A cause of excessive daytime sleepiness. The upper airway resistance syndrome.

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A Cause of Excessive Daytime Sleepiness*

The Upper Airway Resistance Syndrome

Christian Guillemainault, M.D.; Riccardo Strooks, M.D.; Alex Clerk, M.D.; Mindy Cetel, M.D.; and Ibul Maistros, M.D.

Subjects with isolated complaints of chronic daytime sleepiness are usually classified as "idiopathic hypersomniacs", and treated symptomatically. A group of these subjects was investigated during nocturnal sleep and daytime naps. In a subgroup of them, sleep was fragmented by very short alpha EEG arousals throughout the sleeping period. These short arousals are usually ignored in sleep analyses, but their impact is significant (in the 15 subjects identified with the syndrome, the mean sleep latency in multiple sleep latency tests was 5.1 ± 1 min). These arousals are directly related to an abnormal increase in respiratory efforts during sleep (the mean peak inspiratory esophageal pressure measured in our subjects in the respiratory cycle just preceding a transient arousal was \(-33±7 \text{ cm H}_2\text{O}\)). Typically, an arousal occurs within one to three breaths of flow limitation associated with abrupt but limited reduction in tidal volume (ie, abnormal increase in upper airway resistance during sleep). The arousal restores normal breathing. Snoring was noted in association with these transient arousals in 10 of the 15 subjects; however, snoring was neither sufficient nor necessary for the identification of the clinical syndrome. Both sexes were equally represented in the affected group. All studied subjects had upper airway anatomy that was mildly abnormal. Nasal continuous positive airway pressure, used as an experimental tool, eliminated the daytime sleepiness (multiple sleep latency mean score = 13.5 min), the transient arousals (mean alpha EEG arousal index decreased from 31.3 ± 12.4 to 8 ± 2 per hour of sleep), and the abnormal upper airway resistance. Chronic daytime sleepiness is a major cause of social, economic, and medical impairment. Recognition of this syndrome and its cause is important, as specific treatments can be developed to eliminate the problem.

*Chest 1993; 104:781-87

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**METHODS**

Initial Screening (Night 1)

Men and women 18 years and older referred to the clinic for a complaint of excessive daytime sleepiness were systematically investigated during a 6-month period. Each subject was asked to fill out a standardized and validated sleep/wake questionnaire, the Sleep Questionnaire and Assessment of Wakefulness. A complete medical evaluation was performed, including a clinical interview investigating medical, neurologic, psychiatric, and sleep-wake his...
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recreational drugs that might affect sleep

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Drug intake was reviewed, and all subjects

a minimum of 15 days from therapy with any psychoactive or

recreational drugs that might affect sleep or sleep/wake cycles. Urine drug screens were performed after the 15-day period. Schedules were structured to maximize and regulate nocturnal sleep for 8 days prior to the polygraphic recordings. Each subject underwent a nocturnal polygraphic monitoring with lights-out time set at 10:30 PM and lights-on time at 7 AM (ie, 8½ hours of dark time).

The monitoring included EEG (C3/A2, C4/A1, O2/A1 of the international electrode placement system); electro-crologum (EOG); chin and leg electromyogram (EMG); and ECG (modified V-2 lead). Respiration was investigated by oronasal airflow, thoracic and abdominal movements (inductive plethysmography), morming sounds (subminiatue electric microphone type MCE-2000 [ME-SAM-4 equipment, Conrad Electronics, Hirchau, Germany] taped above the larynx), and oxygen saturation (pulse oximetry). Records were scored following the Rechtschaffen and Kales' international criteria for sleep/wake determination, and the published international criteria for scoring sleep-onset REM periods, periodic leg movements, restless legs, etc., were used for determination of specific sleep-related syndromes. Abnormal breathing patterns were scored using the current criteria for identifying sleep apnea and sleep hypoapnea.10,16

The morning after the nocturnal polygraphic monitoring, a MSLT was performed, with five naps scheduled at 9:30 and 11:30 AM and 1:30, 3:30, and 5:30 PM. This initial screening identified subjects with excessive daytime somnolence and indicated well-known syndromes (narcolepsy, obstructive sleep apnea, restless leg syndrome, etc) as causes of the somnolence in part of the population. Those patients who did not fit any of these well-defined syndromes were the subject of further systematic investigations:

Night 2

Ambulatory monitoring with a digital portable recorder (MESAM 4, Madaus, Inc)28,38 continuously recorded heart rate, body position, and snoring sounds through an electric subminiatue microphone. (This equipment performs spectrum analysis of breathing noises and gives breath-by-breath information on snoring, with scoring on three levels of loudness.) Pulse oximetry was also performed. This ambulatory test was performed to investigate the presence of snoring and abnormal breathing patterns in the home environment.

Night 3

A new nocturnal polygraphic recording was made with the same variables as before and, in addition, there was monitoring of snoring sounds and of respiratory efforts by measurement of esophageal pressure (Pes). The esophageal catheter was placed transnasally and calibrated following the technique described by Baydur et al. Once the subject was comfortable in bed, a baseline recording was obtained for 30 min during quiet supine wakefulness.

The new nocturnal polygraphic recording was scored following the Rechtschaffen and Kales' international criteria. This recording and the baseline recording was then scored for presence/absence of short (transient) alpha EEG arousals, defined as alpha EEG bursts lasting a minimum of 3 s in the central EEG derivation. This analysis found that all subjects presented short arousals of 3 to 14 s. However, some subjects presented many more than others. In a previous investigation of seven normal subjects (mean age 27 years), none presented more than ten short, transient alpha arousals per hour of sleep in one nocturnal sleep recording. Thus, we chose a cut-off point of ten short arousals per hour of sleep when selecting patients for further respiratory investigation during sleep.

Night 4

All subjects with more than ten of these transient alpha EEG arousals per hour of sleep in either of the two laboratory recordings underwent a third laboratory night recording (ie, a fourth night of investigation). During this night, quantification of airflow was performed using a tight fitting mask and a pneumotachometer. The mask covered the nose and mouth and was opened to the atmosphere via the heated pneumotachometer connected to a transducer (Valdyne MP45). Esophageal pressure was again measured using the method described by Baydur et al., and all other previously described variables were again monitored. In half of the subjects, PCO2 was also measured with a transcutanous tCO2 electrode (SensorMedic, Inc).

With the data from these four nights we identified the patients with a daytime sleepiness complaint, abnormal multiple sleep latency scores, more than ten transient EEG arousals per hour of sleep, and an abnormal breathing pattern with increased respiratory efforts (Pes monitoring) and increased upper airway resistance (pneumotachometer monitoring). Data analysis used to identify this subgroup is described in "Data Analysis and Selection of Subgroup for the Nasal CPAP Therapeutic Trial."

In the "positive" subgroup, a therapeutic trial with nasal continuous positive airway pressure (CPAP) was performed, with titration of the necessary pressure. The methods used to calibrate nasal CPAP were as follows: as none of the subjects presented with a significant number of sleep apneas or hypopneas as classically defined,10,11 nasal CPAP titration was primarily based on measurement of Pes. The CPAP pressure was set at the point at which Pes nadirs were equal to or less negative than 1 SD below the mean Pes nadir measured during 30 min of quiet supine wakefulness. As is customary in our clinic, two nights of recordings were performed for CPAP titration. Patients were prescribed continuous nightly use of CPAP for a minimum of 3 weeks. They then returned for clinical evaluation and nocturnal polygraphy with nasal CPAP and a following-day multiple sleep latency test. This last polygraphic monitoring was similar to the initial one, ie, only sensors placed on the body were used, and Pes was not monitored. The schedule of the different recordings is presented in Figure 1.

Before initiation of nasal CPAP, cephalometric radiographs were obtained. They were obtained following the technique reported by Riley et al, with the subject awake, seated, and at end-inspiration without swallowing.

Data Analysis and Selection of Subgroup for the Nasal CPAP Therapeutic Trial

Polygraphic monitorings were analyzed following the different international criteria used to score sleep/wake and sleep-related abnormalities.10,11 To evaluate presence/absence of snoring, the data obtained during the first three investigative nights (nights 1 and 3 in the laboratory and night 2 at home) were used. Patients were classified as "regular snorers" if they snored on all three nights, "irregular snorers" if they snored only on one or two nights. Patients were called "continuous snorers" if they snored 75 percent of the night or more, "intermittent snorers" if they snored less than 75 percent of the night.

Recordings on the second and third laboratory nights (nights 3 and 4) were analyzed to determine the relationship between alpha EEG arousals and abnormal breathing, based on the following criteria.

In night 3 recordings, transient alpha EEG arousals lasting 3 to 14 s were identified. Each breath in the preceding 10 min before the arousal was analyzed, and each Pes nadir was determined. (1) If the Pes nadir preceding the alpha EEG arousal was more negative than 1 SD below the mean Pes nadir monitored during baseline quiet supine wakefulness, (2) if it was the most negative nadir of the scoring period, and (3) if the breath following the alpha EEG arousal was associated with an abrupt reduction in Pes nadir, the alpha EEG arousal was scored as "related to" the increased respiratory effort indicated by Pes.

In all of the night 4 recordings, total sleep time was reduced, as
the facial mask with pneumotachograph disturbs nocturnal sleep. This recording was performed to evaluate the relationship between the abnormal breathing pattern and the repetitive transient alpha EEG arousals. It was never used for evaluation of sleepiness. Five periods with well-consolidated sleep, ending with a transient alpha EEG arousal, were randomly selected from each night 4 recording for breath-by-breath analysis of Pes, airflow, and tidal volume.

In night 4 recordings, a short alpha EEG arousal was related to the breathing behavior preceding it (1) if the immediately preceding Pes nadirs were more negative than 1 SD below the mean Pes nadir monitored during quiet supine wakefulness, (2) if the most negative Pes nadirs in a long sequence of breaths were seen just prior to the arousal, (3) if a simultaneous decrease in flow occurred with the peak negative Pes nadir, (4) if no other polygraphic events had occurred that could cause arousal, and (5) if just after the short arousal a less negative Pes nadir was observed with increase in flow.

For comparison, transient alpha EEG arousals were also identified in the recording performed 1 month after initiation of nasal CPAP treatment. This alpha EEG arousal index was compared with that obtained prior to any treatment.

Statistical Analyses
Descriptive statistics (paired t tests, repeated measures analysis of variance) were used to evaluate significance.

RESULTS

Initial Population
Forty-eight subjects, 20 men and 28 women, mean age $33 \pm 9$ years, were diagnosed as having "idiopathic hypersomnia" (ICSD code 780-54-7), i.e., did not fit the criteria for a well-defined syndrome at the end of the screening evaluation. The mean multiple sleep latency test score for the group was $6.1 \pm 1.6$ min.

Snoring
Eighteen of 48 subjects (8 women and 10 men) snored intermittently or continuously at home, in the laboratory, or both. Thirty subjects did not snore. When all polygraphic data had been analyzed, only 13 of these intermittent or continuous snorers fit the criteria for "upper airway resistance syndrome." We defined upper airway resistance syndrome as the combination of a clinical complaint (daytime sleepiness, presence of abnormal MSLT) with demonstration of flow limitation (Pes monitoring) and demonstration of increased respiratory efforts with arousal just following peak negative inspiratory Pes.

Nocturnal Polygraphy
None of the 48 subjects had obstructive sleep apnea syndrome as currently defined. Thirty-three subjects (13 women, 20 men) had very few or no transient alpha EEG arousals; their mean alpha arousal index was $7 \pm 2$ on the first monitoring night. No significant change in Pes nadir was seen during sleep compared with quiet supine wakefulness in these subjects. They had a mean Pes nadir during sleep of $-6.6 \pm 2.5$ cm H$_2$O and a mean Pes nadir of $-5.5 \pm 2.1$ cm H$_2$O during 30 min of quiet supine wakeful breathing. Five men in this group had light, intermittent snoring. Their mean lowest Sa$_{O_2}$ was $94.5 \pm 1.6$ percent. Their mean sleep latency was $5.3 \pm 2.8$ min. These 33 subjects were believed to have "idiopathic hypersomnia."

Positive Subgroup
Fifteen subjects (8 women and 7 men) of the 48 presented with frequent (ie, $10/h$) transient alpha EEG arousals. These 15 individuals were slim, with a mean body mass index of $23 \pm 3.2$ kg/m$^2$ and a mean age of $37.5 \pm 7$ years. The seven men had a mean body
Table 1—Population With Upper Airway Resistance Syndrome*

<table>
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<th>Subject No./Sex</th>
<th>Age, yr</th>
<th>BMI, kg/m²</th>
<th>TST, min</th>
<th>Arousal Index</th>
<th>MSLT, min</th>
<th>Arousal Index</th>
<th>Pes Nadir, cm H₂O</th>
<th>CPAP Titration Maximum, cm H₂O</th>
<th>Follow-up CPAP Night Maximum, cm H₂O</th>
<th>Follow-up CPAP Night TST, min</th>
<th>Follow-up CPAP Night MSLT, min</th>
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<td>33</td>
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<td>492</td>
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<td>-27</td>
<td>-8</td>
<td>9</td>
<td>398</td>
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<td>31</td>
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<td>-6</td>
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<td>-5</td>
<td>6</td>
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<tr>
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<td>-6</td>
<td>9</td>
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<tr>
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<td>Int</td>
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<td>456</td>
<td>42</td>
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<tr>
<td>15/39/M</td>
<td>+</td>
<td>26</td>
<td>484</td>
<td>49</td>
<td>5.1</td>
<td>509</td>
<td>37</td>
<td>-42</td>
<td>-5</td>
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<td>413</td>
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<tr>
<td>Mean 37.5</td>
<td></td>
<td>23.6</td>
<td>490.4</td>
<td>31.3</td>
<td>53</td>
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<td>SD 7.0</td>
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<td>3.2</td>
<td>12.93</td>
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<td>9.2</td>
<td>7.1</td>
<td>1.1</td>
<td>2.3</td>
<td>15</td>
</tr>
</tbody>
</table>

*BMI = body mass index; RDI = respiratory disturbance index; TST = total sleep time; Pes = esophageal pressure; Nights 1, 2, 3, = first, second, third nocturnal polysomnographic nights; MSLT = multiple sleep latency test (on day following a recording); CPAP = nasal continuous positive airway pressure; Follow-up CPAP = monitoring with CPAP after nightly use of CPAP for 1 month; + = continuous snoring; Int = intermittent snoring; 0 = no snoring.

Snoring in This Subgroup

Two women never snored, two men and one woman had intermittent, light snoring, and ten subjects (five and five women) were regular snorers.

Night 1 Polysomnographic Monitoring in the 15-Subject (Without Pes and Pneumotachograph Monitoring)

Mean total sleep time was 490.4 ± 13 min, and the mean sleep latency in the MSLT was 5.3 ± 1 min. The mean lowest SaO₂ was 94 ± 1.4 percent. The mean respiratory disturbance index was 2.1 ± 1.7. The mean alpha EEG arousal index calculated from transient alpha EEG arousals that could not be related to other well-defined sleep disturbances was 31.3 ± 12.4 arousals per hour of sleep (Table 1). Investigation of nocturnal sleep state and stage distribution indicated an abnormally low amount of stages 3 to 4 NREM sleep (mean percentage: 1.2 ± 2 percent). Percentage of REM sleep was 17.6 ± 1.6 percent.

Polysomnographic Monitoring With Pes Measurement (Night 3) in the 15-Subject Subgroup

Mean total sleep time was 473 ± 25 min. The mean peak Pes nadir related to transient alpha EEG arousals was −33 ± 7 cm H₂O. The mean alpha EEG arousal index was 31 ± 9. No increase in CO₂ within the reliability range of the tcPCO₂ electrode was noted in the seven patients monitored with this equipment.

In ten subjects (regular snorers), the behavior of the Pes curve changed from snoring to nonsnoring. When snoring occurred, the nadir of the Pes curve (at the end of inspiration of each respiratory cycle) became more negative. Changes varied with the individual; the mean peak Pes nadir increase from the period just prior to snoring to the snoring period was 108 ± 47 percent.

In the two nonsnoring subjects and the three intermittent snorers, the mean supine quiet wakefulness Pes nadir was −5.1 ± 1 cm H₂O. Peak Pes nadir during sleep just prior to EEG oscillated between −20 and −29 cm H₂O in these five subjects, regardless of whether snoring was present.

Polysomnographic Monitoring With Pneumotachograph (Night 4) in the 15-Subject Subgroup

In the randomly selected segments on which we performed tidal volume calculations, the mean tidal volume 100 breaths before an alpha EEG arousal was 490 ± 96 ml. The breath just prior to the alpha EEG arousal presented a mean tidal volume decrease of 22 ± 6 percent compared with breathing measured during quiet sleep without increase in Pes nadir.

These changes were not progressive throughout the studied periods; they mainly involved the one to three

*Excessive Daytime Sleepiness (Guilleminault et al)
breathe preceding an arousal. Figure 2 presents a polygraphic recording obtained just prior to the transient alpha EEG arousal: the inspiratory Pes nadir is at its maximum during the two breaths just prior to the arousal, and peak flow decreases with an associated drop in tidal volume for these two breaths. This drop did not affect the oxygen saturation curve (pulse oximetry) in any of our patients.

**Therapeutic Trial**

Nasal CPAP was set at a mean of 7±1 cm H2O in this group of 15 subjects. The transient alpha EEG arousal index decreased to 8±2 per hour of sleep during CPAP therapy. Nocturnal sleep monitoring indicated a nonsignificant change in the percentage of REM sleep (18.2±1.6 percent), but a significant increase in the percentage of stages 3 and 4 NREM sleep (9.7±1.9 percent, p<0.0001). Scores in the follow-up MSLT after 1 month of nasal CPAP treatment had a mean of 13.5±2.1 min. This was significantly different from the initial test scores (analysis of variance, p<0.0001). The MSLTs were performed following a nocturnal recording with a mean total sleep time of 399.6±15 min. This polygraphic improvement was associated with the subjective report of disappearance of daytime sleepiness.

**Cephalometric X-ray Results**

All 15 subjects presented a narrow posterior airway space (space behind the base of the tongue). The mean
posterior airway space was 5.3 \pm 1.8 \text{ mm}, compared with a normal mean of 11 \text{ mm}.^{20} \text{ One of the two women without snoring presented cervical malformations, including fusion of C3-C4 and C5-C6.}

**Discussion**

Our study demonstrates that in some cases, isolated daytime sleepiness may be related to an abnormal breathing pattern during sleep, which we have named the “upper airway resistance syndrome.”

This syndrome consists of transient, repetitive alpha EEG arousals that may be as short as 3 s.\textsuperscript{18} These transient arousals lead to sleep fragmentation. While preliminary data\textsuperscript{6,7} have indicated that some snorers exhibit marked sleepiness, our results indicate that snoring does not define patients with the upper airway resistance syndrome. The lowest number of arousals needed to induce a complaint has not yet been determined. Based on a previous study in normal subjects,\textsuperscript{19} we chose ten such arousals per hour of sleep as a cutoff point. We chose this rather conservative number as we did not wish to submit our patients to 3 weeks of nasal CPAP without a solid rationale. Interestingly, 10 arousals per hour was also the upper limit observed after 4 weeks of nasal CPAP treatment in the patients who received this treatment. This group’s baseline scores were much higher (lowest score: 17 per hour of sleep). There was a fair amount of within-subject variation in number of arousals per hour from night to night (maximum variation: five transient alpha arousals per hour of sleep).

These transient arousals have an impact on nocturnal sleep structure. When REM sleep is well defended and maintained at an adequate level, the arousals have a very significant impact on slow-wave sleep (stages 3 to 4 NREM sleep). Although our subjects had a mean age of 37.5 years, their mean percentage of stages 3 to 4 NREM sleep was only 1.2 percent, an abnormal finding probably related to the transient arousals.

These arousals are linked to increased respiratory effort. The 15-subject affected group expended increased inspiratory effort during sleep, indicated by increase in negative esophageal pressure. In most breaths, tidal volume was maintained. However, pneumotachometer/face mask measurements indicated that in the breaths just preceding an arousal, a brief period of reduced airway patency occurred, causing a reduction in tidal volume. An alpha EEG arousal always occurred within three breaths of such a decrease in tidal volume. The arousal interrupted obstructed breathing long before it had the opportunity to affect oxygen saturation. Each short arousal was immediately followed by a decrease in inspiratory efforts (Fig 2).

To confirm that the abnormal upper airway resistance was responsible for the transient arousals, and to try to reverse the problem, we used a well-known device: nasal CPAP. Nasal CPAP is known to create an “airsplint” in patients diagnosed as having obstructive apneas and to eliminate upper airway obstruction during sleep. The use of this equipment brought about a significant decrease in transient alpha EEG arousals, elimination of the clinical complaint, improvement in the nocturnal sleep structure with significant increase in stages 3 to 4 NREM sleep, and improvement in MSLT scores (p<0.001). The changes in MSLT scores following nasal CPAP were similar to those already reported in nonapneic snorers.\textsuperscript{6}

In a recent investigation, we used auditory simulation to reproduce in normal young subjects repetitive, short transient arousals (mean duration: 11 s). Sleep time was extended in the morning to maintain baseline total sleep time. In one night of repetitive transient arousals, stages 3 to 4 NREM sleep during nocturnal sleep were significantly reduced. The MSLT scores the following day were reduced from a mean of 14 min to a mean of 8.5 min. This experimental sleep fragmentation in normal subjects confirmed that transient arousals without sleep deprivation can lead to daytime sleepiness.\textsuperscript{19}

We do not advocate nasal CPAP as a long-term treatment of this syndrome. That our population was shown to have mildly abnormal upper airway anatomy in cephalometric radiographs suggests that other means of treatment, such as surgery, may be considered. Two subjects requested surgery after improvement had been demonstrated with nasal CPAP, but long-term follow-up (12 months postsurgery) has not yet been obtained in either subject. Thus, subjects may receive different treatments for this syndrome. Finally, we would like to emphasize that in our affected population, there were nearly as many women as men, a finding different from that of the obstructive sleep apnea and hypopnea syndromes.\textsuperscript{13,14}

Considering the frequency and impact of unexplained sleepiness, it is important to recognize cases of abnormal upper airway resistance during sleep and to make use of the treatments available. As isolated sleepiness is most often treated by stimulants, it is imperative that this syndrome be singled out. Monitoring of increased respiratory efforts indicated by analysis of the integration of thoracic EMG signals or by monitoring of Pes nadir may help in recognizing this condition. In snorers, identification of increased intensity of snoring before alpha EEG arousals may suggest the syndrome. However, this more “patient friendly” technique is not sufficient, as it produces a significant number of false negatives.\textsuperscript{21}

ACKNOWLEDGMENTS: We thank Laura Wilkinson for her help in manuscript preparation.
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