Intracranial Pressure and Obstructive Sleep Apnea

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In order to describe variation in AP and ICP during OSA, six patients with severe OSA were examined, with determination of ICP, AP, CVP, respiration, tcPO2, tcPCO2, and nocturnal sleep polygraphy. During apnea, elevations of AP and ICP were observed, related to the apneic episodes. The elevations in pressure were only observed in relation to apneic episodes. While awake, none of the patients showed pressure elevations. There were highly significant correlations between duration of apnea and variation in AP and ICP and between variations in AP and ICP. Values for ICP while awake were above normal (>15 mm Hg; intracranial hypertension) in four of six patients. Morning ICP was higher than evening ICP. Systolic, mean, and diastolic ICP and AP increased during sleep above awake values. The ICP increased during NREM stages 1 to 4, and the highest values were observed during REM sleep. Vascular response was not changed during REM sleep, and the higher ICP during REM could solely be explained by the longer apneas during REM sleep. The CPP decreased during apnea.

Since its description in 1965 by Gastaut et al., OSA has been widely recognized as a clinical entity consisting of excessive daytime sleepiness, loud irregular snoring, obesity, dementia, and headache, especially morning headache. A central element in the pathogenesis of the condition is the upper-airway closure induced by sleep, giving rise to sleep apnea, increasing inspiratory efforts, hypoxic and hypercapnic episodes, and variations in intrathoracic and arterial pressures.

High blood pressure, complaints of headaches, and dementia are prevalent in patients with severe sleep apnea. Although the cerebrovascular hemodynamics are known to be of major importance in the regulation of the AP, very little is still known about the cerebrovascular hemodynamics and regulation during sleep apnea.

Hypercapnia and hypoxia are known to influence cerebrovascular hemodynamics by increasing ICP because of cerebral vasodilatation. It was therefore supposed that ICP might increase during apnea related to sleep. In order to test this hypothesis and to describe the relation between ICP, AP, and CVP, the present study was performed.

Materials and Methods

Six patients were selected by the following criteria: (1) mean number of apneas (apnea index) more than 40 apneas per hour; (2) mean duration of apnea longer than 20 seconds; (3) only OSA; (4) no medication taken; (5) normal findings on neurologic examination; and (6) a normal CT of the brain. Sleep was analyzed by use of central and occipital electrodes (C3, C4, O1, and O2), EOG, and chin EMG. Sleep scoring was performed according to standard methods.

Respiration was measured by inductive plethysmography (Respitrace Corp.). Obstructive apnea was determined by observations of paradoxic movements in the thoracic and abdominal band.

The tcPO2 and tcPCO2 were measured in the supraclavicular fossa (by use of Radiometer TCM 2 and 20, respectively). A 1.2-mm catheter was placed in the radial artery in the nondominant hand after ensuring sufficient circulation in the ulnar artery. A catheter was placed in the superior central vein via the brachial vein. Correct localization was ensured by a normal pressure curve for CVP. An epidural pressure sensor (Plastimed) was placed in the right frontal region and was connected to a pressure transducer (AE 840).

Parametric statistics were used (linear regression analysis and t-test). A value below 0.05 was considered significant (two-sided test). The statistics were computed on the SPSS-PC+ program (SPSS Inc.).

The study was registered and accepted by the central university ethical committee. All participants gave written informed consent.

Results

The patients' clinical data are given in Table 1. The body mass index and blood pressure were slightly above normal for all participants. No patient showed signs of papilledema by ophthalmoscopy.

The CT of the brain was normal in all patients, without atrophy, peri-ventricular edema, or dilation of the ventricular system. While patients were awake,

<table>
<thead>
<tr>
<th>Table 1 — Clinical Data of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient, Sex, Age, yr</td>
</tr>
<tr>
<td>------------------------</td>
</tr>
<tr>
<td>1, M, 43</td>
</tr>
<tr>
<td>2, M, 42</td>
</tr>
<tr>
<td>3, M, 43</td>
</tr>
<tr>
<td>4, M, 52</td>
</tr>
<tr>
<td>5, F, 44</td>
</tr>
<tr>
<td>6, M, 68</td>
</tr>
</tbody>
</table>

*Apneas per hour (apnea = respiratory arrest > ten seconds).

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the ICP was elevated (>15 mm Hg) and significantly higher in the morning than in the evening (20.7 ± 0.8 mm Hg vs 17.7 ± 0.5 mm Hg; p<0.02 by paired t-test) (Table 1).

The mean number of apneic episodes included for analysis were 309 observations (range, 168 to 409). During sleep, especially NREM stages 2 and 3 and REM sleep, the ICP increased, exceeding values while awake. No NREM sleep stage 4 was observed in any of the patients.

While asleep, all patients developed ICP elevation associated with the episodes of OSA (Fig 1). These pressure elevations were seen synchronously with the apneas, with a frequency from one to two pressure elevations per minute, thereby fulfilling the criteria for intracranial B waves. While the patients were awake, no ICP waves were observed in any of the patients.

Several phases could be described in the AP and ICP variations. In the beginning of the apnea, there was a decrease in AP and ICP. During the apnea, ICP increased, associated with decreasing tcPo2 and increasing tcPaco2. At the termination of the apnea, there was a steep pressure increase, both in the AP and in the ICP, while CVP varied associated with the respiratory movements.

Table 2—Regression Lines and Correlation Coefficients for All Six Patients for the Association between Apnea Duration and Systolic AP Elevations during Apnea

<table>
<thead>
<tr>
<th>Case</th>
<th>Regression Line</th>
<th>Correlation</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.726x + 10.2*</td>
<td>0.74</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>2</td>
<td>0.684x + 15.4</td>
<td>0.65</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>3</td>
<td>0.637x + 25.2</td>
<td>0.57</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>4</td>
<td>2.375x + 20.1</td>
<td>0.61</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>5</td>
<td>1.157x + 45.2</td>
<td>0.60</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>6</td>
<td>0.894x + 23.4</td>
<td>0.73</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Beta-coefficient in regression line (a*x + β) is arbitrary value, representing intercept on Y axis in relative ICP variations during apnea.
In all patients, there was a highly significant correlation between the duration of apnea and systolic AP variations (Fig 2 and Table 2), between the duration of apnea and systolic ICP variations (Fig 3 and Table 3), and between systolic AP and ICP elevations. The same correlation was observed for diastolic AP and ICP. The correlations were significant ($p < 0.0001$) for all patients, but the slopes of the apnea-AP curve and of the apnea-ICP curve were different between the patients (Tables 2 and 3). There was a significant association between the slope of the AP variations and the slope of ICP variations during the apneas ($r = 0.89; p < 0.02$).

Maximum diastolic and systolic AP and ICP elevations were significantly higher during NREM sleep stage 1 to NREM stages 2 to 3 and highest during REM sleep (Fig 4 and 5) ($p < 0.0001$; paired t-test). Minimum systolic AP decreased during NREM stages 1 to 3 ($p < 0.01$) and increased to the awake value during REM sleep. Minimum diastolic ICP did not change during NREM sleep but increased during REM sleep.

Although AP decreased during apnea, while ICP was unchanged or increased, the CPP (CPP = AP - ICP) decreased (maximum $d[CPP] = -11.2 \pm 7.8$ mm Hg from baseline; $p < 0.001$) during the apnea.

Rapid-eye-movement sleep was associated with longer apnea and greater pressure variations; however, the slopes of the apnea-AP and apnea-ICP curves were not significantly different during REM sleep than NREM sleep, indicating that REM was not associated with changes in distensibility in the arterial or cerebrovascular system.

**DISCUSSION**

The present study has shown (1) that awake values for ICP are pathologically elevated in patients with severe OSA, (2) that the ICP increases further during sleep, especially NREM stages 2 to 3 and REM sleep related to the apneic episodes, and (3) strong correlations between durations of apnea and AP and ICP elevations and between AP variations and ICP elevations.

Elevations in ICP related to respiration, especially Cheyne-Stokes respiration, are well known. Elevations in ICP during OSA have been described by Sugita et al. The CSF pressure was measured via a lumbar cannula in two patients. In this study, significant associations between apnea, hypoxia, and CSF pressure were found; however, AP was not measured.

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**Table 3—Regression Lines and Correlation Coefficients for All Six Patients for Association between Apnea Duration and Systolic CP Elevations during Apnea**

<table>
<thead>
<tr>
<th>Case</th>
<th>Regression Line</th>
<th>Correlation</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$0.7882x + 8.015^*$</td>
<td>0.62</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>2</td>
<td>$0.6471x + 8.203$</td>
<td>0.61</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>3</td>
<td>$0.5592x + 7.068$</td>
<td>0.59</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>4</td>
<td>$1.176x + 9.756$</td>
<td>0.76</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>5</td>
<td>$1.012x + 8.372$</td>
<td>0.58</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>6</td>
<td>$0.965x + 7.059$</td>
<td>0.81</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Beta coefficient in regression line ($\alpha x + \beta$) is arbitrary value, representing intercept on Y axis in relative ICP variations during apnea.
During apnea, at least three phases can be distinguished in ICP: an initial decrease, a slow increase, and a steep increase in ICP. The observed slow increase in ICP during the apnea, associated with hypercapnia and hypoxia, indicates that carbon dioxide retention and hypoxia play a role for the initial ICP increase, possibly due to cerebral vasodilation; however, the steep increase in ICP that terminates the apneic episodes cannot be explained solely as induced by cerebral hypoxia or hypercapnia, but is possibly related to the steep simultaneous increase in the AP and central venous pressure, thereby increasing ICP (Fig 1).

Different mechanisms are suggested as important in developing the AP variations during apnea: the Müller maneuver; pulmonary blood pool affecting cardiac stroke volume (Starling mechanism); baroreceptor reflexes, hypercapnia, and hypoxia causing increased peripheral sympathetic outflow; increased TPR; and increased intrathoracic pressure at the termination of the apnea due to increased ventilation.5-9

Elevations in ICP, hypoxia, and hypercapnia have been found to give rise to increased AP due to increased sympathetic activity.10-13 The ICP elevations during apnea should increase sympathetic output and TPR; however, as far as we know, no study has measured TPR during apnea. Some studies have found increased sympathetic activity in patients with apnea, but this has not been found in other studies.14-18

Hypercapnia and hypoxia increase ICP, due to a cerebral arterial vasodilation, decreasing cerebral resistance, and increasing CBF.10,11 We found a decrease in the CPP during apnea. Loeppky et al.19 found an abnormal cerebrovascular response to carbon dioxide in awake patients with sleep apnea. It is therefore not known whether CBF decreases (due to decreasing stroke volume6,12), increases (due to decreasing cerebral resistance), or remains unchanged during the apneic episode. If CBF is affected during the apnea, then the cerebral autoregulation is overcome.

If CBF ceases during apnea, this might even worsen the cerebral hypoxia developing during the apneic episodes. In our opinion, this is of major importance and should be determined in future studies in order to understand the cerebral consequences of sleep apnea.

Awake ICP was found to be elevated in these patients. Awake values for Po2 and PCO2 were normal. None of the patients had any known cause for the increased ICP evaluated by the CT scan, and only one patient had hypertension (>160/95 mm Hg). None of the patients showed any signs of hypertensive encephalopathy; however, repetitive ICP and CBF variations are assumed to dispose to increased ICP.11 This assumption is supported by the finding that ICP was higher in the morning.

The ICP pressure waves observed in these patients are characterized as pressure elevations following the apneic episodes, with an occurrence of one to three per minute, and this fulfills the definition of "B waves." The ICP elevations during REM sleep can be included in the definition of ICP A waves. Symon et al.20 noted that A waves occurred during REM sleep. The findings in this study point out that the ICP elevations during REM sleep are due the longer apneic episodes in this
sleep stage and thereby ICP elevations giving rise to ICP A waves.

The awake and sleep apnea-related ICP elevations may be of importance in understanding the cerebral symptoms in patients with sleep apnea, especially the headaches and cognitive impairment which are prevalent in patients with sleep apnea.

In epidemiologic studies, snorers have been found to have an increased prevalence of cardiovascular complications. The ICP, CPP, and the possible changes in CBF during apnea indicate that one of the major risks for patients with sleep apnea is cerebral ischemia. This assumption is supported by the finding that snorers have a higher incidence of strokes.

Little is still known about the natural history of OSA, but the findings in this study indicate that one of the major risks in OSA is cerebrovascular complications. Moreover, in patients with B waves and A waves in the ICP during sleep, OSA should be considered.

References
15. Fletcher E, Miller J, Schaaf J, Fletcher JC. Urinary catecholamines before and after tracheostomy in obstructive sleep apnea an hypertension. Sleep 1987; 10:35-44
17. Vitiello MV, Ralph DD, Vieth RC, Frommlet M, Printz PN. Sleep apnea, REM sleep and night hypoxia are associated with elevated plasma norepinephrine levels. Gerontologist 1985; 25:119