Impaired cerebral autoregulation in obstructive sleep apnea

Fred Urbano,1,3 Francoise Roux,1 Joseph Schindler,2 and Vahid Mohsenin1,3

1Yale Center for Sleep Medicine, Department of Medicine, 2Department of Neurology, and 3John B. Pierce Foundation Laboratory, Yale University School of Medicine New Haven, Connecticut

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Urbano F, Roux F, Schindler J, Mohsenin V. Impaired cerebral autoregulation in obstructive sleep apnea. J Appl Physiol 105: 1852–1857, 2008. First published October 16, 2008; doi:10.1152/japplphysiol.90900.2008.—Obstructive sleep apnea (OSA) increases the risk of stroke independent of known vascular and metabolic risk factors. Although patients with OSA have higher prevalence of hypertension and evidence of hypercoagulability, the mechanism of this increased risk is unknown. Obstructive apnea events are associated with surges in blood pressure, hypercapnia, and fluctuations in cerebral blood flow. These perturbations can adversely affect the cerebral circulation. We hypothesized that patients with OSA have impaired cerebral autoregulation, which may contribute to the increased risk of cerebral ischemia and stroke. We examined cerebral autoregulation in patients with and without OSA by measuring cerebral artery blood flow velocity (CBFV) by using transcranial Doppler ultrasound and arterial blood pressure using finger pulse photoplethysmography during orthostatic hypotension and recovery as well as during 5% CO2 inhalation. Cerebral vascular conductance and reactivity were determined. Forty-eight subjects, 26 controls (age 41.0 ± 2.3 yr) and 22 OSA (age 46.8 ± 2.3 yr) free of cerebrovascular and active coronary artery disease participated in this study. OSA patients had a mean apnea-hypopnea index of 78.4 ± 7.1 vs. 1.8 ± 0.3 events/h in controls. The oxygen saturation during sleep was significantly lower in the OSA group (78% ± 2% vs. 91 ± 1% in controls). The dynamic vascular analysis showed mean CBFV was significantly lower in the OSA group (0.06 cm/s; P < 0.05, respectively). The OSA group had a lower rate of recovery of cerebral vascular conductance for a given drop in blood pressure compared with controls (0.06 ± 0.02 vs. 0.20 ± 0.06 cm/s·mmHg−1; P < 0.05). There was no difference in cerebrovascular vasodilatation in response to CO2. The findings showed that patients with OSA have decreased CBFV at baseline and delayed cerebrovascular compensatory response to changes in blood pressure but not to CO2. These perturbations may increase the risk of cerebral ischemia during obstructive apnea.

Address for reprint requests and other correspondence: V. Mohsenin, 290 Congress Ave., New Haven, CT 06519 (e-mail: vahid.mohsenin@yale.edu).

Increased platelet aggregation in OSA patients during sleep (33, 35). Although these circulating risk factors can contribute to the risk of stroke, they would not explain the total risk.

Cerebral vascular reactivity is considered an index of the capacity of the cerebral vessels to adapt to the metabolic demands of the brain. Any reduction in this property could be interpreted as an increased risk of cerebral ischemia and stroke (3, 13, 32). Episodes of OSA during sleep and voluntary breath holding during wakefulness in normal subjects perturb the cerebral circulatory control (5, 17, 40, 41). Specifically, there is a progressive rise in systemic blood pressure and cerebral blood flow velocity (CBFV) during the apneas followed by an abrupt decrease in both in the postapnea hyperventilation period. The changes in CBFV parallel the changes in systemic blood pressure, suggesting impaired cerebral autoregulation.

Cerebral autoregulation is a tightly controlled mechanism to maintain a relatively constant blood flow during fluctuations in its perfusion pressure (1). The exact underlying mechanisms for cerebral autoregulation are unknown. Endothelium plays an important role in the regulation of blood flow by establishing resting tone in cerebral vessels through basal release of nitric oxide. This vascular tone acts as a background for other dilator and constrictor processes. On increased neural activity, active neurons and astrocytes release a multitude of vasoactive factors that act in concert on smooth muscle cells to increase or decrease cerebral blood flow commensurate with the metabolic needs of the brain (20, 21). In addition, myogenic response to changes in perfusion pressure is thought to be a contributor to the vascular resistance adjustments involved in cerebral autoregulation (26). There is accumulating evidence that vascular oxidative stress leads to profound alterations in cerebral autoregulation (10). OSA is associated with increased oxidative stress due to hypoxemia-reoxygenation (14). We hypothesized that patients with OSA have impaired cerebral autoregulation in response to changes in blood pressure, and this may contribute to the increased risk of cerebral ischemia and stroke. The purpose of the present study was to assess the cerebrovascular autoregulatory capacity in patients with OSA in the absence of clinical evidence of cerebrovascular disease. Accordingly, subjects with OSA and controls were subjected to orthostatic hypotension and hypercapnia separately while we measured the CBFV and its dynamic responses to these perturbations.

METHODS

Patients with moderate-to-severe OSA [apnea-hypopnea index (AHI) ≥ 30 events/h] and control subjects (with AHI < 5 events/h) were recruited from the Yale Center for Sleep Medicine. Subjects were excluded if they were on β-blockers or allopurinol and had...
known coronary artery disease, cerebrovascular disease, syncope, or any musculoskeletal abnormality, based on responding to a standardized questionnaire and information obtained from their physicians. Subjects with controlled hypertension on calcium channel blockers, angiotensin-converting enzyme inhibitors, or diuretics were allowed to participate. None of the subjects with OSA had received treatment for their OSA before study. Subjects refrained from having any caffeine-containing beverages or smoking within 6 h of the study. On the day of the study blood pressure was measured in seated position three times every 5 min using an appropriately sized arm cuff. Each subject was informed of the experimental procedures and signed the consent form, approved by the Human Investigation Committee of Yale University School of Medicine.

**Experimental Protocol**

We employed orthostatic hypotension and CO₂ inhalation separately to assess cerebral autoregulatory control by simultaneously measuring, CBFV beat-to-beat arterial blood pressure, end-tidal CO₂, and respiratory rate. Standing from a 2-min squatting position results in an abrupt and transient hypotension challenging the cerebral vascular autoregulation to compensate for a decrease in cerebral perfusion pressure. We determined the time from squatting-to-standing position for the blood pressure and the CBFV to return to >90% of baseline levels as a measure of cerebral autoregulation in the setting of transient hypotension or hypercapnia. In addition, autoregulatory capacity was assessed by the measurement of the rate of change of cerebrovascular conductance during transient hypotension, expressed as the ratio of CBFV and mean arterial blood pressure (MAP), over time. Orthostatic maneuver was repeated three times with 5-min rest period in between each run. Orthostatic maneuver preceded the hypercapnic challenge. During hypercapnia trials, gas mixture of 5% CO₂ with 21% O₂ and a balance of N₂ was added to the breathing circuit with a two-way valve and reservoir bag to maintain the inspired CO₂ level at a constant concentration of 5%. Each trial of hypercapnia lasted 2 min. The data from the last 15 s of each exposure, which included blood pressure, CBFV, respiratory rate, and end-tidal CO₂, were averaged and used for statistical analysis. The two trials were separated by at least 5 min of room air breathing to allow the blood pressure and CBFV to return to baseline levels.

**Procedures**

Assessment of sleep and sleep-disordered breathing. Baseline polysomnography was performed for all subjects between 9 PM and 7 AM using a computerized Grass data acquisition system (Astro-Med, West Warwick, RI) as previously described (29). Sleep state was recorded with four channels of electroencephalogram (C₃/A₂, C₄/A₁, O₂/A₁, O₁/A₂), two channels of electrooculogram, and one-channel submental electromyogram. Breathing was assessed by monitoring chest and abdominal movements with strain gauge pneumographs, and nasal and oral airflow was measured using pressure transducers. Arterial oxygen saturation was measured using a pulse oximeter. Leg movements were recorded with two channels of electromyogram, and electrocardiogram was monitored continuously for heart rate. Apnea was defined as at least an 80% reduction in airflow for ≥10 s. OSA was defined when respiratory efforts were present and central apnea when respiratory efforts were absent. Hypopnea was scored when there was a 30–80% decrease in airflow signal with a ≥4% decrease in oxygen saturation (44).

**General procedures.** Continuous arterial blood pressure was recorded at heart level (arm sling) noninvasively using finger pulse photoelectric plethysmography (Finapres, Ohmeda). The instrument was calibrated against blood pressure measured by an arm cuff sphygmomanometer. CBFV was measured by using a 2 MHz pulsed Doppler ultrasound system (Multidop X, DWL, Sipplingen, Germany). Optimization of Doppler signal from proximal segment of middle cerebral artery was performed by standardized method of varying the sample volume depth in incremental steps and at each depth, varying the angle of insonation to obtain the best quality signals from the Doppler frequency (2). Once the optimal signal-to-noise ratio was obtained, the probe was secured with a headband (Spencer Technologies, Seattle, WA). The transcranial Doppler ultrasound measurements were obtained by two investigators (F. Urbano and V. Mohsenin). End-tidal CO₂ was measured in mmHg with a Beckman LB-2 medical gas analyzer. The instrument was calibrated using a certified standard gas mixture before each experiment. All variables were recorded continuously in real time at a sampling rate of 100 Hz using a MacLab 400 (ADInstruments, Colorado Springs, CO) for subsequent analysis.

**Data analysis.** The data for baseline period averaged during the 2 min of squatting before standing for each trial. The nadirs of MAP and peak CBFV were determined after standing. The time from standing to nadirs of MAP and peak CBFV and from nadirs of these to return to >90 of baseline levels were noted (Fig. 1). The peaks and nadirs of MAP and CBFV were determined manually by examining each waveform using a built-in caliper in the MacLab 400 software by an investigator blinded to subject group. The data of three runs were averaged. The cerebrovascular autoregulation curves CBFV/MAP (conductance) as a function of time were constructed using second-order polynomial equations. The difference in the slopes was analyzed using F-test (GraphPad Software, San Diego, CA). The hypercapnic response, as an absolute increase in peak CBFV or percent change from baseline to 5% CO₂ was compared between the groups. Other parameters were compared between the two groups by unpaired t-test (with Welch correction if applicable). A P < 0.05 was considered statistically significant. Data are expressed as means ± SE.

**RESULTS**

**Baseline Characteristics:**

We studied 26 controls (age 41 ± 2 yr; body mass index 33 ± 1 kg/m²; 9 men and 17 women) and 22 subjects with OSA (age 47 ± 2 yr; body mass index 38 ± 2 kg/m²; 19 men and 3 women) (Table 1). There was no statistically significant difference in age. Although there were subjects with hypertension in both groups, their blood pressure at the time of study was normal. The awake O₂ saturation and end-tidal CO₂ were heavier with AHI 78 ± 7 events/h and had significantly lower mean minimum O₂ saturation during sleep than the control group. These subjects had significantly lower mean CBFV at baseline while awake compared with controls (48 ± 3 vs. 55 ± 2 cm/s; P <0.05).

**Orthostatic Challenge**

The change in position from squatting to standing resulted in a significant transient drop in systemic blood pressure in both groups. The average decrease was 27.4 ± 2.3 and 31.1 ± 2.7 mmHg in the control and OSA group, respectively (Fig. 2A). The difference between the groups was not statistically significant (P = 0.306). Similarly, the drop in CBFV was also comparable (control 12.1 ± 1.1 cm/s and OSA 14.9 ± 1.8 cm/s; P = 0.174) (Fig. 2B). The recovery time of MAP was significantly longer in the OSA group compared with controls (11.1 ± 0.9 s vs. 7.8 ± 0.4 s; P = 0.001; Fig. 3A). Similarly, the rate of recovery of CBFV was significantly slower in OSA subjects compared to controls (4.2 ± 0.5 s vs. 2.7 ± 0.3 s; P = 0.018) (Fig. 3B). When cerebral autoregulation was expressed as the rate of change of vascular conductance (the slope of CBFV/MAP as a function of time) the OSA group had a
significantly slower compensatory rate than the control group during orthostatic hypotension \((P < 0.05\); Fig. 4). There was no significant change in end-tidal CO\(_2\) during and after orthostatic hypotension to affect the slope of cerebrovascular reactivity.

Hypercapneic Challenge

The hypercapneic challenge did not alter the respiratory rate in either group (controls 15 ± 1 and OSA 16 ± 1 breaths/min). Inhalation of fixed concentrations of 5% CO\(_2\) in inspired gas mixture for 2 min increased the end-tidal CO\(_2\) from baseline of 33 ± 1 to a mean of 48 ± 0.7 mmHg in controls and from 35 ± 1.5 to a mean of 47 ± 1 mmHg in the OSA group. The mean end-tidal CO\(_2\) was the average of end-expiratory values of each breath during the last 15 s of hypercapneic challenges. This resulted in an absolute increase in peak CBFV of 27 ± 2 cm/s in controls and 31 ± 4 cm/s in OSA subjects, which was not a statistically significant difference \((P = 0.30)\).

DISCUSSION

The aim of this study was to test the hypothesis that OSA with associated intermittent hypoxemia stress impairs the cerebrovascular response to hypoperfusion and hypercapnia, as one of the underlying mechanisms of stroke in this population. Subjects with and without OSA underwent orthostatic and hypercapneic challenges to assess the cerebral autoregulatory capacity. Orthostatic hypotension resulted in a reduction in

Fig. 1. Original tracings of orthostatic challenge in control and obstructive sleep apnea (OSA) subjects showing the magnitude of the drop of blood pressure (BP) and cerebral blood flow velocity (CBFV) and the time points for calculation of recovery time to 90% of baseline values of mean arterial blood pressure (MAP) and peak CBFV.

Table 1. Baseline characteristics of the subjects

<table>
<thead>
<tr>
<th></th>
<th>Control ((n = 26))</th>
<th>OSA ((n = 22))</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>41.0 ± 2.3</td>
<td>46.8 ± 2.3</td>
<td>NS</td>
</tr>
<tr>
<td>Male, %</td>
<td>36</td>
<td>86</td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m(^2)</td>
<td>33.1 ± 1.2</td>
<td>38.8 ± 2.3</td>
<td>0.027</td>
</tr>
<tr>
<td>Hypertension, (n)</td>
<td>6</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>120 ± 2.3</td>
<td>127 ± 2.7</td>
<td>NS</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>80 ± 1.9</td>
<td>67 ± 2.4</td>
<td>NS</td>
</tr>
<tr>
<td>Apnea-hypopnea index, events/h</td>
<td>1.8 ± 0.3</td>
<td>78.4 ± 7.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean (S_aO_2), awake, %</td>
<td>95 ± 0.5</td>
<td>95 ± 0.4</td>
<td>NS</td>
</tr>
<tr>
<td>End-tidal (PcO_2) awake, mmHg</td>
<td>33 ± 1</td>
<td>35 ± 2</td>
<td>NS</td>
</tr>
<tr>
<td>Nadir asleep (S_aO_2), %</td>
<td>91 ± 1</td>
<td>78 ± 2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean CBFV, cm/s</td>
<td>55 ± 2</td>
<td>48 ± 3</td>
<td>0.037</td>
</tr>
</tbody>
</table>

Values are means ± SE; \(n\), no. of subjects. OSA, obstructive sleep apnea; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CBFV, cerebral blood flow velocity; \(S_aO_2\), arterial \(O_2\) saturation; NS, not significant.
CBFV in both groups. Subjects with OSA had significantly slower rate of recovery of blood pressure, CBFV, and cerebrovascular conductance than the control group, indicating impaired compensatory response to cerebral hypoperfusion. The vasodilatory response to hypercapnia was normal.

Patients with OSA are at risk of stroke independent of known risk factors, including hypertension (4, 36, 47). Patients with AHI of >30 events/h have a more than threefold increased risk of stroke or death (47). Altered cerebral hemodynamics can be considered a sign of increased risk factors for stroke. This is demonstrated by several investigations showing an association between risk factors for stroke such as smoking (42) or carotid lesions (8, 25, 43) and the presence of reduced cerebrovascular reserve capacity. During OSA, there is a progressive rise in arterial blood pressure reaching 250 mmHg systolic with a sudden drop below baseline after the termination of apnea (5). Similarly, there is a rise and fall in CBFV during and after apneas exceeding more than 60% fluctuation around the baseline velocity. The intermittent surges in blood pressure and hypotension and resultant fluctuations in CBFV subject the brain to vascular damage and risk of ischemia. These responses to sleep apnea and hypoxemia are likely to be key mechanisms responsible for increasing the shearing stress and mismatch between the capacity of the cerebral vessels to adapt and metabolic demands of the brain. Our findings provide evidence for one of the underlying reasons for higher risk of stroke during sleep and after rising (27). Our subjects were studied during the day and hours after awakening with no evidence for hypoxemia, hypercapnia, or uncontrolled hypertension at the time of the experiments, indicating persistent cerebrovascular dysregulation outlasting the immediate effects of apneas and hypoxemia during sleep.

Our study showed a normal response of the cerebrovasculature to hypercapnia. Based on the previously reported relationship that every 1-Torr change in arterial PCO₂ changes CBFV by ~3% in the same direction (34) our control and subjects with OSA demonstrated this expected increase in CBFV during hypercapneic challenge. Our findings are in contrast to a report showing impaired responsiveness to hypercapnia in OSA patients using a breath-holding method for raising CO₂ (32). Breath holding is associated with progressive hypoxemia and possible alteration of sympathetic and cardiovascular and cerebrovascular reactivity (51). The intact hypercapnic response in OSA subjects may prevent cerebral vasoconstriction to occur after the termination of apnea when the blood pressure surges due to hypercapnia-induced vasodilation during obstructive apnea (7). This may lead to increased shearing force on the cerebral blood vessels.

Fig. 2. Decrease in MAP (A) and peak CBFV (B) from squatting to standing position. Values are means ± SE; n, no. of subjects.

Fig. 3. Time from nadirs of MAP (A) and peak CBFV (B) to reach 90% of baseline values as a measure of the efficiency of the vasoregulatory capacity. Values are means ± SE; n, no. of subjects.
vessels (15) is impaired in OSA, but the underlying mechanism for this alteration remains to be established.

The exact mechanisms of cerebral autoregulation are still a matter of debate, but it is most commonly explained by either the metabolic or myogenic hypotheses. Endothelial factors, cytoskeletal matrix components, and gap junctions between vascular and/or astroglial cells appear to be involved when metabolic demands exceed the O2 supply, e.g., during cerebral hypoperfusion. Endothelial cells play an important role in the regulation of vascular tone by releasing potent vasoactive factors, such as nitric oxide, free radicals, prostacyclin, endothelium-derived hyperpolarizing factor, and endothelin (11). The myogenic hypothesis states that the arterial vessels, principally arterioles, are intrinsically sensitive to intravascular pressure such that when pressure rises, the vessels constrict (23). There is accumulating evidence that vascular oxidative stress leads to profound alterations in vascular tone regulation in the brain (10) and in the systemic circulation in OSA (12, 18). Patients with OSA have abnormal endothelium-dependent and -independent vasodilation (22, 24) and blunted cerebrovascular response to hypoxia (13). In our study, we observed delayed compensation in both arterial blood pressure and CBFV in the OSA group, indicating impairment in vasoregulatory control. The reduction in cerebrovascular reactivity to apnea, as measured by breath-holding index, was associated with a 30% increased risk of ischemic events regardless of previous stroke (46). It is important to note that our subjects had no known cerebrovascular disease and on average were 15 yr younger than the population our laboratory previously demonstrated to have a more than threefold increase in the risk of stroke and death due OSA (47). This subclinical perturbation in vasoregulatory control appears to precede increased risk of stroke by more than a decade. The treatment of OSA with airway pressurization for 4–6 wk has been shown to normalize cerebral autoregulation and response to hypoxia (9, 13). However, to date there has been no randomized controlled study to show that treatment of OSA decreases stroke rate.

Limitations

In the present study, we measured CBFV to reflect changes in cerebral blood flow. This assumption is only valid if the diameter of the insonated artery remains constant. Measurement of middle cerebral artery diameters in humans have shown that the diameters do not change during orthostatic hypotension or alteration of end-tidal CO2 (16, 38). Some of our subjects in both groups had the diagnosis of hypertension but had a normal blood pressure during the study day. The dynamics of cerebral autoregulation are well preserved in hypertensive patients despite a rightward shift in the lower limit of autoregulation (45). In the latter study the efficiency of treatment of hypertension had no effect on the cerebrovascular response to orthostatic hypotension, which was comparable to the control group (45). Furthermore, there is little existing evidence that antihypertensive agents reduce cerebral blood flow despite their effects on lowering blood pressure (37). The OSA patients in our study demonstrated a delayed correction of MAP after standing, suggesting a change in baroreflex sensitivity or changes in peripheral vascular function. However, this would not entirely explain the blunted cerebrovascular response to hypotension because cerebral autoregulation supposed to be independent of systemic response and shown to be preserved in hypertensive patients. The fact that the slopes of cerebral autoregulation curves were significantly less steep in OSA patients than controls indicates an inherent perturbation of cerebral vasoreactivity independent of delayed blood pressure compensation. Another potential limitation of the study is sex distribution and higher body mass index in the OSA group. Sex does not appear to play a significant role in cerebral autoregulation (28). We have no a priori knowledge of alteration of cerebrovascular reactivity due to only obesity. Both control and OSA patients were obese, although the latter group was heavier. We employed orthostatic challenge, which represents a possible situation in daily life as opposed to pharmacological or thigh-cuff deflation methods for manipulation of blood pressure in supine position. These latter interventions can activate a whole series of compensatory mechanisms and provoke discomfort (thigh inflation) potentially affecting the cerebral dynamic vasoregulation.

In summary, we have shown a decrease in CBFV in awake patients with OSA with an attenuated cerebrovascular response to hypotension. The vasodilatory response to hypercapnia was normal. These findings suggest increased risk of cerebral ischemia and shearing stress on cerebral vessels during hypotension and surges in blood pressure as a result of obstructive apneas during sleep. The impaired cerebral autoregulation may contribute to increased risk of stroke in OSA patients.

ACKNOWLEDGMENTS

The authors thank Adam Bennett for his technical support.

Fig. 4. Rate of change of vascular conductance in response to orthostatic hypotension as a measure of cerebral autoregulation. The OSA patients had significantly lower compensatory rate (the slope of CBFV/MAP/time) (P < 0.05) and longer time course than the controls.
REFERENCES