Sleep Apnea in Acute Cerebrovascular Diseases: Final Report on 128 Patients

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Summary: Although obstructive sleep apnea (OSA) appears to be a cardiovascular risk factor, its frequency in patients with transient ischemic attack (TIA) and stroke remains poorly known. We prospectively studied 128 patients (mean±SD age=59±15 years) with stroke (n=75) or TIA (n=53). Assessment included body mass index (BMI); history of snoring and daytime sleepiness; cardiovascular risk factors and diseases; and severity of stroke (Scandinavian Stroke Scale=SSS). Polysomnography (PSG) was obtained in 80 subjects (group 1), a mean of 9 days (range, 1-71 days) after TIA or stroke. In 48 subjects (group 2), PSG was not available, refused, or inadequate. Groups 1 and 2 were similar with the exception of gender distribution. Clinical and PSG data were compared to those of 25 healthy controls matched for age, gender, and BMI. An apnea-hypopnea index (AHI) >10 was found in 62.5% of subjects and 12.5% of controls. Between patients and controls there was a significant difference in AHI (mean [range]: 28 (0-140) vs 5 (0-24), $p<0.001$), maximal apnea duration (mean+SD: 37±23 vs 23±13 seconds, $p=0.009$), and minimal oxygen saturation (mean+SD: 82±10% vs 90±5%, $p<0.001$). Conversely, frequency and severity of OSA were similar in stroke and TIA subjects. Multiple regression analysis identified age, BMI, diabetes, and SSS as independent predictors of AHI. Sleep apnea has a high frequency in patients with TIA and stroke, particularly in older patients with high BMI, diabetes, and severe stroke. These results may have implications for prevention, acute treatment, and rehabilitation of patients with acute cerebrovascular diseases.
Key words: TIA; stroke; sleep apnea; snoring; diabetes; cerebrovascular risk factors

Obstructive sleep apnea (OSA) occurs frequently, and is estimated to affect 4% to 9% of the adult population.[1] Several studies suggest an association between OSA and increased vascular morbidity. Subjects with habitual snoring and OSA have an increased risk of hypertension (present in 50% to 90% of patients with OSA), coronary artery disease (CAD), congestive heart failure (CHF), and vascular mortality.[2-5] On the other hand, the prevalence of OSA is higher in subjects with hypertension, CAD, myocardial infarction, and CHF than in normal controls.[6-9] Furthermore, a dose-response relationship between OSA and blood pressure, independent of known confounding factors, was recently found in a sample of 1060 adults aged 30 through 60.[10] Finally, treatment of OSA can improve blood pressure control and cardiac function, and—possibly—decrease vascular mortality.[3,11,12]

Only a few studies have assessed the relationship between OSA and cerebrovascular diseases.[13] Single cross-sectional and case-control studies suggest that habitual snoring may represent an independent risk factor of stroke, with odds ratios ranging from 2.1 to 3.3.[14] The link between snoring and stroke appears particularly likely when snoring is habitual (always or almost always present) and associated with symptoms/signs suggestive of SA.[15] Recently, small and mostly retrospective polysomnographic studies suggested a ≥50% frequency of OSA in stroke

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victims, which we also found in a preliminary analysis of the present, prospective study.[16-18]

At the present time, the association of snoring and OSA with cardiovascular and cerebrovascular morbidity remains controversial.[19,20] As a contribution to the debate on health consequences of OSA, we assessed the prevalence of OSA in a consecutive series of patients with TIA and stroke, and looked for predictors of OSA in this population.

METHODS

Over a 40-week period, all subjects between the ages of 18 and 80 years admitted to the University of Michigan Hospitals with acute (retinal or cerebral) TIA or ischemic stroke were considered for the study. Subjects in stupor or coma, and those with unstable medical conditions such as severe pneumonia or decompensated congestive heart failure (CHF), were excluded. Subjects were examined with a standard protocol that included a structured interview consisting of about 80 questions (see below), clinical examination, and standard work-up for TIA and stroke. Among 128 eligible subjects, 82 (64%) gave informed consent for overnight polysomnography (PSG), 25 (20%) refused PSG, and 21 (16%) could not be studied in a timely manner. A total of about 160 variables per subject were entered in a database for subsequent analysis. The study protocol was approved by the institutional review board of the University of Michigan.

Clinical Stroke Assessment.

Subjects were assessed clinically by one of the authors (CB), usually within the first 2 days of hospitalization. The above-mentioned questionnaire included questions about such cardiovascular risk factors (as defined before[16]) as family history of stroke, hypertension, diabetes, hypercholesterolemia, smoking (pack-years), and alcohol consumption (drinks/week). Any history of CAD and CHF, and time of onset of TIA and stroke, were also noted. Clinical examination included assessment of weight, height, blood pressure, and pulse at admission, severity of stroke, and presence of orofaciopharyngeal weakness (severe, mild, none). BMI was calculated as (weight in kg)/(height in meters)^2. Maximal stroke severity was assessed with the Scandinavian Stroke Scale (SSS, range 0-58 21, by which different neurological functions including consciousness, language, motor and sensory functions, and walking abilities are represented. The maximal score (no neurologic deficit) is 58. A score <30 represents severe stroke.

Clinical Sleep Assessment.

We assessed sleep-wake habits and disturbances preceding TIA and stroke, including history of disturbed or insufficient sleep, snoring, or daytime sleepiness. Snoring was considered habitual when it was reported to occur often or always. Sleepiness was estimated with the Epworth Sleepiness Scale (ESS),[22] and considered excessive (hypersomnia) when the ESS was >10. The sleep apnea questions from the Sleep Disorders Questionnaire (SDQ-SA[23]), including questions on frequency of loud snoring, and history of witnessed apneas, nocturnal choking sensations, and nocturnal sweating was also administered. In this questionnaire the patients also provide information on smoking habits, history of hypertension, and current body mass index. Questions on the SDQ-SA are answered using a scale from 0 (never or strongly disagree) to 5 (always or strongly agree). Scores of the SDQ-SA ≥36 in men and ≥32 in women (abnormal SDQ-SA) have a sensitivity and a specificity of about 80% for PSG-proven OSA.[23] When a reliable history could not be obtained from a subject because of aphasia or confusion, information was obtained from relatives. Sleep apnea was considered to be clinically probable (P-SA) when there was (1) habitual snoring and hypersomnia; (2) habitual snoring and abnormal SDQ-SA; or (3) hypersomnia and abnormal SDQ-SA.

Stroke Studies

Stroke work-up included standard blood tests, 12-lead ECG, chest radiography, doppler ultrasonography, and brain computer tomography (CT) or magnetic resonance imaging (MRI), or both, in all subjects. Echocardiography was performed in 85% of subjects, and conventional or MR angiography in 56%. Etiology of stroke was classified according to the criteria of the Trial of Acute Stroke Treatment in large artery disease, small artery disease, cardioembolism, others (eg, carotid dissection), and unknown.[24] Outcome was classified at discharge from the hospital as good (no deficits or deficits without restriction of lifestyle = independent), or poor (deficits with restriction of lifestyle = dependent).[25]

Polysomnography.(PSG) was performed between 2200 hours and 0600 hours at the wards (84%) or in the sleep laboratory (16%), using an 18-channel paper recording system at a paper speed of 10 mm/second. We recorded eight electroencephalogram channels, two electrooculogram channels, one chin electromyogram (EMG) channel, nasal/oral airflow (thermistor), chest and abdominal wall excursion, heart rate, hemoglobin saturation (SaO_2), and two tibialis anterior EMG channels. Snoring volume during the study was scored with a five-grade scale from 0 (none) to 5 (very loud). Only PSGs with a total recording time ≥5.5 hours and a total sleep time ≥2 hours were considered adequate. Sleep-stage scoring was done visually according to standard criteria.[26] Apnea was defined as >80% reduction in nasal/oral airflow lasting ≥10 seconds. Hypopnea was scored when there was an obvious reduction (usually

>20%) in airflow or effort or both lasting ≥10 seconds and accompanied by an arousal or a decrease in SaO_2 of at least 4%. Central apneas were identified by the absence of respiratory effort during cessation of airflow. The number of apneas and of apneas plus hypopneas per hour of sleep was expressed as apnea index (AI) and apnea-hypopnea index (AHI). The AHI was calculated for the first 2 hours of sleep and for the whole night. Sleep apnea was diagnosed when the (whole night) AHI was ≥10. We also noted maximal and average duration of respiratory events, and minimal SaO_2. The presence of cardiac arrhythmias was noted according to Guilleminault et al.[27]

Control subjects.—Normal controls were 25 healthy volunteers (16 men, 9 women) with a mean ± SD age of 59±14 years (range, 22-75 years), recruited through the University of Michigan Alcohol Research Center. Control subjects were free by history and clinical examination of diabetes; 25% were, however, hypertensive but none had uncontrolled hypertension. There were also no history, symptoms, or signs of heart disease, chronic obstructive pulmonary disease, TIA, stroke, neurologic or psychiatric disease. All controls had limited alcohol consumption (Audit-score <8.[28])

Statistical analysis.—Nominal data were analyzed with the chi-square test. For continuous data, we used the unpaired *t* test and the ANOVA test with Bonferroni post hoc corrections. Correlation analyses were done with the Pearson test for continuous data and the Spearman rank test for ordinal data. Multiple stepwise regression models (with entry and elimination alpha levels set to 0.05) were tested with forward, backward, and stepwise elimination by means of SAS statistical software. Continuous values are given as mean plus standard deviation. Statistical significance was set at $p<0.05$.

Results

The group of 128 subjects included 57 women and 71 men with a mean ± SD age of 59±15 years (range, 19-80 years). There were 53 subjects with TIA and 75 subjects with stroke, of whom 61 had a first stroke. The estimated time of onset of TIA and stroke was similar in both groups (1100 hours), with a peak time between 0800 and 1000 hours. Only 21% of all events occurred between midnight and 0600. The mean SSS score was 38 (range, 2-58). Stroke was nonlacunar (>1.5 cm in diameter) in 78% of subjects, and supratentorial in 78%. Etiology of stroke was determined in 69% of subjects, and included macroangiopathy (24%), microangiopathy (12%), and cardioembolism (15%). Before the onset of TIA or stroke, sleep was considered disturbed or insufficient by 43% of subjects, habitual snoring was reported by 51%, and hypersomnia by 37%. The presence of OSA was presumed on clinical grounds (P-SA) in 42% of subjects.

Table 1.—Clinical characteristics of patients who did and did not undergo polysomnography

	Studied (n=80)	Not studied (n=48)	
Age	60± 14	58 ±17	NS
Male:Female (% males)	50:30 (63)	21:27 (44)	p=0.038
Body mass index	29.2 ± 8.4	27.4 ± 5.7	NS
Hypertension	65%	70%	NS
Diabetes	32%	30%	NS
Hypercholesterolemia	53%	48%	NS
Smoking (pack/years)	22 (range 0-100)	20 (range 0-100)	NS
Alcohol (drinks/week)	3 (range 0-76)	6 (range 0-150)	NS
"I have a sleep problem"	44%	40%	NS
Habitual snoring*	56%	42%	NS
Hypersomnia **	34%	20%	NS
Clinically probable SA ***	47%	34%	NS
TIA:Stroke	32:48	21:27	NS
Scandin. Stroke Scale score	39 ± 14	40 ±20	NS

Continuous variables are expressed as mean ± SC, SA = sleep apnea
NS = not significant, * snoring often/always, ** Epworth Sleepiness Score > 10
*** see text for criteria

Table 2.—Prevalence and severity of obstructive sleep apnea in patients with stroke and TIA, and normal controls

	Stroke n=48	TIA n=32	Normals n=25	
Mean age	60±14	58±14	59±14	NS
range	26 - 80	19 - 77	22 - 75	
Male:Female (% males)	30 :18 (62.5)	20 :12 (62.5)	16:9 (64)	NS
BMI	28.7±8.2	29.9±8.7	26.1±3.6	NS
Habit.snoring*	52%	62%	12%	p=0.004
SDQ-SA score**	34±8	35±7	27±7	p=0.004
AHI	32 (range 0-140)	23 (range 0=81)	5 (range 0-24)	p=0.012
Apnea index	14 (range 0-106)	6 (range 0-33)	3 (range 0-33)	NS
Max. apnea duration (sec)	37±20	36±27	23±13	p=0.031
Av. Apnea duration (sec)	17±6	18±8	14±7	NS
Minimal SaO_2	83±9	80±12	90±5	P=0.004

Continuous variables are expressed as mean ± SD
NS = not significant, *often or always, **sleep apnea questionnaire (see text)

PSG was performed in 82 subjects and considered to be adequate in 80 of these. Table 1 compares studied and non-studied subjects. Patients not studied were more commonly women, lighter, less sleepy, and snored less. However,

Table 3.—Comparison of patients with no, mild-moderate, and severe sleep apnea

	AHI<10 n = 30	AHI=10-30 n = 25	AHI>30 n = 25	
AHI	5±3	20±6	66±35	p<0.001
Minimal SaO_2	87±5	81±7	75±15	p<0.001
Mean age	54±15	60±14	64±11	p=0.050[1]
Males:Females (% males)	15:15 (50)	17:8 (68)	18:7 (72)	NS
BMI	28.1±5.5	27.2±3.9	33.5±12.9	NS
Hypertension	66%	60%	70%	NS
Diabetes mellitus	17%	32%	52%	p =0.023[2]
Heart disease (CAD, CHF)	31%/15%	29%/13%	41%/33%	NS/NS
Systolic BP*	143±30	147±27	168±22	p=0.009
Diastolic BP*	83±16	83±17	91±14	NS
Habitual snoring**	45%	56%	74%	NS
ESS score	9±4	9±5	11±5	NS
SDQ-SA score *** (males)	35±8	33±7	36±8	NS
(females)	33±9	34±7	39±9	NS
Clinically probable SA ****	38%	42%	70%	p=0.050[3]
Time of stroke onset	11 a.m. (±6h)	11 a.m. (±5h)	1 p.m. (±6h)	NS
TIA:Stroke (% TIA)	10:20 (33)	14:11 (56)	8:17 (28)	NS
SSS score	42±14	38±12	34±14	NS

Continuous variables are expressed as mean ±SD
AHI = Apnea-hypopnea index, SA = obstructive sleep apnea, CAD = coronary artery disease, BMI=body mass index, ESS= Epworth Sleepiness Scale, SSS=Scandinavian Stroke Scale, CHF = congestive heart failure
*at admission, **often or always, ***sleep apnea questionnaire (see text), ****see text for criteria
[1]AHI<10 vs AHI>30 p=0.018, [2]AHI<10 vs AHI>30 p=0.019, [3]AHI<10 vs AHI>30 p=0.023

Table 4.—Independent predictors of apnea-hypopnea index (AHI)

Variable	Estimate	Standard error	t	p value
All subjects (patients and normal controls)				
Age	0.341	0.198	1.722	0.088
Snoring	3.642	2.008	1.814	0.072
BMI	1.361	0.391	3.477	<0.001
Full model: F(3,99)=9.093, p<0.001, R-square=0.221				
Stroke and TIA patients				
Age	0.514	0.251	4.17	0.045
BMI	1.492	0.429	12.08	<0.001
Diabetes mellitus	-18.201	7.940	5.25	0.025
Full model: F(3,67)=9.95, p<0.001, R-square=0.318				
Stroke patients				
BMI	1.471	0.624	2.356	0.023
Scandinavian Stroke Scale	-0.684	0.374	-1.828	0.075
Diabetes mellitus	-26.757	11.254	-2.377	0.022
Full model: F (3,42)=6.618, p=0.010, R-square=0.337				

only the difference in gender distribution was statistically significant between studied and nonstudied patients.

PSG wás recorded 9 days (range, 1-71 days) after the acute event. Total recording time and total sleep time were 415±33 and 276±76 minutes respectively. Moderate to very loud snoring was noted during PSG in 42% of subjects. A good correlation (Spearman correlation coefficient rho=0.58) was found between loudness of observed snoring and reported frequency of loud snoring. Sleep apnea (AHI>10) was found in 50 (62.5%) of 80 subjects, and 3 (12.5%) of 25 controls. An AHI >30 and an AI >20 were found in 25 (31%) and 10 (12.5%) subjects respectively, but in none of the controls. Sleep apnea was obstructive or mixed in 94% of subjects and in all controls. In 6% of patients, sleep-disordered breathing consisted of central apneic events.

A detailed analysis of sleep disturbances according to stroke topography is provided in a second study.[28a] There was a strong correlation (Pearson correlation coefficient=0.898) between the AHI calculated for the first 2 hours of sleep (23; range, 0-140) and the whole-night AHI (28; range, 0-122). Significant cardiac arrhythmias (sinus arrest >2.5 seconds, second-degree atrioventricular block, ventricular tachycardia, >2 premature ventricular beats/minute) were noted during PSG in 44% of patients. Stroke outcome was good in 58% of subjects, with a trend for a better outcome in subjects without OSA (71% vs 46%, p=0.077).

As shown in Table 2, stroke and TIA subjects differed significantly from normal controls in AHI, maximal apnea duration, and minimal oxygen saturation. Conversely, stroke and TIA subjects were similar in all variables considered.

Table 3 shows the comparison of subjects with no OSA (AHI <10), mild to moderate OSA (AHI 10 to 30), and significant OSA (AHI >30). Compared to subjects with no OSA, subjects with significant OSA were older, and more often had P-SA and diabetes mellitus; and their admission systolic blood pressure was higher. All other variables were similar in the three groups.

Table 4 shows the independent predictors of AHI in the final models for the whole population studied, for TIA and stroke subjects, and for stroke subjects only. The following variables were analyzed by stepwise multiple linear regression for prediction of AHI (dependent variable): age, gender, BMI, snoring, ESS, cardiovascular risk factors (hypertension, smoking, alcohol consumption, diabetes, hypercholesterolemia), CAD and CHF, SSS, and orofaciopharyngeal weakness. Age, BMI, and diabetes mellitus accounted for 32% of variance of AHI in subjects with TIA or stroke. In stroke subjects, BMI, SSS, and diabetes mellitus explained 34% of variance of AHI.

DISCUSSION

The main result of this study is the demonstration of a high prevalence of OSA in patients with TIA and stroke. The 62.5% OSA prevalence determined in our study is similar to the 69% to 95% range found in smaller and selected series of patients with stroke previously reported.[16-18] Despite important methodological differences, all studies found a significant OSA (AHI >30) in 30% to 50% of patients with stroke.

Several factors suggest that our findings are of general validity—first, the characteristics of our TIA and stroke patients, including age and gender distribution; cardiovascular risk factors profile; time of onset, topography, severity, etiology, and outcome of stroke are similar to those reported in larger series of patients with acute cerebrovascular disease.[29-31] Second, the 51% prevalence of habitual snoring found in our patients is similar to the 48% to 58% reported by others in large and unselected series of patients with stroke.[4,32] Third, the 12.5% prevalence of OSA in our normal controls is similar to the 5% to 6% (for women) and 12% to 18% (for men) found using a similar cut-off point for the diagnosis of OSA (AHI>10) in the large epidemiologic study of Young et al.[1] Fourth, two-thirds of eligible subjects could be studied and—with the exception of gender distribution—there were no significant differences between subjects who did and did not undergo polysomnography.

It was not the aim of this study to determine whether OSA represents an independent risk factor for stroke. For this purpose, a larger number of controls matched not only for age, gender, and BMI (as in this study), but also for other cardiovascular risk factors would be needed. However, the unreported observation made in this study of a similar OSA frequency in TIA and stroke patients suggests that OSA may more often represent a risk factor for than a consequence of acute brain damage. In single patients it is still conceivable that OSA is aggravated (eg, by sleep disruption or periodic breathing—see below) or even caused "de novo" (eg, medullary infarction, pharyngeal palsy) by acute brain ischemia. This could explain (1) the trend toward higher AHI and AI in patients with stroke compared to those with TIA; (2) SSS as an independent predictor of AHI in patients with acute stroke (see below); and (3) the spontaneous improvement over time of OSA after acute stroke observed in single patients (unpublished observations).

Sleep apnea can influence the course of cerebrovascular diseases in different ways. The neurohumoral consequences of recurrent respiratory events and hypoxemia may lead to hypertension, heart disease, increased platelet aggregation, decreased fibrinolysis, and increased atherogenesis.[33] Even mild OSA (AHI 5-15) may carry an increased risk for elevated blood pressure.[10] Acutely, hypopneas and apneas may lead to brady- and tachyarrhythmias, hypotension, decreased cardiac output, increased intracranial pressure, decreased cerebral blood flow,[34] and eventually brain ischemia. Reports on habitual snoring as a risk factor for strokes occurring at night are rare and contradictory.[35,36] Our unreported observation of a similar incidence of nocturnal TIA and stroke in patients with and without sleep-disordered breathing suggests, however, that the onset of stroke may rarely be precipitated acutely by respiratory events.

Clinical prediction of OSA appears to be more arduous in patients with cerebrovascular diseases than in the general population. Considering the good correlation found between reported and observed snoring, TIA and stroke victims appear to be reliable in providing a sleep history. Rather, the difficult clinical prediction could reflect (1) risk factor sharing between OSA and cerebrovascular diseases, and (2) factors related to acute brain damage affecting breathing control. In accord with this interpretation, our multiple-regression analysis did not find gender, history of snoring, smoking, alcohol consumption, sleepiness (as assessed by the Epworth Sleepiness Score), and hypertension—which are usually strongly associated with OSA—to be independent predictors of AHI in patients with acute cerebrovascular diseases. Eventually, only age, BMI, diabetes mellitus, and severity of stroke (as estimated by the SSS) were predictive of SA. Age and BMI are well-known risk factors for OSA, and do not deserve further comments.[20] The association between SSS and sleep-disordered breathing is probably multifactorial and related to such factors as sleep disruption and periodic breathing secondary to acute brain damage, which enhance instability of breathing and increase upper airway resistance[37]; decreased residual volumes due to lung aspiration and pneumonia; recumbent position; and impaired lung mechanics secondary to motor deficits. The finding of a strong, independent association between OSA and diabetes mellitus was unexpected, and somewhat contradicts a recent study in which the relationship between insulin resistance and OSA (in otherwise healthy and normotensive subjects) was entirely dependent on the confounding factor of body mass.[38] It is possible that diabetes—particularly when associated with autonomic neuropathy—may predispose to OSA by means of reduced airway vagal tone or impaired respiratory reflexes.[39] Alternatively, the association between OSA and diabetes may be due to a diabetogenic effect of OSA secondary to a disturbance of glucose metabolism by increased cortisol and catecholamine levels or increased insulin resistance.[40]

The high frequency of OSA found in this study has potential implications for the prognosis and management of patients with cerebrovascular diseases. First, in TIA patients, treatment of OSA may reduce vascular morbidity

and risk of stroke by means of an improved control of hypertension[11] and heart disease,[12,41,42] as well a positive influence upon altered blood viscosity,[43] coagulation, and platelet aggregation functions.[44,45] Second, in patients with acute stroke, recurrent hypoxemia and hemodynamic instability associated with OSA may limit the chances of recovery of ischemic but not-yet-irreversibly-damaged neurons (ischemic penumbra). We found a trend toward a poorer short-term stroke outcome in patients with OSA. Others reported a poorer evolution in stroke patients with snoring, initial pathologic nocturnal oximetry, and PSG-proven OSA.[17,18] Third, in patients recovering from acute stroke, hypersomnia and recurrent nocturnal hypoxemias secondary to OSA may have an adverse effect on neuropsychologic recovery and more generally stroke rehabilitation.[18]

Although the exact cause-effect relationship between OSA and cerebrovascular diseases remains unclear, the presence of sleep-disordered breathing has adverse effects on cerebral hemodynamic and brain oxygenation, and should favor, in our opinion, an aggressive assessment for OSA in these patients. The clinician should have a particularly high degree of suspicion for OSA in older subjects with high BMI, diabetes mellitus, severe stroke, and history of frequent-loud-irregular snoring and witnessed apneas. The best diagnostic strategy (eg, recording technique and interval after TIA or stroke) for OSA in patients with acute cerebrovascular diseases remains unknown. Based on our data and recent reports in the literature, a split-night study—consisting of a baseline study followed by CPAP-titration in the second part of the night—may be considered for initial assessment.[46] The use of so-called "intelligent" CPAP machines may represent an alternative to conventional polysomnography because of their easier feasibility and lower costs.[47,48] Further studies are, however, needed to determine whether early recognition and treatment of OSA will alter the short- and long-term prognosis of patients with cerebrovascular diseases.

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