Intracranial Hemodynamics in Sleep Apnea

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Intracranial pressure changes and poor cerebral perfusion have been reported in sleep apnea syndrome (SAS), but such studies have been limited due to lack of a reliable noninvasive study method. We determined the systolic (Vs), diastolic (Vd), and mean (Vm) cerebral blood flow velocities of the middle cerebral artery in 23 individuals (12 severe SAS patients and 11 control subjects) using transcranial Doppler sonography before sleep, during sleep (NREM and REM) and upon awakening. All three velocities (Vs = 87.4 cm/s compared to 104.7 cm/s, Vd = 41.6 cm/s compared to 47.7 cm/s, and Vm = 57.0 cm/s compared to 67.0 cm/s) were decreased in patients with SAS and Vs and Vm were significantly lower than in control subjects (p = 0.005 and p = 0.033, respectively). The end-tidal CO2 (PetCO2) in the SAS patients (47.3 mm Hg) compared to the control subjects (41.8 mm Hg) was significantly higher (p = 0.003). When the Vm was adjusted to normalized CO2 using the Markwalder’s equation, the reduction in velocity in patients with SAS (47.5 cm/s) compared to control subjects (63.0 cm/s) became more significant (p = 0.005). This study shows that cerebral blood flow velocities are lower in patients with SAS compared to control subjects and that transcranial Doppler sonography may be useful in such evaluations.

Obstructive sleep apnea syndrome (SAS) is characterized by daytime hypersomnolence, nocturnal snoring, obesity and frequent cessation of breathing during sleep. Neurologic problems in SAS patients include lethargy, cognitive impairment, poor memory, and high risk for cerebral infarction. The pathogenesis of the neurologic abnormalities is incompletely understood. After treatment for sleep apnea, these patients experience increased awareness and improved cognitive performance.

Patients with SAS experience recurrent and severe changes in blood pressure, intracranial pressure and cardiac output and become hypercarbic and hypoxic. The effect of such changes on cerebral hemodynamics in SAS patients is uncertain. Noninvasive, reliable and reproducible techniques such as transcranial Doppler sonography (TCD) are now available for the study of intracranial blood flow velocities (BFV) and their response to chemo-stimuli. As TCD is noninvasive, BFVs can be evaluated during the awake and sleep states without disturbing the polysomnographic procedure. A single reported TCD study done on one patient with SAS showed marked fluctuations of the blood flow velocities in the apneic periods during sleep. However, there have been no published studies of TCD evaluation of SAS patients comparing awake and sleep states.

We report the results of TCD studies performed by

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BFV = blood flow velocity; SAS = sleep apnea syndrome; TCD = transcranial Doppler sonography; VD = diastolic velocity; Vm = mean velocity; Vs = systolic velocity

PATIENTS AND METHODS

Twenty-three individuals, ages 24-69, from the Medical College of Georgia Sleep Disorders Center participated in this study. There were 12 SAS patients (mean age 40.5 ± 11.3 years) and 11 controls (mean age 37.1 ± 3.2 years). The controls were chosen from those individuals who had negative polysomnogram results. Individuals with a history of stroke, papilledema, anemia, or existing cerebrovascular abnormality were excluded from the study. No individual included in the study had any clinical indication for brain imaging.

End tidal CO2 (PetCO2) measurements were made using an end tidal CO2 analyzer (Engstrom-Lisa MO) and hemoglobin oxygen saturation levels using a pulse oximeter (Nellcor). Eight-hour polysomnographic evaluation was performed with a multi-channel polygraph (Nicolet) and Respitrace system using standard methods. During the polysomnogram, the electroencephalogram, electrooculogram, electrocardiogram, electromyogram of the chin and leg, oronasal airflow, and movements of the chest and abdomen were monitored. Analysis of data included sleep stages and total number of apneas and apneas per sleep hour (apnea index). Obstructive apneas were defined by continuation of chest and abdominal movements during cessation of airflow for more than 10 s.

Data were collected for each patient in four states: before sleep, during non-REM sleep, REM sleep, and after sleep. The first TCD examination was done by measuring the blood flow velocity (BFV) of the middle cerebral artery (MCA) through the temporal window using standard methods. The systolic (Vs), end diastolic (Vd), and mean (Vm) blood flow velocities (BFV) were recorded on hard copy. The Vm was computed by the equipment using standard methods. During polysomnography, recordings were made using the TCD headband monitoring system. The BFVs were measured from the right MCA during non-REM (stage 2 or 4) and REM sleep during normal respirations. In the morning, at the completion of the polysomnographic study, a repeat TCD examination was done.

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RESULTS

Since not all patients and control subjects went through all stages of sleep, we had a total of 75 TCD measurements. There were 40 TCD measurements in 12 SAS patients (before sleep 12, NREM 10, REM 7, and after sleep 11) and 35 measurements in 11 control subjects (before sleep 11, NREM 9, REM 4, and after sleep 11).

The blood flow velocities during various sleep states of patients with severe SAS compared to control subjects are shown in Table 1. Each of the parameters of the measured blood flow velocities, \( v_s \), \( V_D \), and \( V_M \), were reduced in patients with severe SAS, when compared to control subjects throughout the awake and sleep states. The \( V_M \) is considered to be the closest reflection of the mean blood flow going through a segment of a vessel at any one time. The total \( V_s \) and \( V_M \) were both significantly reduced (p = 0.005 and p = 0.03, respectively) at all times. The measurements of the \( V_M \) in severe SAS followed the pattern of the control subjects through different stages of sleep and wakefulness, however, at a significantly lower level.

The \( P_{ECO2} \) was high in SAS patients compared to controls (Table 2). The \( P_{ECO2} \) in the patients with severe SAS remained significantly higher than in the control subjects throughout sleep and awake states. Using Markwalder's equation, the \( V_M \) of both SAS and control group were adjusted to a \( CO_2 \) of 40 mm Hg, and the results are shown in Figure 1. The difference in \( V_M \) in SAS patients compared to control subjects became even more significant after eliminating the effect of changes in the \( P_{ECO2} \) (p = 0.005).

DISCUSSION

The technical method of using TCD for the evaluation of BFVs of intracranial vessels, specifically the middle cerebral artery (MCA), has been well established. Even though the clinical utility of TCD has been successfully demonstrated in cerebrovascular disturbances such as vasospasm from subarachnoid hemorrhage, stroke, cerebral vasculopathies, and increased intracranial pressure, it has not been used in the clinical evaluation of sleep disturbances. The successful use of TCD in the evaluation of normal sleep and a limited examination of a single patient with SAS introduced the possibility of using TCD as a clinically related investigative tool for the evaluation of the intracranial hemodynamics of SAS patients.

Almost all of the previous studies examining cerebral blood flow in SAS patients and normal sleep have been volume measurements using radioactive tracers (xenon 133). Such studies are not conducive to dynamic monitoring nor are they used as routine clinical tools. We chose TCD to examine the intracranial hemodynamics in SAS patients because this is a clinically relevant and technically well established test which can be reproduced reliably.

Of all the BFVs studied using TCD (\( V_s \), \( V_D \), and \( V_M \)), the \( V_M \) most closely reflects the qualitative changes occurring in cerebral blood flow and may serve as an index of flow without being an absolute measure of cerebral blood flow. When the \( V_M \) is adjusted to normative \( CO_2 \) using Markwalder's equation, the \( V_M \) correlates even closer as an index of CBF.

Our study assessed the changes in BFV using TCD in patients with severe SAS and compared them to age-matched individuals in a similar environment during the stages of sleep and on awakening. The major physiologic variables which impact on the BFVs

**Table 1—Systolic, Mean, and Diastolic Velocities (Mean ± SE) Before (BS), during (NREM, REM), and After Sleep (AS) in SAS and Control Subjects**

<table>
<thead>
<tr>
<th></th>
<th>( V_s ) cm/s</th>
<th>( V_D ) cm/s</th>
<th>( V_M ) cm/s</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SAS</td>
<td>Control</td>
<td>SAS</td>
</tr>
<tr>
<td>BS</td>
<td>103.5 ± 11.6</td>
<td>48.3 ± 5.0</td>
<td>66.0 ± 3.0</td>
</tr>
<tr>
<td>±7.3</td>
<td>±7.6</td>
<td>±4.0</td>
<td>±5.1</td>
</tr>
<tr>
<td>NREM</td>
<td>51.0 ± 101.8</td>
<td>36.0 ± 42.7</td>
<td>54.8 ± 60.9</td>
</tr>
<tr>
<td>±6.8</td>
<td>±8.0</td>
<td>±6.6</td>
<td>±7.5</td>
</tr>
<tr>
<td>REM</td>
<td>69.9 ± 95.0</td>
<td>36.5 ± 46.5</td>
<td>43.7 ± 60.0</td>
</tr>
<tr>
<td>±7.4</td>
<td>±15.1</td>
<td>±5.0</td>
<td>±5.3</td>
</tr>
<tr>
<td>AS</td>
<td>86.9 ± 99.6</td>
<td>42.7 ± 45.8</td>
<td>57.5 ± 67.6</td>
</tr>
<tr>
<td>±8.1</td>
<td>±8.5</td>
<td>±4.7</td>
<td>±5.9</td>
</tr>
<tr>
<td>Weighted average</td>
<td>87.4 ± 104.7</td>
<td>41.6 ± 47.7</td>
<td>57.0 ± 67.0</td>
</tr>
<tr>
<td>p value*</td>
<td>0.005†</td>
<td>0.008†</td>
<td>0.033†</td>
</tr>
</tbody>
</table>

*Significant at p < 0.05.
†Control > SAS.

**Table 2—\( P_{ECO2} \) (Mean ± SE mm Hg) in SAS and Control Subjects**

<table>
<thead>
<tr>
<th>Stage</th>
<th>SAS</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>BS</td>
<td>48.6 ± 1.8</td>
<td>43.9 ± 1.3</td>
</tr>
<tr>
<td>NREM</td>
<td>50.8 ± 3.9</td>
<td>39.3 ± 2.1</td>
</tr>
<tr>
<td>REM</td>
<td>46.7 ± 4.8</td>
<td>42.5 ± 2.1</td>
</tr>
<tr>
<td>AS</td>
<td>43.4 ± 1.0</td>
<td>41.8 ± 2.1</td>
</tr>
<tr>
<td>Overall Mean</td>
<td>47.3</td>
<td>41.8</td>
</tr>
</tbody>
</table>

*SAS > Control = p < .005. BS = before sleep; AS = after sleep; NREM = non-rapid eye movement; REM = rapid eye movement.
such as age, hematocrit, and CO\textsubscript{2} were taken into account for the interpretation of these study data.\textsuperscript{27} Age and hematocrit were controlled by age matching and none of the patients was anemic. The P\textsubscript{ETCO\textsubscript{2}} was documented with each TCD recording.

Results of this study reveal two new aspects: (1) that the BFVs of the patients with SAS are reduced at all times during sleep as well as during wakefulness when compared to control subjects (Table 1), (2) that if the CO\textsubscript{2} effect is removed or normalized, the reduction of BFVs in SAS patients persists (Fig 1).

The major neurologic effects reported in SAS patients are cognitive,\textsuperscript{28} although stroke has been described in patients with SAS.\textsuperscript{29,30} Measurements of BFV with TCD during cognitive activity reveal an increase in VM in the areas from which the cognitive function is being generated.\textsuperscript{31} It is possible that the decreased VM measured by TCD (in our study) and decreased cerebral blood flow reported by invasive methods\textsuperscript{32,33} in patients with SAS compared to normal individuals may be a contributing factor for depressed brain activity. This decrease in CBF and BFVs may be reflected as excessive daytime somnolence and cognitive lethargy classically described in patients with SAS.\textsuperscript{3}

Sleep is a complex physiologic state. The most accepted division of sleep into stages is NREM and REM, based on polysomnographic data.\textsuperscript{34} In this study, the VM of the SAS patients followed the pattern of the changes occurring during NREM, REM and awakening in controls, but at a significantly reduced level.

The normal response of the brain vasculature, when exposed to high levels of P\textsubscript{CO\textsubscript{2}}, is to increase VM. This is considered to be a function of intact autoregulation.\textsuperscript{12,33} In our study, the most dramatic change occurred in SAS patients during REM when VM decreased (43.7 cm/s compared to the usual values of 60-80 cm/s)\textsuperscript{9} despite higher P\textsubscript{ETCO\textsubscript{2}} levels. In previously reported CBF volume studies in sleep apnea patients, CBF has also been noted to be decreased during REM by 35-43 percent of awake levels.\textsuperscript{32} The reason for this decrease in CBF during REM in SAS patients has not been elucidated; however, it has been postulated that the rejuvenating metabolic activity, reflected as an increase in CBF in normal individuals and in animals during REM\textsuperscript{34,35} may be lacking in patients with SAS.

During REM in normal individuals, blood flow (volume) increases compared to NREM. In our study using TCD, the number of normal individuals studied during REM is small and there is no appreciable change in VM (velocity) between NREM and REM. However, when the P\textsubscript{ETCO\textsubscript{2}} effect is normalized in control subjects, the adjusted VM appears to decrease slightly. It is not completely apparent whether this decrease in adjusted VM during REM is a new finding since there have been no previous studies describing BFVs with adjustment of VM by normalizing the CO\textsubscript{2} effect. Larger studies on normal individuals using TCD during sleep will answer this question satisfactorily.

Two questions arise from the results of our study. Why are the BFVs decreased in the face of a high P\textsubscript{ETCO\textsubscript{2}}, and what is the significance of reduced blood flow velocities? Blood flow velocity can decrease at the MCA stem for two reasons: either the stem itself has dilated and is thus slowing the VM through a vessel whose caliber has increased, or a widely dilated small vessel bed distally may slow down the VM. A combination of both factors may be operational in patients with SAS. Increased intracranial pressure (ICP) has been reported in patients with SAS\textsuperscript{36} and may effect BFVs. The first effect of increased ICP would be that the Vs would increase against resistance, but the Vd would decrease without appreciable changes in the VM which is not seen in our patients.\textsuperscript{37} Another factor may be a reduction in venous return; however, changes in cerebral venous return have not been studied.

The changes in intracranial hemodynamics during sleep that have been reported in previous animal and human evaluations of cerebral blood flow using xenon blood flow inhalation methods\textsuperscript{38-40} are similar to
our study using TCD even though the methodologies as well as the parameters of measurements are different. A decrease in CBF velocity has been shown in the common carotid artery with carotid duplex Doppler sonogram during apneic spells in patients with SAS.\(^9\) Using the TCD in our study, we extended this interrogation of BFVs to the intracranial vessels. The clinical significance of reduced BFVs has been reported in some neurologic diseases.\(^{16}\) In SAS, its correlation with the clinical symptomatology of cognitive depression and occurrence of stroke in SAS patients can potentially be studied by TCD in a larger study.

Until now, the studies assessing cerebral blood flow have been volumetric, invasive, and technically cumbersome and have, therefore, not found wide acceptance as a clinical tool in sleep disorders. TCD, on the other hand, is a clinically accepted tool widely used in a variety of neurologic disorders,\(^{10}\) but has not been routinely used for the clinical study of sleep disorders. This study provides a clinical method of assessing the hemodynamic disturbances in SAS. Although this is a small case series, it demonstrates a significant reduction of CBFV in SAS patients, whether they are awake or asleep, thus opening a realm of possibilities for further research in cerebrovascular hemodynamics of sleep disorders with a clinically relevant tool.

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