

From Obstructive Sleep Apnea Syndrome to Upper Airway Resistance Syndrome: Consistency of Daytime Sleepiness

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Summary: Some patients with excessive daytime sleepiness who do not present the features of obstructive sleep apnea syndrome (OSAS) present a sleep fragmentation due to transient alpha EEG arousals lasting between three and 14 seconds. These transient EEG arousals are related to an abnormal amount of breathing effort, indicated by peak inspiratory esophageal pressure (Pes) nadir. In the studied population, these increased efforts were associated with snoring. Usage of nasal CPAP, titrated on Pes nadir values, for several weeks eliminated subjective daytime sleepiness and improved Multiple Sleep Latency Test scores from baseline evaluations. Patients suspected of CNS hypersomnia should be asked about continuous snoring, and their clinical evaluation should include a good review of maxillo-mandibular and upper airway anatomy.

I. INTRODUCTION FROM "PICKWICK" TO OBSTRUCTIVE SLEEP APNEA AND UPPER AIRWAY RESISTANCE

Our understanding of upper airway obstruction during sleep has evolved since its earliest investigations. As sleep apnea was discovered through studies of the "Pickwickian syndrome" (1), early research focused on the severely obese patient with multi-morbidity. However, in 1972 normal-weight subjects with obstructive sleep apnea were presented (2,3). Progressively, our current notion of "obstructive sleep apnea syndrome" was developed (4). Hypopnea (partial obstruction of the upper airway) was discovered and defined by several authors. Gould et al. (5) required that an event last a minimum of 10 seconds and cause a decrease in airflow to 50% of baseline. Lugaresi et al. (6) developed a theory of a snoring scale and "snoring disease", in which snoring represented the stage 0 of obstructive sleep apnea syndrome. In all investigations, more men than women were found with sleep apnea. Male/female ratios of between 10/1 and 60/1 were reported. In general, women with obstructive sleep apnea syndrome were significantly more overweight than men with the syndrome.

Recent research has advanced our ideas further. Our group and others have found that snoring is not necessarily associated with clinical complaints. Although snoring may produce increased resistance in the upper airway, the resistance may not be sufficient to produce an increased number of transient arousals, a significant increase in respiratory effort or any clinical symptoms (7,8). Furthermore, increased upper airway resistance may occur without snoring, possibly more often in men than in women. When snoring does exist, it may cause variations in symptomatology (7).

II. EXCESSIVE SLEEPINESS, UPPER AIRWAY RESISTANCE AND SNORING: AN INVESTIGATION

To confirm that increased upper airway resistance without sleep apnea or hypopnea leads to clinical complaint, we performed a study on subjects who had come to the sleep clinic with complaints of isolated sleepiness and snoring.

Methods

Selection of the population

Patient records were collected from the Stanford University Sleep Disorders Clinic data base. All patients (male and female) had been seen between Jan-

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uary 1985 and March 1989 for a complaint of excessive daytime sleepiness that had been present for more than 1 year. None of the known causes of daytime sleepiness (including history of head trauma within 18 months of onset of the complaint) could have been identified. All subjects were given a nocturnal polysomnogram followed by a multiple sleep latency test (MSLT) (9). The MSLTs must have demonstrated abnormal sleep latency, but no sleep-onset REM periods.

Based upon clinical and nocturnal and daytime polygraphic investigations, they had been diagnosed with idiopathic-CNS hypersomnia and had been prescribed stimulant medications. In addition, the report of snoring, indicated by the patient or a family member or noted during the nocturnal polygraphic monitoring, must have been entered on the data base by the polysomnographic technologist. Sixty-five patients (28 women and 37 men) fit the required entry profile. Fifty-eight of them responded to phone/mail inquiry concerning the persistence of their daytime somnolence and the need for daily stimulant drug intake. Fifty-four (24 women and 30 men) agreed to undergo further investigation after withdrawal from their stimulant medication for 7 days.

Tests

Each subject had a clinical interview and evaluation to determine the current symptomatology. The initial polygraphic records and multiple sleep latency tests were pulled out of storage and reviewed, and new nocturnal and daytime polygraphic monitorings were obtained. In the initial nocturnal recordings, the following standard variables were recorded: EEG (C3/A2-C4/A1 of the 10-20 international electrode placement system); electrooculogram (EOG); chin and leg electromyogram (EMG); and ECG (modified V-2 lead). Respiration was monitored by uncalibrated inductive respiratory plethysmography (Vitalog[®]) bands indicating abdominal and thoracic efforts. Airflow was monitored by nasoro thermistors and oxygen saturation with pulse oximetry (Biox-Ohmeda[®], Colorado).

In the second monitorings, all of the above variables were collected, and two more were added. (1) Snoring was evaluated with a subminiature electric microphone, type MCE-2000 (Conrad Electronics, Hirschau, Germany), which was placed above the larynx and linked also to MESAM[®] equipment (10,11). This equipment performs spectrum analysis of breathing noises and gives breath by breath information on snoring (10,11). (2) Measurement of esophageal pressure (Pes), an indirect measure of upper airway resistance, was performed after placement of an esophageal catheter following the technique described by Baydur et al.

(12). The following day a new multiple sleep latency test was performed, including, as always, five naps at 0930, 1130, 1330, 1530 and 1730 hours (9).

All polygraphic monitorings were run at 10 mm/second, except for 3 minutes every hour in which they were run at 25 mm/second, for investigation of ECG tracing. The results of the two polysomnographic and multiple sleep latency test investigations were analyzed and compared. Sleep/wake values were scored by 30-second epochs following the criteria of Rechtschaffen and Kales (13). Apnea and leg movements during sleep were scored following the criteria of Guilleminault et al. (4). The multiple sleep latency test was scored following the international guidelines (8). The new nocturnal polygraphic recording was also scored to determine changes in peak negative inspiratory esophageal pressure (Pes nadir) with each respiratory cycle: subjects who snored during more than 10% of their total sleep time and who presented snoring associated with a peak end inspiratory pressure more negative than the mean + 1 standard deviation from baseline wakeful supine Pes (measured for 30 minutes during quiet wakefulness before sleep onset) had their recordings submitted to a new nocturnal sleep scoring with determination of "transient" or "alpha EEG" arousals. Using the central EEG derivations (C3 or C4 to mastoid), an "alpha EEG-transient arousal" is defined as an abrupt shift in EEG frequency from a sleep EEG frequency background to alpha range that lasts between 3 and 14 seconds; alpha EEG arousals are frequently, but not necessarily, associated with an increase in chin EMG activity, increased heart rate or appearance of eye movement (13). An "alpha arousal index" (number of alpha EEG arousals per hour of sleep) was calculated from the total number of alpha EEG arousals not related to a polygraphic event.

The subjects who responded to all selection criteria were then submitted to 1 night of nasal continuous positive airway pressure (CPAP) titration combined with nocturnal polygraphic monitoring. Because none of these subjects presented classic obstructive sleep apnea or obstructive hypopnea syndromes (4,5), nasal CPAP titration was based upon elimination of snoring and absence of Pes nadir more negative than the mean + 1 SD of Pes nadir measured for 30 minutes during quiet supine wakefulness before sleep onset. After determination of the appropriate position and positive and expiratory pressure (PEEP), subjects were prescribed nightly usage of nasal CPAP. A follow-up assessment was performed 3–4 weeks later, including clinical interview and evaluation, standard nocturnal polysomnography with nasal CPAP at the previously determined PEEP, urine drug screen for evaluation of sleep/wake related drug intake and a multiple sleep latency test the next day, as initially performed.

Results

In all subjects, both nocturnal polygraphic recordings demonstrated an absence of obstructive sleep apnea and hypopnea syndromes (4,5). The shortest total sleep time monitored was 7 hours and 22 minutes and the longest was 8 hours and 46 minutes. The mean of the second multiple sleep latency test was 6.1 ± 2.3 minutes, compared to a mean of 5.7 ± 2.4 minutes in the first test (nonsignificant, paired *t* test). All subjects still complained of somnolence after discontinuation of their stimulant drugs. The new polygraphic recording documented that all subjects snored during nocturnal sleep, but snoring varied a great deal in loudness and duration (from 6 minutes to the entire night). The most negative end inspiratory esophageal pressure during supine quiet wakefulness prior to sleep onset was -7 cm H₂O (mean: -4 ± 1.3 cm H₂O). Fourteen subjects (9 women and 5 men) presented peak esophageal pressure nadirs during sleep that were more negative than the mean $+ 1$ SD of baseline wakeful Pes and snored during part of their total sleep time. Further investigations were performed based on these findings.

Investigation of subgroup with increased peak Pes nadirs

All 14 subjects snored. The lowest cumulative snoring duration during total sleep time was 245 minutes (47% of total sleep time). Snoring was divided into "snoring periods". A snoring period began with the first breath identified as a snore by the MESAM® on the recording and was terminated by an alpha EEG arousal, an awakening longer than 15 seconds or a body movement that interrupted snoring, as defined in the international scoring manual (13). The mean duration of snoring periods was 10 ± 8 minutes. Mean total sleep time, calculated from the Rechtschaffen and Kales criteria (13), was 456 ± 18 minutes. Total time in bed was 540 ± 9 minutes. Nocturnal sleep was disrupted and fragmented; fragmentation was mainly related to transient alpha EEG arousals. The mean lowest SaO₂ was $94.2 \pm 1.0\%$, and the mean apnea/hypopnea index was $2 \pm$ per sleep hour.

Alpha EEG arousals

An alpha EEG arousal analysis was performed to determine whether each alpha EEG arousal was associated with snoring and related to increased esophageal pressure nadir. First, the alpha EEG arousals were identified. Second, each breath in the preceding 10 minutes of the recording was analyzed and each Pes nadir determined. If a) the Pes nadir preceding the alpha EEG arousal was more negative than baseline wakefulness; b) it was the most negative nadir of the

snoring period; and c) the breath following the alpha EEG arousal was associated with an abrupt reduction in Pes nadir, then the alpha EEG arousal was scored as "related to" the increased inspiratory effort indicated by Pes.

A mean of 41 ± 8 alpha EEG arousals were related to increased respiratory effort. The mean sleep latency in multiple sleep latency tests was 5.8 ± 2.5 minutes. None of the subjects presented sleep-onset REM periods. The mean nasal CPAP setting was 7 ± 1.5 cm H₂O.

At follow-up monitoring after 1 month of nightly usage of nasal CPAP treatment, the new nocturnal polygraphic monitoring indicated absence of snoring and a mean total sleep time of 398 ± 21 minutes, for a mean total bed time of 510 ± 15 minutes. The mean alpha EEG arousal index was 8 ± 10 . The following-day mean multiple sleep latency test score was 13 ± 3 minutes. One-way analysis of variance indicated a significant decrease in total sleep time and significant improvement in multiple sleep latency test scores ($p < 0.0001$).

Although the patients presented here lacked many of the symptoms of obstructive sleep apnea syndrome, their sleep disturbance was secondary to an abnormal breathing pattern during sleep. Their subtle respiratory dysfunction is secondary to that noted in certain snorers in a previous investigation. Thus, snoring without sleep apnea or hypopnea can be associated with upper airway resistance and daytime somnolence.

III. PRELIMINARY RESULTS: UPPER AIRWAY RESISTANCE MAY OCCUR WITHOUT SNORING

Recently, women and men who did not snore were found to have abnormal upper airway resistance leading to clinical symptoms (daytime fatigue and sleepiness). This sleepiness seems to be related to repetitive, transient alpha EEG arousals during sleep 2–3 seconds in duration such as those noted with snoring. Upper airway resistance increased for 1–3 breaths to a level at which dilator muscles of the upper airway could not compensate for the "suction" effect and the increased inspiratory effort. Tidal volume increased abruptly during this 1–3-breath segment without demonstrating a significant SaO₂ drop, and a short arousal occurred. Interestingly, in a recent 6-month prospective study, we found nearly as many women as men with this problem.

Conclusions

We suggest that the first step of sleep apnea pathology is increased upper airway resistance, rather than snor-

ing, decreased oxygen saturation or severity of the clinical complaint.

The minimum complaint in abnormal upper airway compliance during sleep is daytime fatigue and sleepiness. With obstruction of the upper airway, respiratory efforts increase. At one point, increased efforts are associated with transient arousals, often of very short duration. Repetitive arousals will cause an increase in daytime sleepiness.

Are repetitive K-complexes as demonstrative as transient EEG arousals as indices of sleep fragmentation? This question is currently being considered. Are the metabolic changes associated with the increased respiratory effort important? This is more difficult to investigate and preliminary studies on factors such as blood insulin and glucose are the only research on this issue to date. We do know that the increased effort has an impact on the cardiovascular system, through increased intrathoracic pressure transmitted to the ventricles. Thus, mechanical changes and sleep fragmentation can have an impact on the cardiovascular system long before the appearance of oxygen desaturation.

It is difficult to determine the natural evolution of upper airway resistance. It is surely affected by a multitude of factors, from weight increase to the change in muscle fiber distribution with aging. Currently, the only studies available are limited morbidity and mortality investigations on obstructive sleep apneic patients and these studies probably do not provide useful information on the morbidity related to abnormal breathing during sleep. Regardless of long-term evolution, daytime sleepiness is a consistent symptom in disordered breathing during sleep and can impair the subjects' well-being, even without SaO_2 decreases or apnea or hypopnea. Only long-term prospective studies on different populations will give us further information on the natural evolution of OSAS and partial upper airway occlusion during sleep.

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REFERENCES

1. Gastaut H, Tassinari CA, Duron B. Etudes polygraphiques des manifestations episodiques (hypniques et respiratoires) diurnes et nocturnes du syndrome de Pickwick. *Rev Neurol (Paris)* 1965; 112:573-9.
2. Sadoul P, Lugaresi E, eds. Hypersomnia with periodic breathing: a symposium. *Bull Pathophysiol Resp* 1972;8:967-1292.
3. Guilleminault C, Eldridge F, Dement WC. Insomnia, narcolepsy, sleep apnea. *Bull Physiopathol Resp* 1972;8:1127-38.
4. Guilleminault C, Tilkian A, Dement WC. The sleep apnea syndromes. *A Rev Med* 1976;27:465-84.
5. Gould GA, Whyte KF, Rhind GB, Airlie MAA, Catterall JR, Shapiro CM, Douglas NJ. The sleep hypopnea syndrome. *Am Rev Resp Dis* 1990;142:295-330.
6. Lugaresi E, Cirignotta F, Coccagna G, Montagna P. Clinical significance of snoring. In: Saunders NA, Sullivan CE, eds. *Sleep and breathing*. New York: Marcel Dekker, 1984:284-9.
7. Stoohs R, Guilleminault C. Snoring during NREM sleep: respiratory timing, esophageal pressure and EEG arousal. *Resp Physiol* 1991.
8. Guilleminault C, Stoohs R, Duncan S. Snoring: daytime sleepiness in regular heavy snorers. *Chest* 1991;99:40-8.
9. Association of Sleep Disorders Centers Task Force on Daytime Sleepiness, Carskadon MA, Chairman. Guidelines for the multiple sleep latency test (MSLT): a standard measure of sleepiness. *Sleep* 1989;9:519-24.
10. Penzel T, Amend G, Meinzer K, Peter JH, Von Wichert P. MESAM: a heart rate and snoring recorder for detection of obstructive sleep apnea. *Sleep* 1990;13:176-84.
11. Stoohs R, Nouriani B, Suh B, Guilleminault C. Validation study of a screening device for sleep apnea: MESAM 4. *Sleep Res* 1991;20:440.
12. Baydur A, Behrakis PK, Zin WA, Jaeger M, Milic-Emili J. A simple method for assessing the validity of the esophageal balloon technique. *Am Rev Resp Dis* 1982;129:788-91.
13. Rechtschaffen A, Kales A, eds. *A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects*. Los Angeles: Brain Information Service/Brain Research Institute, UCLA, 1968.
14. American Sleep Disorders Association Atlas Task Force, Guilleminault C, Chairman. EEG arousals: scoring rules and examples. *Sleep* 1992;15:173-84.