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ORIGINAL COMMUNICATION

Obstructive sleep apnea linked to wake-up strokes

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Abstract Obstructive sleep apnea (OSA) has been considered as one of the risk factors for ischemic stroke, but the impact of OSA on wake-up stroke (WUS) is not well studied. We aimed to determine the relationship between OSA and WUS. We prospectively recruited 71 patients with mild to moderate ischemic stroke during hospitalization. Patients were classified into WUS and non-WUS. A full-night sleep respiratory study was performed between 3 and 14 days after stroke onset. Demographic data, sleep respiratory data, heart rate variability, stroke risk factors, stroke classification and sleep-related scales were recorded. We compared the differences in the variables between the two groups and determined the independent variables associated with WUS. Of the 71 patients, 26 (36.6%) had WUS. The patients with WUS had a significantly higher apnea-hypopnea index (23.1 ± 19.4 vs. 12.5 ± 11.9, $p = 0.016$), obstructive apnea index (7.8 ± 9.7 vs. 3.0 ± 4.0, $p = 0.021$) and lower mean blood oxygen saturation (95.1 ± 1.5 vs. 95.8 ± 1.3, $p = 0.046$) than the non-WUS patients. There were no significant differences in demographic data, stroke risk factors, sleep-related scales or heart rate variability. Logistic regression revealed that severe sleep-disordered breathing (apnea-hypopnea index ≥30) was the only independent variable associated with WUS (OR 6.065, 95% CI 1.451–25.350; $p = 0.014$). We conclude that in patients with mild to moderate ischemic stroke, OSA is the only risk factor associated with WUS, which cannot be distinguished clinically from non-WUS.

Keywords Obstructive sleep apnea · Sleep-disordered breathing · Wake-up strokes · Ischemic strokes

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Introduction

Most ischemic strokes occur in the morning hours [1, 2] when the patient may still be asleep, or after the patient wakes in the morning. A wake-up stroke (WUS), which means that the patient is normal before sleep but wakes up with neurological deficits in the morning, is a stroke that occurs during nocturnal sleep. Because of the uncertain stroke onset time, patients with WUS are considered not to be eligible for thrombolytic therapy using intravenous tissue plasminogen activator, which remains the only medication approved for the treatment of ischemic stroke within 3 h of symptom onset or within 4.5 h for most European countries [3]. Previous studies have shown that WUS comprises 8–28% of all ischemic strokes [4–10] and 14%

in a population-based study [11], but WUS cannot be distinguished from other strokes by clinical features, risk factors or outcome [11]. Although obstructive sleep apnea (OSA) has been considered one of the risk factors for ischemic stroke [12], the impact of OSA on WUS is not well studied. OSA leads to intermittent hypoxemia, sleep fragmentation and sympathetic overactivity, and thus we speculated that the cardiopulmonary variations in OSA predispose patients with preexisting cardiovascular risk factors to WUS. We report here a study to determine the role of OSA in WUS from the viewpoints of the sleep respiratory and autonomic systems.

Subjects and methods

Subjects

We prospectively and consecutively recruited patients with ischemic stroke during hospitalization from 1 September 2009 to 28 February 2010 in the common neurological ward of Kaohsiung Medical University Hospital, a university-affiliated hospital in southern Taiwan. The age of the patients ranged from 45 to 90 years. The patients received a detailed neurological examination and evaluation of stroke severity by neurologists using the National Institutes of Health Stroke Scale (NIHSS) score on admission. Only patients with mild or moderate ischemic stroke on admission, defined as a NIHSS score of $\leq$15, were included. Patients with severe medical disease (acute myocardial infarction, gastrointestinal tract bleeding, and pneumonia), malignancy, evolutional stroke or severe aphasia were excluded. All patients had a brain imaging examination, including brain CT on admission to exclude hemorrhagic stroke and/or brain MRI during hospitalization to confirm the ischemic lesion site. All demographic data such as age, gender, body mass index (BMI) and risk factors for stroke, including hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, old ischemic stroke and smoking, were recorded from medical charts. The timing of the ischemic stroke onset and its relationship with sleep were obtained from patients or their family members. The patients were divided into two groups, WUS (stroke onset during nocturnal sleep) and non-WUS. The study was approved by the Institutional Review Board of Kaohsiung Medical University Hospital (KMUH-IRB-980068). All patients gave their informed consent prior to being recruited into the study.

Sleep respiratory study

We used a portable device, an Embletta portable diagnostic system (PDS; Medcare, Reykjavik, Iceland), to record sleep-related respiratory signals [13]. It contained a data recorder, a respiratory inductive plethysmograph for chest and abdominal respiratory effort, a nasal airflow detector and a pulse oximeter. None of the patients was receiving oxygen via a mask or nasal canula. Within 3–14 days of ischemic stroke onset, all patients underwent an overnight recording with the Embletta PDS in the common neurological ward for at least 4 h attended by night-duty nurses. Because there was no electroencephalographic (EEG) recording available with the Embletta PDS to determine sleep status, the approximate time of sleep onset was taken to be at 5 min following the onset of rhythmic stable breathing. The end of sleep was taken as the patient's or caregiver's report of the final waking time or continuous movement artefacts without returning to a regular breathing pattern. The interval between the onset and the end of the study was calculated as "hours-in-bed". The sleep-related respiratory events were scored based on the AASM manual for the scoring of sleep [14]. We obtained respiratory parameters including the apnea-hypopnea index (AHI), apnea index (AI), obstructive apnea index (OAI), central apnea index (CAI), mixed apnea index (MAI), hypopnea index (HI), oxygen desaturation index (ODI), mean blood pulse oxyhemoglobin saturation (mean SpO_2), minimal blood pulse oxyhemoglobin saturation (min SpO_2), average desaturation, and percentage of time SpO_2 below 90%. Severe sleep-disordered breathing (SDB) was defined as AHI $\geq$30.

Heart rate variability analysis (HRV)

The X30 mode of the Embletta PDS recorded the heart rate and the application software Somnologica® performed the HRV analysis with each epoch of 5 min. The frequency domain parameters were generated based on fast Fourier transformation as very low frequency power (below 0.04 Hz), low frequency power (0.04–0.15 Hz), and high frequency power (0.15–0.40 Hz) [15]. The time domain parameters were calculated as R–R intervals, the standard deviation of all R–R intervals and the square root of the mean of the sum of the squares of differences between adjacent R–R intervals. Each parameter was presented as the average of all 5-min epochs during sleep. Patients with atrial fibrillation noted in the previous history, from chart review or electrocardiography recording on admission were excluded from the analysis.

Sleep-related scales for day-time sleepiness, nocturnal sleep quality and snoring

All patients completed a self-reported sleep questionnaire before the Embletta study. A validated Chinese versions of the Epworth sleepiness scale (ESS), Pittsburgh sleep quality index (PSQI) and snoring outcome surveys (SOS) were used to evaluate day-time sleepiness, nocturnal sleep quality and habitual snoring in the past 1 month prior to stroke,

respectively [16–18]. The range of ESS scores is from 0 to 24 with a higher score indicating worse day-time sleepiness. Excessive day-time sleepiness was defined as an ESS score of ≥10. The range of total PSQI scores is from 0 to 21 with a higher score indicating worse sleep quality. The range of SOS scores is from 0 to 100 with a lower score indicating worse habitual snoring.

Clinical evaluation and classification of ischemic stroke

The NIHSS scores on admission and discharge were recorded. Improvements in NIHSS scores during hospitalization and the number of patients with an improvement in NIHSS score of ≥2 were calculated. The ischemic lesion locations were recorded from the brain CT or MRI scans, and were divided into anterior circulation (anterior cerebral artery or middle cerebral artery territories) and posterior circulation (posterior cerebral artery territory). Ischemic stroke were classified as large-artery atherosclerosis, cardioembolism, small–vessel occlusion, undetermined and "other causes", based on the subtype classification developed for the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) [19].

Statistical analysis

Statistical analysis was performed using Predictive Analytics Software (PASW) 14.0 (SPSS, Chicago, IL). Continuous variables, including age, BMI, sleep respiratory parameters, HRV, and NIHSS, ESS, PSQI and SOS scores, are presented as means ± standard deviation (SD). Nominal variables, including gender, older age (≥65 years), obesity (BMI ≥27 kg/m^2), severe SDB (AHI ≥30), EDS (ESS ≥10) and TOAST classification, are presented as numbers and percentages. We used the two-tailed *t*-test for analyzing the continuous variables and the chi-square test or Fisher's exact test for analyzing the categorical variables to compare the differences between the WUS and non-WUS groups. Forced entry logistic regression analysis was used to find which factors ($p < 0.3$ in univariate analysis) were independently associated with WUS. The entered variables are presented with their odds ratio (OR), standard error (SE), 95% confidence interval (95% CI) and *p*-value after adjusting for confounding variables. A *p*-value <0.05 was considered statistically significant.

Results

Baseline data

There were 89 patients with ischemic stroke recruited into this study, but 15 patients with less than 4 h of recording time were excluded because this might have led to overestimation of the AHI. Another three patients with stroke occurring during the siesta were also excluded because this was not completely compatible with the definition of WUS occurring during nocturnal sleep. Siesta involves a shorter sleeping time than nocturnal sleep. We did not define the length of siesta, which might determine the depth of sleep and the occurrence of rapid eye movement sleep (average 60–90 min after the start of sleep in healthy individuals). In rapid eye movement sleep, cardiovascular status is more unstable than in other sleep stages and thus is associated with the onset of ischemic stroke during sleep. Thus of the 89, 71 finished the full-night Embletta study including 47 men (66.2%) and 24 women (33.8%). The demographic data are presented in Table 1. The mean (±SD) age of the patients was 67.1 ± 10.8 years. The average time of the examination after stroke was 6.2 ± 2.7 days. The average NIHSS score on admission was 4.8 ± 2.8. Of the 71 patients, 21 (36.6%) had WUS and 45 (63.4%) had non-WUS.

Univariate analysis

The demographic data and sleep respiratory parameters of the patients in relation to WUS and non-WUS are shown in Table 1. There were no significant differences in age, gender, BMI or time of examination after stroke between the two groups. The patients with WUS had a higher AHI (23.1 ± 19.4 vs. 12.5 ± 11.9, $p = 0.016$), OAI (7.8 ± 9.7 vs. 3.0 ± 4.0, $p = 0.021$), HI (12.9 ± 11.7 vs. 6.7 ± 7.0, $p = 0.019$) and ODI (22.2 ± 19.6 vs. 11.6 ± 11.6, $p = 0.017$) and lower mean SpO_2 (95.1 ± 1.5 vs. 95.8 ± 1.3, $p = 0.046$) than those with non-WUS. There were no significant differences in stroke risk factors, sleep-related scale scores, NIHSS score or stroke classification between the two groups (Table 2). Data from 55 of the 71 patients were subjected to the HRV analysis (20 patients, 36.4%, with WUS, and 35 patients, 63.6%, with non-WUS) after excluding 9 patients with atrial fibrillation and 7 patients with failure of the heart rate recording. There were no significant differences in any of the time domain and frequency domain parameters of the HRV analysis between the two groups (Table 3).

Multivariate analysis

The confounding factors put into the model for logistic regression analysis of WUS were severe SDB (AHI ≥30), obesity (BMI ≥27 kg/m^2) and diabetes mellitus. The results of forced entry logistic regression are shown in Table 4. After adjusting for confounding variables, severe SDB (AHI ≥ 30; OR 6.065, 95% CI 1.451–25.350, $p = 0.014$) was the only factor independently associated with WUS.

Table 1 Demographic and sleep respiratory data of the study population

Characteristic	Total $n = 71$	WUS $n = 26$ (36.6%)	Non-WUS $n = 45$ (63.4%)	p-value
Age (years)	67.1 (10.8)	65.7 (11.1)	67.8 (10.7)	0.423
Age ≥65 years, *n* (%)	40 (56.3)	13 (50)	27 (60)	0.413
Gender (male), *n* (%)	47 (66.2)	17 (65.4)	30 (66.7)	0.912
BMI (kg/m^2)	25.5 (4.0)	26.1 (3.8)	25.1 (4.1)	0.299
Obesity (BMI ≥ 27), *n* (%)	24 (33.8)	11 (42.3)	13 (28.9)	0.250
Time of examination after stroke (days)	6.2 (2.7)	6.1 (2.6)	6.2 (2.8)	0.854
AHI	16.4 (15.8)	23.1 (19.4)	12.5 (11.9)	0.016
Severe SDB (AHI ≥ 30), *n* (%)	14 (19.7)	10 (38.5)	4 (8.9)	0.003
AI	7.4 (9.9)	10.3 (11.9)	5.8 (8.3)	0.098
OAI	4.8 (7.0)	7.8 (9.7)	3.0 (4.0)	0.021
CAI	1.1 (3.6)	0.6 (1.0)	1.4 (4.5)	0.354
MAI	1.5 (3.5)	1.8 (4.1)	1.3 (3.0)	0.590
HI	9.0 (9.4)	12.9 (11.7)	6.7 (7.0)	0.019
ODI	15.5 (15.7)	22.2 (19.6)	11.6 (11.6)	0.017
Mean SpO_2 (%)	95.5 (1.4)	95.1 (1.5)	95.8 (1.3)	0.046
Minimum SpO_2 (%)	83.6 (6.8)	82.7 (7.0)	84.1 (6.7)	0.415
Proportion of time SpO_2 below 90% (%)	1.9 (3.4)	2.5 (3.9)	1.6 (3.1)	0.285
Average desaturation (%)	5.8 (1.5)	6.0 (1.7)	5.7 (1.4)	0.353

$p < 0.05$ significant, two-tailed *t*-test for continuous variables, Chi-square test or Fisher's exact test for categorical variables

WUS wake-up strokes, *non-WUS* non wake-up strokes, *BMI* body mass index, *AHI* apnea-hypopnea index, *SDB* sleep-disordered breathing, *AI* apnea index, *OAI* obstructive apnea index, *CAI* central apnea index, *MAI* mixed apnea index, *HI* hypopnea index, *ODI* oxygen desaturation index, *SpO_2* blood pulse oxyhemoglobin saturation

Table 2 Clinical characteristics of the study population

Characteristic	Total $n = 71$	WUS $n = 26$ (36.6%)	Non-WUS $n = 45$ (63.4%)	p-value
Stroke risk factors, *n* (%)				
Diabetes mellitus	32 (45.1)	14 (53.8)	18 (40)	0.259
Hypertension	63 (88.7)	22 (84.6)	41 (91.1)	0.404
Dyslipidemia	39 (54.9)	15 (57.7)	24 (53.3)	0.722
Atrial fibrillation	9 (12.7)	3 (11.5)	6 (13.3)	0.827
Old cerebrovascular disease	20 (28.2)	7 (26.9)	13 (28.9)	0.859
Smoking	12 (16.9)	4 (15.4)	8 (17.8)	0.795
Sleep-related scale scores				
ESS	8.3 (5.3)	8.7 (5.3)	8.0 (5.4)	0.602
EDS (ESS ≥10), *n* (%)	24 (35.3)	9 (34.6)	15 (34.1)	0.779
PSQI	6.4 (3.7)	6.5 (3.8)	6.4 (3.6)	0.869
SOS	67.5 (15.7)	65.1 (13.4)	68.9 (16.8)	0.343
NIHSS score				
On admission	4.8 (2.8)	4.7 (2.3)	4.8 (3.0)	0.831
On discharge	3.4 (2.9)	3.7 (2.9)	3.2 (2.9)	0.567
Improvement in score	1.4 (2.1)	1.0 (1.5)	1.6 (2.3)	0.274
Improvement ≥2, *n* (%)	34 (47.9)	9 (34.6)	25 (55.6)	0.089
Lesion location, *n* (%)				
Anterior circulation	39 (59.1)	15 (62.5)	24 (57.1)	0.670
Posterior circulation	27 (40.9)	9 (37.5)	18 (42.9)	
TOAST, *n* (%)				
Large artery	20 (28.2)	8 (30.8)	12 (26.7)	0.697
Cardioembolism	4 (5.6)	2 (7.7)	2 (4.4)	
Small vessel	41 (57.7)	15 (57.7)	26 (57.8)	
Undetermined	6 (8.5)	1 (3.8)	5 (11.1)	
Other	0 (0)	0 (0)	0 (0)	

$p < 0.05$ significant, two-tailed *t*-test for continuous variables, Chi-square test or Fisher's exact test for categorical variables

WUS wake-up strokes, *non-WUS* non wake-up strokes, *ESS* Epworth Sleepiness Scale, *EDS* excessive daytime sleepiness, *PSQI* Pittsburgh Sleep Quality Index, *SOS* snoring outcomes survey, *NIHSS* National Institute of Health Stroke Scales, *TOAST* Trial of ORG 10172 in acute stroke treatment subtype classification

Table 3 HRV data for the study population

	Total $n = 55$	WUS $n = 20$ (36.4%)	Non-WUS $n = 35$ (63.6%)	p-value
Time domain				
R–R interval	875.3 (124.4)	847.0 (118.6)	891.4 (126.5)	0.206
SDNN	66.4 (31.4)	64.6 (32.7)	67.5 (31.0)	0.743
RMSSD	65.6 (45.3)	59.5 (44.5)	69.2 (46.0)	0.450
Frequency domain				
Very low frequency power	6,689.8 (5,232.9)	7,969.5 (7,292.2)	5,958.5 (3,501.4)	0.173
Low frequency power	1,898.2 (1,184.1)	1,970.1 (1,178.0)	1,857.1 (1,202.7)	0.737
High frequency power	1,073.4 (729.6)	1,322.0 (1,052.5)	931.3 (411.3)	0.125
Total power	9,852.2 (6,302.0)	11,436.8 (8,537.6)	8,946.8 (4,474.7)	0.161
Low/high frequency ratio	2.8 (1.7)	2.8 (1.5)	2.9 (1.8)	0.843

$p < 0.05$ significant, two-tailed t-test for continuous variables, Chi-square test or Fisher's exact test for categorical variables

HRV heart rate variability analysis, *WUS* wake-up strokes, *non-WUS* non wake-up strokes, *SDNN* standard deviation of normal to normal intervals, *RMSSD* the square root of the mean of the sum of the squares of differences between adjacent R–R intervals

Table 4 Logistic regression of WUS

Variables	OR	SE	95% CI	p-value
Severe SDB (AHI ≥30	6.065	0.730	1.451–25.350	0.014
Obesity (BMI ≥27 kg/m^2)	0.975	0.610	0.295–3.224	0.967
Diabetes mellitus	1.380	0.535	0.483–3.938	0.548

$p < 0.05$ significant

WUS wake-up strokes, *SDB* sleep-disordered breathing, *AHI* apnea-hypopnea index, *BMI* body mass index

Discussion

The present study showed that patients with WUS, defined as stroke onset during nocturnal sleep, had more severe OSA and lower mean blood oxygen saturation than those with non-WUS. The risk of WUS in patients with severe SDB was six times the risk in those without severe SDB. There were no significant differences between the WUS and non-WUS groups in clinical characteristics or HRV.

We suggest that the impact of OSA on WUS can be explained as follows. First, the coagulation changes caused by OSA might lead to WUS. Studies have shown increased blood fibrinogen and platelet aggregation activity in OSA patients during the morning hours [20, 21]. Second, the hemodynamic changes including decreased middle cerebral artery blood flow [22, 23] and hypoactive cerebral blood vessels [24] were noted in patients with OSA after frequent sleep apnea. Third, increased arterial stiffness and increased sympathetic tone [25] were found to be related to OSA. These findings relating to coagulopathy, hemodynamic change and autonomic variation indicate a higher risk of WUS in patients with OSA. Possible reasons for the lack of significance of autonomic variation between the two groups might lie in the limited number of patients and the method of HRV analysis. We analyzed the whole-night HRV parameters but transient autonomic variations during sleep apnea may have a direct impact on WUS.

Only a few studies have dealt with the relationship between OSA and WUS with different definitions and methods. Palomäki et al. [26] were the first to report snoring as a risk factor for sleep-related brain infarction, defined as (1) stroke onset during nocturnal sleep, and (2) stroke onset during nocturnal sleep and within 30 min of waking. However, snoring does not actually indicate the diagnosis or severity of OSA prior to stroke. Martínez García et al. [27] performed a polysomnography (PSG) study in patients within 72 h of stroke onset and found that OSA was related to stroke onset during nocturnal sleep and onset within 1 h of waking. Stroke occurring during the early hours after waking was found to be associated with variation in blood pressure, heart rate and physical activity [28], but not with OSA. The duration of early hours after waking is still not clearly defined. Bassetti et al. [29] found that "night-time" stroke, defined as stroke onset between 9 p.m. and 6 a.m., was an independent predictor of apnea-hypopnea index (AHI). The definition of "night-time" stroke was based on a fixed time interval which does not accurately represent WUS.

WUS comprises 8–28% of all ischemic strokes [4–10] and 14% in a population-based study [11], but its correlation with clinical features, stroke risk factors and stroke classification are still not conclusive [5–7, 10, 11]. Some studies have concluded that WUS is associated with greater initial stroke severity and worse functional outcome [6–8], but other studies have shown no difference [9, 10]. In our study, 36.6% of patients (26 in 71) had WUS of mild to moderate stroke. The non-WUS group had a higher percentage of early favorable outcomes (as assessed in terms of an improvement in NIHSS score of ≥2 on discharge)

than WUS group (55.6 vs. 34.6%, $p = 0.089$), although the difference did not reach the statistical significance. WUS is not eligible for thrombolytic therapy based on the time restrictions [3] and might be related to poor early outcomes. Clinically, OSA is a treatable disease, and we suggest that treating OSA might benefit patients with pre-existing cardiovascular risk factors by lowering the risk of WUS. Although compliance with continuous positive airway pressure is another noticeable issue with variable results in patients with stroke [30, 31], we consider initiating treatment of OSA when stroke is stabilizing to decrease the risk of WUS.

It is difficult to precisely evaluate the severity of OSA prior to stroke in the general population. Moreover, the sleep respiratory data obtained from PSG in stroke patients might be influenced by the time of examination after stroke and stroke severity. OSA might be overestimated during the hyperacute stroke period as the prevalence of SDB can be as high as 62% during the first night following stroke, and OSA is the most common SDB [32, 33]. The severity of stroke might also have an influence on the severity of OSA due to acute deterioration in the upper airway musculature. Thus, we conducted the study after the hyperacute stroke period (average 6.2 ± 2.7 days after stroke) and selected patients with mild to moderate stroke (average NIHSS score 4.8 ± 2.8 on admission). There was no significant difference between the two groups in the time of examination or stroke severity.

There are some limitations in our study. We conducted a limited sleep study to diagnose OSA using the Embletta PDS for better sleep quality evaluation than the use of PSG in ischemic stroke patients during hospitalization. Although the Embletta PDS we used is classified as level 3 according to the recommendations of the American Academy of Sleep Medicine [34], the device has been validated with high sensitivity and specificity in both Caucasian and Chinese populations in the diagnosis of OSA [13]. Because there was no EEG recording to detect the sleep state, we estimated the sleeping time approximately according to the presence of smooth respiratory movement and nasal flow. Further study using PSG would allow not only the sleeping time to be precisely evaluated but also the impact of sleep respiratory parameters during different sleep stages on WUS to evaluated.

In conclusion, our study indicated that OSA is the only risk factor associated with WUS in those with mild to moderate ischemic stroke. There were no obvious distinguishing features in the clinical characteristics, risk factors, outcomes or autonomic variation between WUS and non-WUS patients. The true relationship between treating OSA and its benefit in lowering the risk of WUS still needs to be clarified by further studies.

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Conflicts of interest None.

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