis (NE) among school children, results of which are published elsewhere.[4] It was a school-based cross-sectional study, done in children aged between 5 and 10 years at three purposively selected schools of Bhopal, India, from July 2015 to November 2015. This study has been approved by the Institutional Human Ethics Committee AIIMS Bhopal.

Sampling procedure and data collection

We have utilized same participants of the study mentioned earlier. Sample size of that study was 1820 individuals. Reported prevalence of OSA by questionnaire method lies between 4% and 11%.[1] Required samples size to estimate prevalence of 11% with 20% relative error and design effect of 2 was 1553 participants. Thus, sample size of 1820 was sufficient for this analysis.

Class teachers were explained about study objectives, and procedures were detailed to them before initiation of the study. Anthropometry was done by teachers of the respective schools. Students were given questionnaire during their class and were instructed to get it filled by their parents. Along with questionnaire, an informed consent and participant information sheet were also provided. Questionnaire had sought information regarding sociodemographic variables, NE frequency, sleeping habits, and a 22-item pediatrics sleep-related breathing disorder (SRBD) scale. Grades in various subjects (Mathematics, Science, English, Hindi, Drawing, and Physical education) of last semester examinations were filled by parents and were checked by teachers before submission. Retrieval of the questionnaire from the students was done within 5–7 days.

Translation of sleep-related breathing disorder scale

SRBD scale was adopted from University of Michigan after permission. This scale has been validated with polysomnography for sleep-disordered breathing. Hindi translation was done after due permission. For Hindi translation, English version of questionnaire was given to five bilingual pediatricians and they were asked to translate in Hindi. The Hindi version was further backtranslated into English by another bilingual pediatrician. Any discrepancy in the two versions was then resolved by consensus. The questionnaire was then given to parents of 30 children attending pediatric OPD. They were asked to fill in questionnaire and report any ambiguity or confusion in questions. Subsequently, a final Hindi version of the scale was contrived after getting due feedback from parents. Cronbach's alpha for 22-item translated questionnaire was found to be 0.70 indicating optimal reliability.

Interpretation of sleep-related breathing disorder scale

SRBD scale contains 22 symptom items about snoring frequency, loud snoring, difficulty in breathing during sleeping, observed apneas, daytime sleepiness, inattentive, or hyperactive behavior. Each of these items was shown to correlate with OSA in children confirmed by polysomnography.[5] There are three options to answer each question in the scale – yes = 1, no = 0, or don't know = missing. The number of symptom-items endorsed positively (“yes”) is divided by the number of items answered positively or negatively; the denominator therefore excludes items with missing responses and items answered as don't know. The result is a proportion that ranges from 0.0 to 1.0. Scores >0.33 are considered positive and suggestive of high risk for a pediatric SRBD and it was taken as indicator of OSA.

Statistical analyses

Data were analyzed using SPSS (version 21.0; IBM, New York, NY, USA). The prevalence is reported as a proportion with 95% confidence interval (CI). Comparison of different sociodemographic and other variables among children with and without OSA was done by Chi-square test. Univariate logistic regression analysis was performed to test association of various risk factors with OSA. Statistically significant and biologically important variables were then entered in logistic regression model to identify independent predictors of OSA. All variables were entered at the same time using ENTER model in SPSS. Hosmer–Lemeshow goodness of fit test was used for testing fit of model. $P < 0.05$ was considered as statistically significant. The results of the multivariable analysis are reported as adjusted odds ratios (ORs) with 95% CI.

RESULTS

Out of 1820 questionnaires distributed, 1528 were retrieved back, resulting in response rate of 83.95%. Out of 1528 forms, 182 (11.9%) forms were incomplete for requested information, and hence, 1346 (74%) questionnaires were finally analyzed.

Demographic characterization

Table 1 depicts association of various demographic and clinical factors with OSA.

The prevalence of OSA was 9.6% (129 out of 1346) (95% CI: 8.1% to 11.7%). OSA was more common in males (11.2% vs. 6.9%) which was significant on univariate analysis, and when multivariate analysis was done on gender as risk factor, it was borderline significant ($P = 0.052$).

Information of some variables was missing for some participants, and number of participants with information is shown in Table 1 for these variables. Since a lot of anthropometric data regarding height was missing in the received questionnaires, we could not calculate body mass index (BMI).

Literacy level of father or mother had no association with positive SRBD questionnaire (8.3% vs. 9.6%; $P = 0.796$ and 15.9 vs. 9.2%; $P = 0.065$, respectively). Although employment of father had no association with positive SRBD questionnaire (8.2% vs. 9.7%; $P = 0.663$), if mother was working, it was significantly

associated with positive SRBD compared to if mother was homemaker (13.5% vs. 8.1%; $P = 0.003$, adjusted odds ratio (OR): 1.8; 95% CI: 1.2–2.7) [Table 2 and 3].

Students with positive SRBD had higher chances of sleep talking (31.7% vs. 11.2%; $P < 0.0001$, adjusted OR: 3.0; 95% CI: 1.9-4.7). Similarly, this group had higher chances of having bruxism (29% vs. 15.4%; $P < 0.0001$, adjusted OR: 1.7; 95% CI: 1.1–2.6), respectively. However, sleep walking was not found to be statistically different in individuals with positive SRBD and negative SRBD [Table 2].

Association of obstructive sleep apnea with sleep duration

Total sleep time was calculated by adding sleep time during night plus duration of naps during day (if any). Sleeping less can lead to obesity in adults and obesity leads to OSA. American Academy of Sleep Medicine has recently recommended that children from 6 to 12 years should sleep 9–12 h (including naps) in 24 h.[6] Hence, to evaluate effect of sleep duration, individuals were clubbed into two groups: who were sleeping <9 h and those sleeping more than 9 h. Individuals with positive SRBD were not statistically different in these two groups (10% vs. 8.3%; $P = 0.391$).

To find association between late sleepers and OSA, students were clubbed on the basis of their sleeping times into two groups: who sleep before 10 P.M. and those who sleep later. This time period was selected on convenient basis. Individuals with positive SRBD were not statistically different in these two groups (8.2% vs. 10.5%; $P = 0.186$).

Association of obstructive sleep apnea with academic performance and nocturnal enuresis

In children with positive SRBD, NE was seen in 30.5% (39/128) which was significantly higher than children with negative SRBD (11.2%; 132/1180; $P < 0.001$, OR 3.48; 95% CI 2.27–5.26).

When academic performance of individuals with positive SRBD was compared with those with negative SRBD, it was found to be significantly and consistently poor in the former group [Table 4]. In all subjects, students with positive SRBD questionnaire were more probable to have poorer grades than their counterparts with negative SRBD.

DISCUSSION

This study showed high prevalence (9.6%) of OSA among Indian children in age group of 5–10 years. In this study, boys were only marginally more prone to develop OSA compared to girls. Boys were statistically at more risk than girls for OSA on univariate analysis, although on multivariate analysis, risk reduced to near significant ($P = 0.052$). Since this study was done in school population of different strata, i.e., public and private, it was near representative of community prevalence of pediatric OSA. In various studies, the prevalence of pediatric OSA has been found to be around 2%–11%.[1] OSA has been seen to be equal in boys and girls in preadolescent children, but after puberty, there is a male predominance.

Literacy levels or occupation of parents has never been studied in relation to OSA. In our study, there was no statistically significant difference in terms of employment of father or literacy level of either parents; but interestingly, if mother was employed, it was a significant risk factor for OSA. This study is probably the first one in which association of working mother and OSA has been found. Whether this is cultural effect or it is consistent throughout world, it needs to be further confirmed in larger studies in different parts of the world.

Sleep talking is highly prevalent in children. In our study, children with positive SRBD were more probable for sleep talking. This could be effect of recurrent arousals occurring due to OSA. Whether this is occurrence of two common disorders or there is any significant association needs to be verified in larger studies.

Bruxism is stereotypical rhythmic movement of mastication muscles which leads to grinding of teeth. It is commonly aggravated by stress, gastroesophageal reflux disease, and medications; it is also now increasingly recognized to be associated with OSA. Studies have shown a positive correlation between sleep-disordered breathing and tooth grinding.[7,8] It is hypothesized that bruxism could be manifestation of increased stress level due to effect of recurrent arousals in OSA. If a child snores and history of bruxism is positive, OSA should be the first disease to rule out until proven otherwise. Sleep walking was not associated with OSA in our study although in few studies, association was found between these two diseases in children.

Nocturia is a significant complication of OSA in adults, and NE has been shown to be a complication in young children.[9,10,11] In our study, NE was found to be very high in students with positive SRBD (OR 3.48; 95%CI 2.27–5.26). Enuresis is postulated to be due to increased urine formation due to excess release of atrial natriuretic peptide by cardiac myocytes in response to distension. Thus, all patients of suspected OSA should be asked about history of NE and vice versa. If enuresis is due to OSA, it can be treated simply by doing adenotonsillectomy (AT). Some patients who do not respond to AT will require CPAP. In a meta-analysis of 14 studies, strong association of OSA and NE was seen; also, significant improvement in enuresis was seen in these children who underwent AT.[12]

Poor academic performance is an important complication of OSA and this could be due to cortical and sympathetic arousals and hypoxemia which affects memory consolidation.[3,13,14,15] In fact, academic performance has now been incorporated as a risk factor in modified version of STOP BANG-modified teen STOP-BANG questionnaire for pediatric patients.[16]

In our study, school grades were consistently poor in all subjects including Mathematics, Science, Hindi, English, Drawing, and Physical education in children with suspected OSA ($P < 0.01$). This shows OSA's overall effect on learning, analytical, and calculating abilities, as well as on speech, language, and physical development. If a child's academic performance is going downhill, OSA should be one of the differentials, and merely asking about snoring, witnessed apnea, and sleepiness/hyperactivity can reveal the possible diagnosis.

The biggest strength of this study is that it is a school-based study, and considering higher school enrollment rates in Bhopal, it is proxy of community-based study. To the best of our knowledge, it is the first study depicting the prevalence of OSA in Indian children. Furthermore, this is the first study in which maternal occupation has been found to be associated with OSA.

The study is limited by the following:

1. Since performing polysomnography is not practical in community studies, we used SRBD questionnaire for the identifications of OSA in this study. SRBD subscale of the Pediatric Sleep Questionnaire has been shown to be both reliable and valid in identifying SDB in children in clinical research[17]
2. Although we have translated and piloted the study instrument in Hindi, there was no direct interface between parent and investigator which implies theoretical possibility of miscomprehension of some items in questionnaire
3. Since a lot of height data were missing, we could not calculate BMI, which is one of the important factors for OSA.

CONCLUSION

OSA is highly prevalent (9.8%) in Indian children. OSA leads to NE and poor academic performance in all subjects. This study found association of maternal occupation and OSA which needs to be confirmed in larger studies.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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Figures and Tables

Table 1

Distribution of sleep-related breathing disorder score by various sociodemographic factors

Variables	SRBD score			*P*
	Positive (>33%), *n* (%)	Negative (≤33%), *n* (%)	Total (*n*)	
All	129 (9.6)	1217 (90.4)	1346	
Age (years)				
<6	20 (8.0)	231 (92.0)	251	0.343
6-7	25 (11.3)	197 (88.7)	222	
7-8	33 (11.3)	258 (88.7)	291	
8-9	23 (8.9)	236 (91.1)	259	
9 and above	20 (13.8)	125 (86.2)	145	
Gender (*n*=1346)				
Male	94 (11.2)	742 (88.8)	836	0.080
Female	35 (6.9)	475 (93.1)	510	
Sleep duration (h) (*n*=963)				
≤9.00	41 (10.0)	371 (90.0)	412	0.391
9.01+	46 (8.3)	505 (91.7)	551	
Sleeping time (h) (*n*=1294)				
<22.00	37 (8.2)	412 (91.8)	449	0.186
22.00+	89 (10.5)	756 (89.5)	845	
Father (*n*=1346)				
Illiterate	3 (8.3)	33 (91.7)	36	0.796
Literate	126 (9.6)	1184 (90.4)	1310	
Unemployed	7 (8.2)	78 (91.8)	85	0.663
Employed	122 (9.7)	1139 (90.3)	1261	
Mother (*n*=1346)				
Illiterate	11 (15.9)	58 (84.1)	69	0.065
Literate	118 (9.2)	1159 (90.8)	1277	
Unemployed or Homemaker	80 (8.1)	902 (91.9)	982	0.003
Employed	49 (13.5)	315 (86.5)	364	

SRBD: Sleep-related breathing disorder

Open in a separate window

Table 2

Association of other sleep disorders with sleep-related breathing disorder

Associated sleep abnormalities	SRBD_33			*P*
	>33.0%, *n* (%)	≤33.0%, *n* (%)	Total, *n* (%)	
Sleep talking				
Yes	39 (31.7)	130 (11.2)	169 (13.2)	<0.001
No	84 (68.3)	1032 (88.8)	1116 (86.8)	
Total	123 (100.0)	1162 (100.0)	1285 (100.0)	
Sleep bruxism				
Yes	36 (29.0)	178 (15.4)	214 (16.7)	<0.001
No	88 (71.0)	976 (84.6)	1064 (83.3)	
Total	124 (100.0)	1154 (100.0)	1278 (100.0)	
Sleep walking				
Yes	3 (2.5)	23 (2.0)	26 (2.1)	0.736
No	118 (97.5)	1115 (98.0)	1233 (97.9)	
Total	121 (100.0)	1138 (100.0)	1259 (100.0)	

SRBD: Sleep-related breathing disorder

Table 3

Logistic regression analysis; dependent variable – sleep-related breathing disorder >33.0%

Variables	Univariate (unadjusted)		Multivariate (adjusted)	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Male gender	1.7 (1.1-2.6)	0.008	1.5 (1.0-2.3)	0.052
Working mother	1.8 (1.2-2.6)	0.003	1.8 (1.2-2.7)	0.004
Illiterate mother	1.9 (1.0-3.6)	0.065	1.9 (0.9-3.9)	0.080
Sleep bruxism	2.2 (1.5-3.4)	<0.001	1.7 (1.1-2.6)	0.027
Sleep talking	3.7 (2.4-5.6)	<0.001	3.0 (1.9-4.7)	<0.001

OR: Odds ratio, CI: Confidence interval

Table 4

Association of obstructive sleep apnea with nocturnal enuresis and school grades

Variables	SRBD score		*P*
	Positive (>33%), *n* (%)	Negative (≤33%), *n* (%)	
Nocturnal enuresis			
No	89 (69.5)	1048 (88.8)	<0.001
Yes	39 (30.5)	132 (11.2)	
Total	128 (100.0)	1180 (100.0)	
Overall school grade			
A	39 (31.5)	506 (43.9)	<0.001
B	49 (39.5)	446 (38.7)	
C	24 (19.4)	168 (14.6)	
D	12 (9.7)	33 (2.9)	
Total	124 (100.0)	1153 (100.0)	
Mathematics			
A	47 (41.2)	593 (56.7)	0.003
B	42 (36.8)	324 (31.0)	
C	19 (16.7)	107 (10.2)	
D	6 (5.3)	22 (2.1)	
Total	114 (100.0)	1046 (100.0)	
Science			
A	31 (31.0)	450 (48.1)	<0.001
B	33 (33.0)	310 (33.1)	
C	24 (24.0)	151 (16.1)	
D	12 (12.0)	25 (2.7)	
Total	100 (100.0)	936 (100.0)	
Hindi			
A	42 (39.3)	551 (54.5)	<0.001
B	37 (34.6)	370 (36.6)	
C	24 (22.4)	78 (7.7)	
D	4 (3.7)	12 (1.2)	
Total	107 (100.0)	1011 (100.0)	
English			
A	47 (41.2)	604 (58.2)	0.006
B	47 (41.2)	313 (30.2)	
C	17 (14.9)	101 (9.7)	
D	3 (2.6)	19 (1.8)	
Total	114 (100.0)	1037 (100.0)	
Drawing			
A	32 (28.8)	486 (47.0)	<0.001
B	39 (35.1)	355 (34.3)	
C	31 (27.9)	158 (15.3)	
D	9 (8.1)	36 (3.5)	
Total	111 (100.0)	1035 (100.0)	
Physical education			

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