Nocturnal Hypoxemia as a Determinant of Vigilance Impairment in Sleep Apnea Syndrome*

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In sleep apnea syndrome (SAS), vigilance impairment is typically associated with highly disrupted sleep, but recently, nocturnal hypoxemia has also been identified as a second pathogenetic factor in patients with a high degree of desaturation. However, although sleep disruption has been demonstrated to play a role in both the propensity to fall asleep and the capacity to stay awake, the role of nocturnal hypoxemia has been implicated only in the latter. In the present study, both sleep disruption and nocturnal hypoxemia were assessed in 20 moderately to severely apneic patients. During the day, vigilance was assessed both by the multiple sleep latency test (MSLT), as a measure of the propensity to fall asleep, and by the four-choice reaction time test (FCRTT), as a measure of the capacity to stay awake in a performance task. Severity of nocturnal hypoxemia was found to predict performance on the MSLT, as well as on the FCRTT, but sleep disruption was found to predict performance only on the FCRTT. These results suggest that in moderately to severely affected SAS patients, nocturnal hypoxemia may play a primary role in the pathogenesis of vigilance impairment.

(Chest 1991; 100:367-70)

EDS = excessive daytime sleepiness; FCRTT = four-choice reaction time test; MSLT = multiple sleep latency test; SAS = sleep apnea syndrome

The most common presenting complaint in patients with sleep apnea syndrome (SAS) is the inability to stay awake during the day, at rest, or even when performing tasks. However, although this vigilance impairment has been well documented in these patients, the causes remain controversial. The number of apneas per hour of sleep (sleep apnea index), which is the most common clinical estimate of SAS severity, was considered by some authors to be the best predictor of daytime somnolence,¹,² whereas others did not find such a relationship.³,⁴ This discrepancy between studies may be explained by the ambiguity of the concept of the apnea index as an estimate of SAS severity. Since sleep apnea induces multiple awakenings as well as blood oxygen desaturations, the apnea index could refer to either of these two features. Thus, in some patients who awaken at each apnea, this index may reflect the sleep disruptions, or in others who awaken less frequently but undergo more severe desaturation during the apneas, this index may reflect the nocturnal hypoxemia.

Direct assessment of sleep disruption and nocturnal hypoxemia has provided further information on the etiology of vigilance impairment in SAS. Guilleminault et al⁵ have shown that somnolent patients can be differentiated from nonsomnolent patients by the degree of their sleep disruption, but not by respiratory impairment. Specifically, in their somnolent SAS subjects, rapid eye movement (REM) sleep and slow-wave sleep were decreased while the number of awakenings and the percentage of light sleep (stages 1 and 2) were found to be higher. These authors concluded that daytime sleepiness in SAS results mainly from sleep deprivation. This hypothesis is reinforced by the fact that treated patients show a reduction of daytime sleepiness which closely follows the improvement of their sleep pattern.⁶

On the other hand, the finding by Orr et al⁷ that the apnea index and degree of sleep disorganization did not differ between somnolent and nonsomnolent patients with SAS suggests that other factors may contribute to this symptom. These authors suggest that the severity of nocturnal hypoxemia, because their somnolent patients had lower and longer desaturations during apneas. Findings in a large SAS population⁸ also corroborate the primary role of nocturnal hypoxemia in distinguishing somnolent from nonsomnolent patients. Unfortunately, somnolence was evaluated only by subjective criteria in these studies, and it is well known that verbal reports of daytime sleepiness do not necessarily correspond to objective evaluations of this symptom.¹,³,⁵

Recently, some authors⁹ have investigated the contribution of both sleep disruption and nocturnal hypoxemia in daytime somnolence of SAS, as measured by the four-choice reaction time test (FCRTT).
objectively by the maintenance of wakefulness test. In this test, patients are asked to remain awake for 40 min in a dark quiet room, and somnolence is indexed by the latency to sleep onset. These authors found that in severe SAS, hypoxemia may be the primary pathogenetic factor of sleepiness, although in a milder form of the syndrome, sleep disruption is more determinant. Two pathogenetic factors seem, therefore, to contribute to the vigilance impairment of SAS, and the respective contribution of these two factors appears to depend on the severity of the syndrome. However, although sleep disruption was demonstrated to play a role in both the propensity to fall asleep and the capacity to stay awake, the role of nocturnal hypoxemia was shown only for the latter. Therefore, results obtained with nocturnal hypoxemia in severe SAS cases should be replicated and corroborated with other measures assessing the two aspects of vigilance.

The aim of the present study was to further document the contribution of sleep disruption and nocturnal hypoxemia in a carefully screened sample of patients with moderate to severe SAS, using measures of two different aspects of vigilance: the multiple sleep latency test (MSLT) and the four-choice reaction time test (FCRTT). The former is a measure of daytime sleepiness based on the simple assumption that sleepy subjects, when compared with alert subjects, will fall asleep more quickly during daytime naps. The FCRTT is a sensitive and validated measure of alertness in which subjects are required to maintain a certain level of arousal to perform correctly on a psychomotor task.

**METHODS**

**Patient Population**

Twenty patients with moderate to severe SAS, aged 35 to 65 years, who came to the sleep clinic for excessive daytime sleepiness, were selected for the study. Criteria for inclusion were a sleep apnea index exceeding 10 and a minimum blood oxygen saturation value of 90 percent or lower. Waking PaO₂ and PaCO₂ values were normal for all patients. Thus, in addition to mildly affected SAS patients, we excluded also from the study those who were hypoxic during the day. Other criteria for exclusion were the presence of alcohol or drug abuse, the use of medications that could adversely affect sleep or respiration during sleep, and the presence of other sleep disorders, such as narcolepsy or periodic leg movements in sleep. Informed consent was obtained from all patients participating in the study.

**Nocturnal Recording**

For two consecutive nights, sleep was recorded and scored according to the standard method, with the use of electro-oculography, chin and right and left anterior tibialis electromyography, central and occipital electroencephalography, and electrocardiography. Sleep variables included number of awakenings and number of sleep stage shifts during the total sleep time, and time awake and time in each sleep stage as a percentage of total sleep time.

Respiratory effort, as well as oral and nasal airflow, were measured by thoracoabdominal plethysmography and oronasal thermistor, respectively. An apnea was defined as a total cessation of airflow lasting for at least 10 s. The sleep apnea index was defined as the number of apneas per hour of sleep, excluding the time awake. The SaO₂ during sleep was measured continuously and noninvasively by transcutaneous ear oximetry. Hypoxemia severity was estimated by the minimum SaO₂ value recorded during total sleep time and by the percentage of total sleep time with SaO₂ lower than 90 percent (percent sleep SaO₂ < 90 percent).

**Assessment of Daytime Vigilance**

Excessive daytime sleepiness (EDS) was assessed by the MSLT with nap recordings carried out at 10:00, 12:00, 14:00, 16:00, and 18:00. Naps were terminated at sleep onset (first occurrence of one consecutive minute of stage 1 sleep or 20 seconds of any other stage of sleep) or after 20 minutes if the patient did not fall asleep. The EDS score was calculated as the mean sleep latency over the five naps.

Each nap was preceded by the administration of the FCRTT. This 10-min test consisted of a modified cassette recorder, on which was mounted a square of four light-emitting diode (LED) lamps and a corresponding square of four push buttons. When an LED lamp was illuminated, the patient was required to press the corresponding button as fast and as accurately as possible. After 12 ms, either the same or a different LED lit up according to a random sequence. The test was self-paced and provided no feedback on performance level. Frequencies for good and bad responses were stored on an audiocassette. Variables derived from these responses included the following: (1) reaction time (RT); (2) number of gaps (ie, long latency responses with RT > 1,000 ms); and (3) percentage of errors. Mean scores were computed for these variables over the five administrations of the test during the day. As recommended by Gleville and Wilkinson, three practice sessions of the FCRTT were performed during the previous evening in order to neutralize the learning effect, which can occur in repeated administration of the test.

**Statistical Analysis**

All data were normally distributed with a kurtosis < 1.5 and a skewness < 1.0. Table 1 gives the mean, range, and standard deviations of each variable. Power analysis with a confidence interval

<table>
<thead>
<tr>
<th>Table 1—Descriptive Information for the Whole Sample (n = 20)</th>
<th>Mean (SD)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>51.9 (8.9)</td>
<td>35-65</td>
</tr>
<tr>
<td>Body mass index</td>
<td>32.9 (6.1)</td>
<td>25.6-50.1</td>
</tr>
<tr>
<td>P0₂</td>
<td>76.2 (7.4)</td>
<td>66-90</td>
</tr>
<tr>
<td>Pco₂</td>
<td>38.4 (2.7)</td>
<td>35-42</td>
</tr>
<tr>
<td>Minimum SaO₂</td>
<td>67.4 (13.5)</td>
<td>44-80</td>
</tr>
<tr>
<td>% Sleep SaO₂&lt;90%</td>
<td>36.1 (33.3)</td>
<td>1.6-89.5</td>
</tr>
<tr>
<td>Apnea index</td>
<td>44.9 (26.5)</td>
<td>14.4-84.4</td>
</tr>
<tr>
<td>MSLT, min</td>
<td>5.6 (3.2)</td>
<td>0.5-12.4</td>
</tr>
<tr>
<td>FCRTT</td>
<td>615.9 (183.5)</td>
<td>400-1018</td>
</tr>
<tr>
<td>No. of gaps</td>
<td>46.3 (44.9)</td>
<td>2.6-153.2</td>
</tr>
<tr>
<td>Errors, %</td>
<td>3.8 (3.5)</td>
<td>0.2-12.5</td>
</tr>
<tr>
<td>No. of awakenings</td>
<td>48.3 (36.7)</td>
<td>6-161</td>
</tr>
<tr>
<td>No. of stage shifts</td>
<td>287.6 (105.7)</td>
<td>63-521</td>
</tr>
<tr>
<td>Wake time in sleep, %</td>
<td>10.5 (6.6)</td>
<td>0.4-23.9</td>
</tr>
<tr>
<td>Stage 1, %</td>
<td>23.2 (11.1)</td>
<td>9.4-55.3</td>
</tr>
<tr>
<td>Stage 2, %</td>
<td>61.2 (12.2)</td>
<td>33.3-84.6</td>
</tr>
<tr>
<td>Slow-wave sleep, %</td>
<td>4.2 (4.5)</td>
<td>0.0-17.0</td>
</tr>
<tr>
<td>REM, %</td>
<td>11.3 (4.6)</td>
<td>3.9-20.7</td>
</tr>
</tbody>
</table>
of 95 percent indicated that sample size was sufficiently large for all variables, with the exception of the percentage of time spent in each of the four sleep stages. Matrix of this power analysis, with the maximum differences tolerated between μ and X, is available on request to authors. Therefore, these four sleep variables were not included in subsequent analyses. The two measures of vigilance were correlated with measures of sleep disruption and nocturnal hypoxemia, using Pearson correlations. In addition, multiple stepwise regression analyses were computed, using sleep disruption and nocturnal hypoxemia as independent variables and the two measures of vigilance as dependent variables. These multiple regressions were performed separately for MSLT and FCRTT to independently investigate the factor of daytime sleepiness and daytime alertness, respectively.

RESULTS

Table 1 gives descriptive information for the entire sample. Respiratory measures during sleep clearly showed the presence of moderate to extremely severe SAS, with the sleep apnea index reaching 84 in the most severe case, and the minimum SaO₂ value, as well as the percent sleep SaO₂<90 percent showing the presence of nocturnal hypoxemia. Sleep disruption in these patients consisted of a high percentage of wake time and time spent in light (stage 1 and 2 non-REM) sleep, and a low percentage of slow-wave (stage 3 and 4 non-REM) sleep and REM sleep.

Results from the MSLT indicated an overall presence of daytime sleepiness. The FCRTT showed abnormally low RT scores and a very high number of gaps. However, the mean percentage of errors during the FCRTT was normal.

Pearson correlations (Table 2) revealed that measures of hypoxemia severity were significantly correlated with results of the MSLT and FCRTT. Specifically, the minimum SaO₂ value showed the largest correlation with both measures of vigilance. The apnea index was correlated with the level of alertness (FCRTT) but was not correlated with sleepiness (MSLT). Indices of sleep disruption, especially wake time and number of awakenings, were also statistically correlated with the FCRTT RT scores, but not with the MSLT.

Because hypoxemia measures and sleep variables were also highly intercorrelated, a multiple stepwise regression analysis was performed to find the best combination of hypoxemia and sleep variables that may explain the vigilance scores. For FCRTT RT scores, respiratory and sleep variables explained 66 percent of the variance (p<0.05) according to the equation: FCRTT RT = 1.14 - 0.89 (minimum SaO₂ value) + 0.16 (number of awakenings). However, for MSLT scores, the minimum SaO₂ value alone accounted for 30 percent of the variance (p<0.05), according to the equation: MSLT = -2.95 + 0.13 (minimum SaO₂ value). No other oximetry or sleep variables contributed significantly to daytime vigilance as assessed by the MSLT.

DISCUSSION

Results of the present study showed that in moderate to severe SAS, measures of hypoxemia were the best predictors of both daytime alertness (FCRTT) and sleepiness (MSLT). Moreover, FCRTT can be predicted, in part, by nocturnal sleep disturbance, especially by the number of awakenings. The MSLT, however, is not significantly correlated with nocturnal sleep disruption. This last result seems to contradict the results of other studies that have shown a strong relationship between daytime sleepiness and nighttime sleep disruption. However, the latter studies were performed in patients with low to moderate hypoxemia during the night. Therefore, as already suggested by others, it is possible that in mildly hypoxic SAS, daytime sleepiness is explained primarily by the number of arousals during sleep, while in more hypoxic SAS patients, the contribution of sleep is overwhelmed by the severity of hypoxemia.

From a different perspective, many studies have shown that effective treatment of SAS both normalizes sleep architecture and significantly improves daytime vigilance. This suggests that sleep disruption during the night may be the primary pathogenetic factor in vigilance impairment during the day. However, one may argue that some degree of somnolence remained even after treatment, since normalization of sleep does not necessarily restore a normal level of vigilance. Such a persistent vigilance impairment may indicate irreversible damage to the structures which regulate the level of vigilance. Permanent anoxic brain damage should, therefore, be suspected, especially in the more severe cases of SAS.

Many studies suggest an anoxic brainstem dysfunction in SAS patients. First, oxygen consumption and cerebral blood flow have been found to be abnormally low in all cerebral structures investigated during sleep in SAS. This lowering occurs more severely in the brainstem-cerebellar area, a characteristic that persists even after treatment. Second, brainstem dysfunction is suggested by the abnormal short-latency auditory evoked potentials that have been found in
patients with SAS.\textsuperscript{22,23} Finally, abnormal cerebral vascular responses to CO\textsubscript{2} have been shown in patients with SAS.\textsuperscript{24,25} Considering the anatomic proximity of respiratory centers, neural structures controlling vigilance, and auditory relays in the brainstem, the impairments described by these studies may all reflect the presence of a localized brainstem hypoxia-induced insult. In this respect, it is noteworthy that in the present study, the minimum SaO\textsubscript{2} value during sleep remained by far the best predictor of vigilance impairment. This measure of hypoxemia may, in fact, indicate a degree of brainstem dysfunction, because it reflects decreased sensitivity of brainstem respiratory centers to hypoxic stimuli.

In summary, vigilance impairment in moderate to severe SAS patients seems to be affected by both nocturnal hypoxemia and sleep disruption. Daytime alertness, as measured by a psychomotor task (FCRRTT), was found to be sensitive to both of these pathogenetic factors. However, sleepiness (MSLT) in these patients was related only to hypoxic variables. Therefore, although both sleep disruptions and nocturnal hypoxemia seem to play a role in vigilance impairment of SAS, hypoxemia may play a greater role in the most severe cases.

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