Obstructive Sleep Apnea before Ischemic Stroke: Clinical Relevance to Infarction Volume and Neurological Recovery

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Background: Obstructive sleep apnea (OSA) is a probable risk factor with speculative roles in the induction or aggravation of acute ischemic stroke (AIS). *Methods:* The association between OSA and AIS severity was retrospectively analyzed using clinical data of first-onset AIS patients, admitted to our hospital between January 2013 and September 2016. Eligible patients were categorized based on the presence of OSA prior to stroke. Stroke severity and functional outcomes were evaluated using the National Institute of Health Stroke Severity Scale (NIHSS) and the modified Rankin scale (mRS), respectively. *Results:* No significant differences were observed among OSA and non-OSA groups for infarction volume, NIHSS at admission and discharge, or mRS at discharge and at the 3-month follow-up (all $P > .05$). OSA prior to stroke negatively correlated with infarction volume ($P = .008$), NIHSS at discharge ($P = .006$), and the 3-month mRS ($P = .015$). In addition to OSA, it was also found that infarction volume significantly correlated with large artery occlusion (LAO), anterior circulation involvement, neutrophil count, and fibrinogen level; NIHSS at discharge significantly correlated with LAO, transient ischemia attack (TIA), neutrophil count, and thrombolysis; and the 3-month mRS significantly correlated with LAO, TIA, age, neutrophil count, and thrombolysis. *Conclusions:* OSA before AIS does not increase the severity of stroke. The negative association between OSA and infarction volume, stroke severity, and clinical outcomes suggests an endogenous neuroprotective effect.

Key Words: Obstructive sleep apnea—acute ischemic stroke—infarction volume—neurological recovery

Introduction

Stroke is a leading cause of death worldwide and also accounts for significant disability and health care costs.[1] Emerging evidence indicates that disordered breathing during sleep, particularly obstructive sleep apnea (OSA), is a possible risk factor for stroke. OSA is a common disorder resulting in repetitive pharyngeal collapse during sleep, and its prevalence in stroke patients accounts for 30%-70%.[2] The pathological mechanisms linking OSA to vascular risk factors include free radical generation, release of proinflammatory and prothrombotic mediators,

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impaired glucose tolerance, variability in cerebral blood flow (CBF), nocturnal hypoxemia, and increases in sympathetic nervous system activity and blood pressure.[3]

Recent studies suggest that OSA affects the clinical outcomes of stroke. In their landmark prospective study, Yaggi et al.[4] reported a 1.97-fold higher risk of a composite endpoint (stroke or death by any cause) in patients with OSA. In poststroke periods, OSA causes poorer functional outcomes at 3 and 12 months, longer hospitalization, and rehabilitation,[5] increased stroke recurrence,[6] as well as increased mortality.[7] However, the relationship between OSA and stroke is not yet clear. First, most studies have been limited by a cross-sectional design[8] or inclusion of a composite endpoint (e.g., stroke or death).[4] Second, no significant association between OSA and stroke was identified in a prospective follow-up study after adjusting for age, sex, and body mass index (BMI),[8] although cross-sectional analysis of the same cohort showed an approximate 4-fold higher risk of stroke in individuals with moderate-to-severe OSA. Moreover, the ability of continuous positive airway pressure to lower the risk of serious adverse outcomes after a stroke remains controversial,[9,10] although treatment improves sympathetic activity and autonomic dysregulation in patients with OSA.[11] Furthermore, OSA is assumed to be both a risk factor for stroke and a complication following stroke[12]; thus, it can play a different role before or after an acute ischemic stroke (AIS).

Most studies on the relationship between OSA and AIS have focused on OSA *after* AIS. Furthermore, in prospective studies on the relationship between OSA (*before* AIS) and AIS-based outcomes as coded within the International Classification of Diseases-10, observations originate from hospital admissions and death records rather than from adjudicated events. Thus, these studies did not measure the severity of stroke nor record the cause of death and, therefore, do not provide definitive evidence for an association between AIS and OSA before AIS. The objective of our retrospective study was to explore the association between AIS and prior OSA by assessing the infarction volume and degree of neurological deficits.

Materials and Methods

Participants

We included patients with first-time onset of AIS, who were admitted consecutively to the Department of Neurology, Xuanwu Hospital of Capital Medical University, China, from January 2013 to September 2016. The study protocol was approved by the local ethics committee of Xuanwu Hospital of Capital Medical University and informed consent was obtained from all patients. We included adult patients (>18 years) presenting with AIS, who were clinically assessed using the National Institute of Health Stroke Severity Scale (NIHSS) and modified Rankin scale (mRS) within 3 days of symptom onset and at follow-up. "Acute" was defined as less than 72 hours from symptom onset until arrival at the hospital. A diagnosis of ischemic stroke was made based on brain imaging and neurological consultation, according to the criteria of the Fourth Chinese National Conference on Cerebrovascular Diseases.[13] During the AIS phase, all patients were managed in accordance with the recommendations of the Chinese Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke.[14] Magnetic resonance imaging (MRI) scans were obtained within 7 days of symptom onset using a 3.0 T Avanto scanner (Siemens, Germany). Patients with previous strokes were excluded to eliminate any potential influence of a previous episode on the occurrence of snoring and sleep apnea. Patients whose neurologic deficits disappeared within 24 hours and those without an MRI-confirmed lesion were not included. The full extent of the exclusion criteria is provided in the Supplementary Files.

Clinical Evaluation of Stroke

The severity of stroke was evaluated with the NIHSS[15] at hospital admission and discharge. Functional outcomes were assessed using the mRS[16] at discharge and in a stroke follow-up clinic 3 months after discharge. Scores ranged from 0 (no symptoms) to 6 (death). A favorable outcome included spontaneous neurological recovery or grades 0-2 on the mRS at hospital discharge. AIS was classified according to the definitions outlined in the Trial of Org 10172 in Acute Stroke Treatment.[17] These definitions categorize subtypes of ischemic stroke based on the cause of stroke as follows: large-artery atherosclerosis, cardioembolism, small-vessel occlusion, and stroke of other or undetermined etiology. Baseline demographic variables and any history of vascular risk factors such as hypertension, diabetes, coronary artery disease, hyperlipemia, atrial fibrillation, valvular heart disease, transient ischemic attack, peripheral vascular disease, hyperuricemia, hyperhomocysteinemia, alcohol consumption, and cigarette smoking were recorded. At admission, patients' blood pressure, complete blood count, fasting glucose level, hemoglobin A1c level, lipid profile, electrocardiogram, duplex ultrasound of the cervical arteries, 24-hour cardiac Holter electrocardiogram, and 2-dimensional echocardiogram were assessed. In some cases, a transesophageal echocardiography was also performed. BMI was calculated as weight (kg)/height $(m)^2$ for all patients.

Clinical Evaluation of OSA

Patients were divided into OSA and non-OSA groups. The OSA group included patients with an apnea-hypopnea index (AHI) greater than or equal to 15 before AIS, but who had not been treated. Patients in the OSA group had completed at least 1 overnight polysomnographic study to identify OSA before an AIS. This cut-off was based on epidemiological studies showing that the risk of adverse cardiovascular

events increases in patients with an AHI greater than or equal to 15.[18] Furthermore, large population-based studies[19,20] have shown that moderate-to-severe OSA is associated with a significant, around 3-fold, increase in stroke risk. The non-OSA group included nonsnorers or patients who only snored occasionally (1 or 2 nights/week).

To assess sleeping habits and identify patients at risk for OSA, the patients and cohabitant relatives completed 2 standardized questionnaires: the Berlin apnea questionnaire and the STOP-Bang questionnaire.[21,22] Patients identified as having a low risk of OSA according to these measures were placed in the non-OSA group. The Berlin questionnaire includes 10 questions, plus information on height and weight, arranged into the following 3 categories: snoring and cessation of breathing (category 1), symptoms of excessive daytime sleepiness (category 2), and BMI and hypertension (category 3). Positive scores in none or 1 of these categories indicate a low risk for OSA.[21] The STOP-Bang questionnaire comprises 4 questions used in the STOP questionnaire plus 4 additional demographic questions,[23] for a total of 8 dichotomous (yes/no) questions related to the clinical features of sleep apnea (snoring, tiredness, observed apnea, high blood pressure, BMI, age, neck circumference, and male sex). Patients with a STOP-Bang score of 0-2 were classified as being at low risk for OSA.

A recent study[24] demonstrated that the sensitivity of a STOP-Bang score greater than or equal to 3 to detect moderate-to-severe OSA (AHI >15) and severe OSA (AHI >30) was 93% and 100%, respectively. The corresponding negative predictive values were 90% and 100%. The probability of moderate-to-severe OSA increases in direct proportion to the STOP-Bang score, which makes this questionnaire an easy-to-use tool for identifying patients with a high risk of OSA. The Berlin questionnaire also has a good sensitivity for detecting clinically relevant OSA (AHI >15).[25] To gain high sensitivity and specificity, we used these 2 methods to screen for OSA in our sample. In addition, interviews of the spouses are very important, considering that self-reporting of sleeping habits can yield an underestimation of habitual snoring.

For patients who were not interviewed during their hospital stay, we reviewed their clinical notes and contacted them by phone. In the case of patients without spouses (unmarried, divorced, absent, or deceased spouse), doubtful information, or when the household member could not provide information on the patient's sleeping habits and disorders, the patient was excluded.

Other Measurements

Two neuroradiologists analyzed all MRI scans. Disagreement was resolved by consensus. Diffusion-weighted imaging scans and apparent diffusion coefficient maps were used to detect new acute ischemic brain lesions. On each scan, the number and distribution of lesions was recorded as well as the vascular territory. Also, the volume of hyperintense lesions, indicating acute cerebral ischemia, was measured. The volumes of separate lesions were calculated by measuring lesion diameter on 3 axes and converted to milliliter.[26] The volume of stroke lesions was calculated by 2 independent observers blinded to the clinical data.

Statistical Analyses

All statistical analyses were performed with SPSS 12.0 (SPSS Inc., Chicago, IL). Results are expressed as the mean, standard deviation, median, and interquartile range (IQR). Between-group differences were tested using the chi-square test for categorical factors, and *t* tests or Wilcoxon rank-sum tests were employed for continuous factors. Probability values are always given as 2-sided and exact. A multiple regression analysis was performed with feature selection in a stepdown manner and without feature selection to evaluate the correlation between lesions volumes, neurological deficits, and OSA. Sex, age, BMI, hypertension, diabetes, prodromal transient ischemia attack (TIA), hyperlipemia, coronary artery disease, atrial fibrillation, hyperuricemia, OSA type (OSA or non-OSA), duration of OSA, hyperhomocysteinemia, smoking, alcohol abuse, lesion site, thrombolysis, responsible large artery occlusion (LAO), red blood cell count, hematocrit, neutrophil count, monocyte count, and fibrinogen plasma level were included in the regression analysis. P values $<.05$ were considered statistically significant.

Results

A total of 173 patients with AIS fulfilled all inclusion criteria for this study. Out of these, 62 were assigned to the OSA group and 111 to the non-OSA group. Overall, OSA prevalence was 35.84% (57 men, 5 women). Forty-three OSA patients provided accurate information including AHI for the polysomnographic study results, and for the rest, an AHI greater than or equal to 15 was confirmed from previous medical records. The history of OSA before stroke ranged from 1 to 23 years (mean 8.05 ± 4.46 years). For all patients, the most common stroke subtype was large-vessel disease (46.24%), followed by small-vessel occlusion (41.62%) and cardioembolism (5.78%). The median NIHSS score at hospital admission was 4 (IQR 2-9; mean 5.82 ± 4.95). At discharge, 43.93% of patients had mRS score greater than or equal to3. Within 1 month after the AIS, 1 patient in the non-OSA group died due to the AIS, and 1 patient in the OSA group had a recurrence of cerebral embolism. During the 1-year follow-up period, 1 and 2 patients in the non-OSA group experienced recurrent cerebral infarction and cerebral hemorrhage, respectively, and 1 patient in the OSA group died of myocardial infarction.

Patient characteristics are shown in Table 1. Patients' ages ranged from 28 to 86 years (mean age 57.66 years), and 77.46% were male. Patients in the OSA group were almost exclusively male (OSA: 91.94%; non-OSA: 70.27%; $P = .001$), had a higher BMI than those in the non-OSA group (27.54

Table 1. *Baseline characteristics of patients with or without previous obstructive sleep apnea*

Characteristic	Overall (N = 173)	OSA, AHI ≥15 (N = 62)	Non-OSA (N = 111)	P value*
Age, y, mean (SD)	57.66 (12.68)	57.66 (11.32)	57.66 (13.43)	1.00
Male, N (%)	134 (77.46)	57 (91.94)	78 (70.27)	.001
Ethnicity, N (%)				
Chinese	173 (100.00)	62 (100.00)	111 (100.00)	1.00
BMI, kg/m^2, mean (SD)	25.65 (3.98)	27.54 (4.73)	24.61 (3.06)	<.001
BMI ≥24, N (%)	102 (58.96)	47 (75.81)	55 (49.55)	.001
Vascular risk factors, N (%)				
Hypertension	125 (72.25)	50 (80.65)	77 (69.37)	.11
Diabetes	81 (46.82)	38 (61.29)	44 (39.64)	.006
Hyperlipemia	84 (48.55)	27 (43.55)	57 (51.35)	.33
Coronary artery disease	26 (15.03)	13 (20.97)	14 (12.61)	.15
Atrial fibrillation	17 (9.83)	7 (11.29)	10 (9.01)	.63
Transient ischemic attack	39 (22.54)	18 (29.03)	21 (18.92)	.13
Hyperuricemia	12 (6.94)	3 (4.84)	9 (8.11)	.42
Hyperhomocysteinemia	36 (20.81)	13 (20.97)	23 (20.72)	.97
Smoking	91 (52.60)	42 (67.74)	49 (44.14)	.003
Alcohol abuse	57 (32.95)	23 (37.10)	34 (30.63)	.39
Thrombolysis, N (%)	15 (8.67)	3 (4.84)	12 (10.81)	.18
Hematological index, mean (SD)				
Total cholesterol, mmol/L	4.25 (1.03)	4.12 (.90)	4.32 (1.09)	.21
Triglyceride, mmol/L	1.55 (.75)	1.66 (.68)	1.49 (.78)	.17
HDL, mmol/L	1.20 (.30)	1.17 (.29)	1.23 (.31)	.22
LDL, mmol/L	2.65 (.90)	2.56 (.80)	2.70 (.95)	.35
RBC, 10^{12}/L	4.71 (.54)	4.83 (.55)	4.65 (.52)	.04
Hematocrit	.422 (.045)	0.432 (.045)	.416 (.044)	.03
Neutrophil, N, 10^9/L	4.92 (1.84)	5.29 (1.87)	4.71 (1.80)	.046
Monocyte, M, 10^9/L	.48 (.16)	0.53 (.17)	.45 (.15)	.003
Fibrinogen, μmol/L	10.55 (3.29)	11.29 (3.20)	10.14 (3.29)	.03
FPG, mmol/L	6.47 (2.12)	6.56 (2.03)	6.41 (2.17)	.66
Sleep study characteristics, median (range)				
AHI	–	36.40 (16.10-68.50)	–	–
Baseline SpO_2	–	93.80 (87.00-98.00)	–	–
Lowest SpO_2	–	76.00 (30.00-84.00)	–	–
Stroke subtypes, N (%)				
Large-artery atherosclerosis	80 (46.24)	29 (46.77)	51 (45.95)	.92
Cardioembolism	10 (5.78)	4 (6.45)	6 (5.41)	1.00
Small-vessel occlusion	72 (41.62)	24 (38.71)	48 (43.24)	.56
Other determined etiology	3 (1.73)	2 (3.23)	1 (.90)	.61
Undetermined etiology	8 (4.62)	3 (4.84)	5 (4.50)	1.00
Lesion site, N (%)				
Anterior circulation	122 (70.52)	43 (69.35)	79 (71.17)	.80
Posterior circulation	51 (29.48)	19 (30.65)	32 (28.83)	
Large artery occlusion, N (%)	46 (26.59)	18 (29.03)	28 (25.23)	.59
Time interval from onset to MRI, d, mean (SD)	3.24 (2.13)	3.26 (2.18)	3.23 (2.11)	.94

Abbreviations: AHI, apnea-hypopnea index; BMI, body mass index; FPG, fasting plasma glucose; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; MRI, magnetic resonance imaging; OSA, obstructive sleep apnea; RBC, red blood cell count; SD, standard deviation; SpO_2, peripheral capillary oxygen saturation.

*P values for continuous normally distributed variables from a t test, skewed variables from a Wilcoxon rank-sum test, or categorical variables from a χ^2 test.

versus 24.61, $P < .001$), and the majority had diabetes mellitus (OSA: 61.29%; non-OSA: 39.64%, $P = .006$) and were smokers (OSA: 67.74%; non-OSA: 44.14%; $P = .003$). Thrombolytic treatment was administered in 4.84% and 10.81% of patients with and without OSA, respectively ($P = .18$). There was no significant difference between the OSA and non-OSA groups in infarction volume as seen by diffusion-weighted imaging (OSA: 3.65 [IQR 18.75] mL; non-OSA: 5.24 [IQR 26.16] mL; $P = .31$).

There was no significant difference between the OSA and non-OSA groups in NIHSS scores at admission (median, 5 versus 4 in OSA and non-OSA groups,

respectively; $P = .35$) or at discharge (median, 2 versus 3; $P = .12$), or in mRS scores at both discharge (median, 2 versus 2; $P = .26$) and at the 3-month follow-up (median, 1 versus 1; $P = .14$). There was also no significant difference in the percentage of patients with a favorable outcome (mRS ≤2) at the 3-month follow-up (OSA: 82.26%; non-OSA: 80.18%; $P = .74$). The severity of stroke, based on symptoms and functional disability scores, was not statistically different between groups in the acute stage (≤3 days), at discharge, or at the 3-month follow-up (Table 2).

The patients in the OSA group had significantly higher levels of red blood cells ($P = .04$), hematocrit (volume fraction of erythrocytes; $P = .03$), neutrophils ($P = .046$), monocytes ($P = .003$), and fibrinogen ($P = .03$) than those in the non-OSA group. The levels of cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and fasting plasma glucose were similar between groups (discussion on the hematological indices analyzed is provided in the Supplementary File).

OSA showed a significant negative correlation with infarction volume, NIHSS score at discharge, and the mRS score at the 3-month follow-up. The infarction volume significantly correlated with OSA ($P = .008$; 95% confidence interval [CI] −.502 to −.075), LAO ($P < .001$; 95% CI .311-.777), anterior circulation territory stroke ($P < .001$; 95% CI .404-.847), neutrophil count ($P = .001$; 95% CI .040-.163), and fibrinogen plasma level ($P = .007$; 95% CI .040-.244; Table 3). NIHSS scores at discharge significantly correlated with OSA ($P = .006$; 95% CI −.576 to −.098), LAO ($P < .001$; 95% CI .552-1.076), TIA ($P = .005$; 95% CI −.670 to −.124), neutrophil count ($P < .001$; 95% CI .069-.194), and thrombolysis ($P = .023$; 95% CI −.862 to −.064; Table 3).The 3-month mRS significantly correlated with OSA ($P = .015$; 95% CI −.139 to −.015), LAO ($P < .001$; 95% CI .100-.237), TIA ($P < .001$; 95% CI −.203 to −.060), age ($P = .001$; 95% CI .002-.006), neutrophil count ($P < .001$; 95% CI .017-.050), and thrombolysis ($P = .048$; 95% CI −.208 to −.001; Table 3). There was no significant correlation between OSA and NIHSS scores at admission ($P = .139$) or mRS scores at discharge ($P = .053$). Multiple linear regression analysis showed no significant correlation between OSA duration and infarction volume ($P = .101$), NIHSS scores at admission ($P = .136$), NIHSS scores at discharge ($P = .506$), mRS scores at discharge ($P = .211$), or mRS scores at the 3-month follow-up ($P = .084$).

Discussion

Previous studies have shown that OSA is a negative predictor for all-cause mortality, prognosis, and recurrent vascular events following a stroke or prodromal TIA.[27] However, it is unclear whether a correlation between OSA and stroke exists. For example, a prospective follow-up study[8] found no significant association between OSA and stroke after adjusting for age, sex, and BMI. Our study differs from previous ones as it focused exclusively on the effects of OSA before AIS and it only recruited patients with first-time cerebrovascular events. Pre-existing cerebrovascular disease might reflect reverse causal pathways, with OSA as the consequence rather than the cause of AIS.

We found that patients with and without previous OSA had similar infarction volumes, neurological pictures on admission, and favorable outcomes at 3 months, although those with OSA had higher risks for atheroma, due to diabetes, obesity, and cigarette smoking. Furthermore, OSA significantly negatively correlated with the infarction volume, NIHSS score at discharge and mRS score at the 3-month follow-up after adjustment for confounding factors. To our knowledge, this is the first study to suggest that OSA before AIS does not increase infarction volume or symptom severity in AIS. Although OSA leads to a high incidence of stroke, this does not indicate more severe symptoms at the time of onset.

We found that OSA is a negative predictor of the brain infarction volume, NIHSS score at discharge and mRS score at the 3-month follow-up. This is because having

Table 2. *Neurological severities, clinical outcomes, and infarction volumes in patients with or without previous obstructive sleep apnea*

Characteristic	Overall (N = 173)	OSA, AHI ≥15 (N = 62)	Non-OSA (N = 111)	P value*
Neurological assessment, Median (IQR)				
NIHSS score at admission	4 (7.00)	5 (7.25)	4 (7.00)	.35
NIHSS score at discharge	3 (6.00)	2 (5.50)	3 (6.00)	.12
mRS score at discharge	2 (3.00)	2 (2.50)	2 (3.00)	.26
mRS score at 3 months	1 (2.00)	1 (2.00)	1 (1.00)	.14
mRS score ≤2 at 3 months, N (%)	140 (80.92)	51 (82.26)	89 (80.18)	.74
Infarction volume, median (IQR)	4.68 (22.52)	3.65 (18.75)	5.24 (26.16)	.31
Nonlacunar stroke, N (%)	125 (72.25)	45 (72.58)	80 (72.07)	.94

Abbreviations: AHI, apnea-hypopnea index; IQR, interquartile range; mRS, modified Rankin scale; NIHSS, National Institute of Health Stroke Severity Scale; OSA, obstructive sleep apnea.

*P values for continuous normally distributed variables from a t test, skewed variables from a Wilcoxon rank-sum test, or categorical variables from a chi-square test.

Table 3. *Multiple linear regression analysis of risk factors associated with infarction volume or National Institute of Health Stroke Severity Scales core at discharge*

Dependent variable	Independent variable	Beta	Coefficients				Adjusted R^2
			t	Sig. (*P*)	95.0% confidence interval for beta		
					Lower	Upper	
Infarction volume	Lesion site	.344	5.574	.000	.404	.847	.370
	LAO	.289	4.608	.000	.311	.777	
	Neutrophil	.223	3.257	.001	.040	.163	
	Fibrinogen	.191	2.757	.007	.040	.244	
	Previous OSA	−.167	−2.669	.008	−.502	−.075	
NIHSS score at discharge	LAO	.406	6.139	.000	.552	1.076	.320
	Neutrophil	.273	4.175	.000	.069	.194	
	TIA	−.187	−2.870	.005	−.670	−.124	
	Previous OSA	−.182	−2.782	.006	−.576	−.098	
	Thrombolysis	−.149	−2.292	.023	−.862	−.064	
MRS score at 3-month follow-up	LAO	.328	4.892	.000	.100	.237	.304
	TIA	−.242	−3.653	.000	−.203	−.060	
	Neutrophil	.272	4.085	.000	.017	.050	
	Age	.213	3.269	.001	.002	.006	
	Previous OSA	−.163	−2.453	.015	−.139	−.015	
	Thrombolysis	−.131	−1.994	.048	−.208	−.001	

Abbreviations: LAO, large artery occlusion; mRS, modified Rankin scale; NIHSS, National Institute of Health Stroke Severity Scale; OSA, obstructive sleep apnea; TIA, transient ischemia attack.

OSA beforehand might induce intrinsic neuroprotective mechanisms. Ischemic preconditioning could result in neuroprotection, promote endogenous neurogenesis and angiogenesis,[28] and render the brain more tolerant to subsequent occurrences of persistent cerebral ischemia, consequently resulting in a better prognosis.[29,30] The chronic intermittent hypoxia during OSA may result in similar changes as those observed in cerebral ischemia reperfusion, like ischemic preconditioning. Sleep apnea is associated with profound changes in CBF.[31] Apnea-induced hypoxemia combined with reduced cerebral perfusion may predispose patients with OSA to nocturnal cerebral ischemia.[32] Patients with OSA show a 15% reduction in middle cerebral artery blood flow and a 20% reduction in mean CBF velocity.[33] Moreover, prolonged recurrent apnea is thought to lead to hypoxemia.[34] This type of hypoxia has 2 obvious characteristics: (1) intermittent hypoxia frequently occurring during sleep, where the attack cycle is short, lasting only a few seconds to minutes; and (2) it is chronic, repeating for years. Consistent with these findings, Siebler et al[35] did not obtain evidence supporting the hypothesis that cerebral hypoperfusion during sleep is a risk factor for AIS. In addition, brain blood flow regulation has been studied as a CBF response to a vasoactive stimulus, termed cerebrovascular reactivity (CVR); CVR impairment has been associated with an increased risk of stroke.[36] Ryan et al[37] monitored CBF using blood oxygen level-dependent magnetic resonance signal changes after standardized hypercapnic stimulation and reported a greater CVR in patients with OSA than in control individuals. Based on this body of research, our observations raise the possibility that ischemic tolerance in patients with previous OSA might improve the cerebrovascular reserve capacity and, consequently, reduce the risk of a larger infarction volume and of more severe symptoms.

This study has some limitations. First, the sample size was quite small. Furthermore, due to between-group differences in baseline data, it is difficult to clearly interpret our results, even though potential confounders were adjusted for in the multiple regression analysis. A larger sample size might reduce these differences and their potential effects on the results. Indeed, diabetes, smoking, and obesity result in more severe AISs[38-40]; hence, patients should be matched in this regard. Second, the non-OSA group did not previously undergo polysomnographic examination to exclude OSA before AIS, and the questionnaires used were not as accurate as a polysomnography. Third, we did not examine other factors associated with stroke outcomes or their association with OSA and did not consider the duration of each apnea episode.

Conclusions

The present study revealed that OSA is significantly negatively associated with infarction volume and neurological recovery, suggesting that OSA presents before an AIS protects the human brain, potentially by a mechanism similar to ischemic tolerance. However, considering the paucity of data in this field, carefully designed prospective studies are necessary to further test this hypothesis in humans. Further research is also imperative for the stratification and phenotyping of individuals with the greatest risk of OSA and those in whom treatment is deemed necessary, in order to determine the correct timing and modality of treatment. This will advance our understanding regarding the interplay among vascular remodeling, neuroplasticity, and OSA. A more sophisticated, personalized approach would also be required; individualized treatment of OSA according to severity may better prevent and treat ischemic stroke.

Authors' Contributions

Xunming Ji and Li Zhang gave their substantial contributions to the conception of the work. Li Zhang, Ran Meng, and Xunming Ji contributed to the study design. All authors acquired, analyzed, and interpreted data; and provided administrative, technical, and material support. Li Zhang wrote the draft and Chuanjie Wu, Ran Meng, Di Wu, and Xunming Ji revised it critically for important intellectual content. All authors approved the final version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work be appropriately investigated and resolved.

Supplementary materials

Supplementary data to this article can be found online at doi:10.1016/j.jstrokecerebrovasdis.2019.04.008.

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