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SCIENTIFIC INVESTIGATIONS

Association of Sleep Disordered Breathing with Wake-Up Acute Ischemic Stroke: A Full Polysomnographic Study

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Study Objectives: Sleep disordered breathing (SDB) is a frequent comorbidity in stroke patients. SDB is one of the independent risk factors for ischemic stroke. Conversely, stroke may contribute to SDB onset or aggravate premorbid SDB. Multiple mechanisms underlying SDB might be responsible for the development of stroke. The aim of this study was to compare polysomnographic, clinical, and laboratory characteristics of wake-up (WUS) and non-wake-up acute ischemic strokes (NWUS).

Methods: We prospectively enrolled 88 patients with acute ischemic stroke. Clinical characteristics of the population were recorded on admission, and blood samples were obtained in the fasting condition following morning. SDB was assessed using standard overnight polysomnography in the acute phase of the stroke.

Results: WUS were present in 16 patients (18.2%), and NWUS in 72 patients (81.8%). In WUS compared to NWUS, we observed significantly higher values of apnea-hypopnea index (24.8 vs. 7.6, p = 0.007), desaturation index ([DI] 26.9 vs. 8.8, p = 0.005), arousal index (22.6 vs. 13.1, p = 0.035), diastolic blood pressure (91.6 mm Hg vs. 85.2 mm Hg, p = 0.039), triglyceride levels ([TG] 1.9 mmol/L vs. 1.2 mmol/L, p = 0.049), and significantly lower levels of D-dimer (0.4 µg/L vs. 0.7 µg/L, p = 0.035). DI (CI: 1.003–1.054, p = 0.031) and TG (CI: 1.002–1.877, p = 0.049) were the only independent variables significantly associated with WUS in binary logistic regression model.

Conclusions: Although the design of our study does not prove the causal relationship between SDB and WUS, higher severity of SDB parameters in WUS supports this hypothesis.

Commentary: A commentary on this article appears in this issue on page 467.

Keywords: Sleep disordered breathing, acute ischemic stroke, wake-up stroke, polysomnography

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INTRODUCTION

A recent population-based study has shown that wake-up strokes (WUS) comprise 14% of all ischemic strokes. The same study concludes, that WUS do not differ from non-wake up strokes (NWUS) in clinical features, risk factors, or outcome.[1] There is a diurnal variation in the onset of stroke. Sleep tends to promote ischemic stroke, and there is a higher frequency of strokes occurring in the morning.[2,3] Sleep disordered breathing (SDB) is present in up to 72% of stroke patients and is one of the independent risk factors for stroke.[4,5] However, stroke may also aggravate premorbid SDB or even contribute to SDB onset.[6] Multiple mechanisms might link SDB with the onset of cerebral ischemia during the sleep, including coagulation changes, hemodynamic changes, blood pressure (BP) surges, inflammatory overactivity, increased arterial stiffness, increased sympathetic tone, paradoxical embolization, or the development of cardiac arrhythmias.[7–11] Currently, WUS patients are excluded from revascularization therapy; therefore, a thorough search for predictors and risk factors of WUS is desirable. The aim of this study was to compare polysomnographic, clinical, and laboratory characteristics of WUS and NWUS with mild-to-moderate severity.

BRIEF SUMMARY

Current Knowledge/Study Rationale: Currently, wake-up stroke patients are excluded from revascularization therapy, so a precise search for predictors and risk factors of wake-up strokes is desirable. The aim of this study was to compare polysomnographic, clinical, and laboratory characteristics of wake-up strokes and non-wake-up strokes with mild-to-moderate severity.

Study Impact: We emphasize the importance of significantly higher frequency of moderate-to-severe sleep apnea syndrome among the wake-up stroke population, as this population is indicated for positive airway pressure therapy. Our results suggest that there seems to be no superior pathomechanism linking sleep disordered breathing with wake-up stroke onset. However, several potential mechanisms including reduction of cerebral blood flow, decreased cardiac output, and baroreceptor and endothelial dysfunction should be investigated in future prospective studies.

METHODS

The study population consists of patients hospitalized in the stroke unit of the 1st Department of Neurology, Comenius University Bratislava from January 2011 to December 2014 with the

diagnosis of acute ischemic stroke of mild-to-moderate severity (National Institutes of Health Stroke Scale [NIHSS] < 15). Only those patients were enrolled into the study whose family members were able to determine the time of onset of ischemic stroke. WUS was defined as the occurrence of new symptoms suggestive of stroke detected upon waking up from sleep (not depending on the time of the day) and NWUS when symptoms were detected during the awake state. Subjects were excluded from the study in a case of more severe neurological deficit, impairment of consciousness, agitated confusion, acute chest infection, chronic lung disease, or if they refused to participate. The study was approved by the institutional ethics committee. All patients gave their informed consent prior to being recruited into the study.

The diagnosis of stroke was confirmed clinically, and the site of the ischemic lesion was confirmed by computed tomography (CT) or magnetic resonance imaging (MRI). Stroke workup included assessment of baseline stroke severity according to NIHSS and modified Rankin Scale (mRS), and the classification of etiology of stroke according to the TOAST (Trial of Org 10172 in Acute Treatment) criteria.[12–14] To determine the etiology of cerebral ischemia, we used carotid and transcranial ultrasonography, CT/MRI angiography, and echocardiography. In the detailed search for atrial fibrillation (AF), we reviewed medical records of all patients to search for the premorbid presence of AF. In further workup, we used native 12-lead electrocardiogram (ECG), continuous ECG monitoring in stroke unit, ECG monitoring during polysomnography, and 24-h Holter ECG monitoring.

Demographic data and vascular risk factors including age, gender, BP, neck circumference, waist circumference, body mass index (BMI), and current smoking habit were recorded on admission.

Blood tests were performed in fasting condition following morning. Samples were processed in local hospital laboratory, and parameters were set, including glycemia, leucocyte count, levels of total cholesterol, low density lipoproteins (LDL), high density lipoproteins (HDL), triglycerides (TG), C-reactive protein (CRP), fibrinogen, and D-dimer.

The sleep study was performed within 0–16 days (median 4 days) after stroke onset in standard sleep laboratory settings. All study subjects underwent full standard overnight polysomnography using Alice 5 device (Philips-Respironics, Netherlands). For recording, we used channels for electroencephalogram (EEG), electrooculogram, chin electromyogram, tibialis electromyogram, finger arterial oximetry, body position, and ECG. Pulse transit time (PTT) was determined as the time between the R-wave on the ECG and the subsequent arrival of the pulse wave in the pulse oximeter clipped on the subject's finger. Mean duration and number of PTT drops was recorded. To assess the airflow and breathing effort, nasal cannula, chest belt, and abdominal belt were used. Sleep parameters and respiratory events were scored according to standardized criteria. Apnea was defined as the cessation or the reduction of airflow ≥ 90% for > 10 s, hypopnea as a reduction in airflow ≥ 50% for 10 s with oxygen desaturation > 3%.[15] Scores were blinded to the time of stroke onset. The Epworth Sleepiness Scale (ESS) was used to assess the excessive daytime sleepiness.[16]

The statistical analyses were performed using SPSS version 18 (SPSS Inc., Chicago, USA). Categorical variables were expressed as numbers and proportions (%), continuous variables as means ± standard deviation or median, interquartile range (IQR), minimal and maximal values. To compare groups, χ^2 test, Student t-test, and Mann-Whitney test were used for particular variables. Binary logistic regression analysis was used to identify factors that contributed to the WUS. p values < 0.05 were considered statistically significant.

RESULTS

The study population consisted of 32 females (36.4%) and 56 males (63.6%), with a mean age 65.4 ± 13.0 years. Included patients suffered mild-to-moderate neurological deficit; median NIHSS was 4 (range 1–12) and mean mRS 2.4 ± 0.9. No significant disability or slight disability (mRS ≤ 2) was present in 49 patients (55.7%), moderate disability (mRS = 3) in 25 patients (28.4%), and moderately severe disability (mRS = 4) in 14 patients (15.9%). WUS were present in 16 patients (18.2%) and NWUS in 72 patients (81.8%). Of 16 WUS, 15 strokes (93.8%) occurred during nighttime sleep and 1 WUS (6.2%) occurred on awaking from daytime sleep (at 16:00). Characteristics of patients with WUS and NWUS are included in **Table 1**. In WUS compared to NWUS, we observed significantly higher values of apnea-hypopnea index ([AHI] 24.8 vs. 7.6, p = 0.007, see **Figure 1**), desaturation index ([DI] 26.9 vs. 8.8, p = 0.005, see **Figure 2**), arousal index ([AI] 22.6 vs. 13.1, p = 0.035), diastolic BP (91.6 mm Hg vs. 85.2 mm Hg, p = 0.039), TG levels (1.9 mmol/L vs. 1.2 mmol/L, p = 0.049), and significantly lower levels of D-dimer (0.4 μg/L vs. 0.7 μg/L, p = 0.035). The frequency of sleep apnea syndrome ([SAS] defined as AHI > 5) in WUS (13 subjects, 81.3%) did not significantly differ from the frequency in NWUS (43 subjects, 59.7%; p = 0.105). However, the frequency of moderate-to-severe SAS (AHI > 15) was significantly higher in WUS (11 subjects, 68.8%) than in NWUS (21 subjects, 29.2%; p = 0.003; see **Figure 3**. Similarly, the frequency of severe SAS (AHI > 30) was significantly higher in WUS (7 subjects, 43.8%) than in NWUS (11 subjects, 15.3%; p = 0.011). Obstructive sleep apnea (OSA) was the more frequent type of SDB among both populations. This was present in 10 patients (76.9%) among WUS population and 26 patients (60.5%) among NWUS population. The difference was not statistically significant (p = 0.278). The remaining patients suffered central sleep apnea (CSA), which was present in 3 patients (23.1%) among the WUS population and 17 patients (39.5%) among the NWUS population (**Table 2**). DI (CI: 1.003–1.054, p = 0.031) and TG (CI: 1.002–1.877, p = 0.049) were the only independent variables significantly associated with WUS in binary logistic regression model. The populations did not differ in stroke characteristics (severity of the stroke, site of stroke), demographic data (age, gender, neck circumference, waist circumference, BMI), or in current smoking habit.

DISCUSSION

Among our population with acute ischemic strokes of mild-to-moderate severity (in WUS compared to NWUS), we observed

Table 1—Characteristics of patients with wake-up stroke and non-wake-up stroke.

	Wake-Up Stroke	Non-Wake-Up Stroke	p
Patients	16 (18.2%)	72 (81.8%)	
Female/male sex	5/11 (31.3%/68.7%)	27/45 (37.5%/62.5)	0.638
Age, years	62.8 ± 13.8	65.9 ± 12.8	0.385
NIHSS	4.0, 1.0 (1.0–9.0)	4.0, 3.0 (1.0–12.0)	0.665
mRS	2.0, 1.8 (1.0–4.0)	2.0, 1.0 (1.0–4.0)	0.658
Supratentorial location	12 (75%)	58 (80.6%)	0.618
Cerebellar location	1 (6.3%)	5 (7.0%)	0.921
Brainstem location	2 (12.5%)	6 (8.3%)	0.600
Supra and infratentorial location	1 (6.3%)	3 (4.2%)	0.717
BMI, kg/m^2	29.3 ± 4.3	27.7 ± 4.7	0.205
Neck circumference, cm	40.9 ± 3.8	39.6 ± 4.4	0.261
Waist circumference, cm	103.9 ± 13.6	102.3 ± 11.0	0.639
Smoking habit	7 (43.8%)	15 (20.8%)	0.056
Glycemia, mmol/L	7.3 ± 3.0	6.0 ± 2.1	0.049*
Leucocyte count, ×10^9/L	8.1, 4.7 (3.5–27.7)	7.7, 2.9 (3.5–14.9)	0.527
TG (mmol/L)	1.9, 1.5 (0.1–11.8)	1.2, 0.8 (0.5–7.4)	0.049*
Total cholesterol, mmol/L	5.3 ± 1.3	4.9 ± 1.4	0.336
LDL, mmol/L	3.7 ± 1.1	3.4 ± 1.2	0.364
HDL, mmol/L	1.1 ± 0.3	1.2 ± 0.3	0.220
CRP, mg/L	1.6, 5.7 (0.2–18.7)	3.2, 7.8 (0.1–73.2)	0.344
Fibrinogen, µg/L	3.2 ± 1.0	3.1 ± 1.0	0.888
D-dimer, µg/L	0.4, 0.5 (1.2–1.6)	0.7, 1.2 (0.2–11.8)	0.035*
Systolic BP, mm Hg	164.4 ± 28.7	157.4 ± 22.5	0.287
Diastolic BP, mm Hg	91.6 ± 13.6	85.2 ± 10.4	0.039*
PTT, ms	356.6 ± 24.8	359.9 ± 33.2	0.704
PTT drops/h	19.7, 26.1 (4.1–60.1)	14.0, 22.9 (0.7–85.5)	0.191
TST, min	386.2 ± 86.2	394.4 ± 66.4	0.676
AHI, events/h	24.8, 46.8 (0.5–79.3)	7.6, 18.0 (0.0–87.4)	0.007**
DI, events/h	26.9, 45.4 (1.5–80.0)	8.8, 16.9 (0.0–98.4)	0.005**
AI, events/h	22.6, 20.3 (2.1–46.4)	13.1, 13.4 (0.9–66.3)	0.035*
Average sat, %	91.5 ± 2.4	92.6 ± 2.1	0.074
Minimal sat, %	84.9 ± 5.5	86.8 ± 5.3	0.206
ESS	4.0, 4.8 (1.0–8.0)	3.0, 4.5 (0.0–13.0)	0.400
% of TST in supine position	84.9 ± 5.5	84.9 ± 5.5	0.412

Values in table are presented as n (%), mean ± standard deviation or median, interquartile range (min–max). *p < 0.05. **p < 0.01. AHI, apnea-hypopnea index; DI, desaturation index; AI, arousal index; BMI, body mass index; ESS, Epworth Sleepiness Scale; sat, saturation of blood with oxygen, mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; TG, triglycerides; LDL, low density lipoprotein; HDL, high density lipoprotein; BP, blood pressure; PTT, pulse transit time; CRP, C-reactive protein; TST, total sleep time

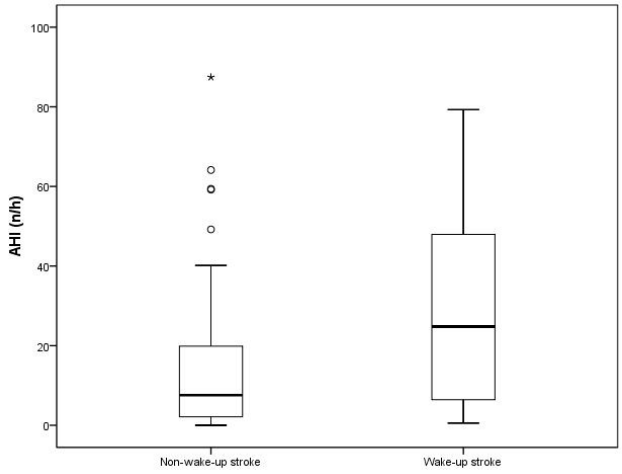
Table 2—Frequency of sleep apnea syndrome in population with wake-up stroke and non-wake-up stroke.

	Wake-Up Stroke	Non-Wake-Up Stroke	p
SAS (AHI > 5)	13 (81.3%)	43 (59.7%)	0.105
OSA	10 (76.9%)	26 (60.5%)	0.278
CSA	3 (23.1%)	17 (39.5%)	0.278
Moderate-to-severe SAS (AHI > 15)	11 (68.8%)	21 (29.2%)	0.003**
Severe SAS (AHI > 30)	7 (43.8%)	11 (15.3%)	0.011*

*p < 0.05. **p < 0.01. SAS, sleep apnea syndrome; OSA, obstructive sleep apnea; CSA, central sleep apnea; AHI, apnea-hypopnea index

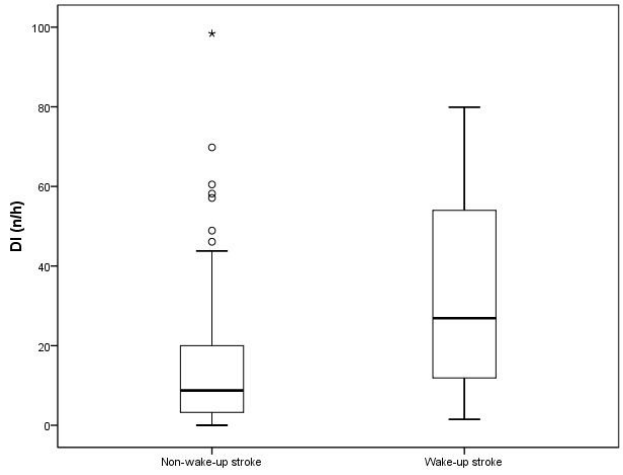
significantly higher values of AHI, DI, AI, diastolic BP, and TG levels, and significantly lower levels of D-dimer. DI and TG were the only independent variables significantly associated with WUS in binary logistic regression model. The frequency of SAS in WUS did not significantly differ from the frequency in NWUS. However, the frequency of moderate-to-severe SAS

Figure 1—Apnea-hypopnea index (AHI) in patients with wake-up stroke and non-wake-up stroke (24.8 vs. 7.6, p = 0.007).



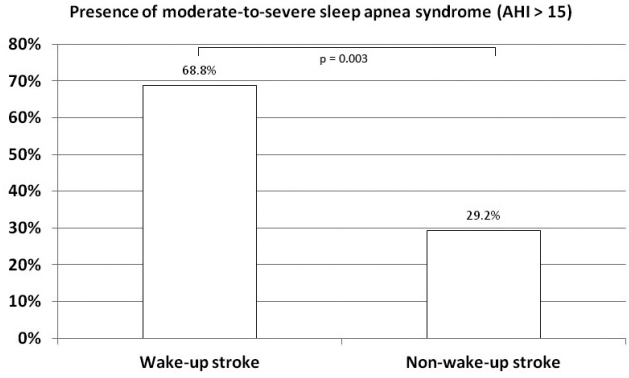
Open circles and asterisks represent extreme values of AHI.

Figure 2—Desaturation index (DI) in patients with wake-up stroke and non-wake-up stroke (26.9 vs. 8.8, p = 0.005).



Open circles and asterisks represent extreme values of DI.

Figure 3—Presence of moderate-to-severe sleep apnea syndrome in patients with wake-up stroke and non-wake-up stroke (68.8% vs. 29.2%, p = 0.003).



(AHI > 15, that is a threshold for a positive airway pressure therapy) was significantly higher in WUS than in NWUS. Similarly, the frequency of severe SAS was significantly higher in WUS than in NWUS. OSA was more frequent type of SDB in both populations. Populations did not differ in stroke site and severity or in demographic data.

A population-based study of 1,854 ischemic strokes has shown that WUS do not differ from NWUS in clinical features, traditional risk factors, or outcome.[1] Limited possibilities for revascularization therapy in WUS make a precise search for predictors and preventable risk factors of WUS highly reasonable. Our study, as well as previous studies, confirmed the association of WUS with SDB, which is a treatable risk factor of vascular diseases.[17–19] Using respiratory polysomnography (Autoset Portable Plus II device) in 164 patients with diagnosis of acute stroke, Martinez Garcia et al. found significantly higher AHI (33.3 vs. 24.7), greater nighttime desaturation, and a greater probability of SDB symptoms prior to stroke in strokes occurred during sleep or on waking compared to the strokes that occurred during the rest of the day.[18] Bassetti et al. among 152 patients with acute ischemic stroke found age, diabetes mellitus, and nighttime stroke onset to be independent predictors of AHI. SDB was assessed using a portable automatic CPAP (continuous positive airway pressure) device (AutoSet-diagnostic mode, ResMed).[19] Use of full polysomnography as the test for diagnosing SDB is one of the strengths of our study. In a recent prospective study of 71 patients with acute mild-to-moderate ischemic stroke, the patients with WUS had a significantly higher AHI (23.1 ± 19.4 vs. 12.5 ± 11.9, p = 0.016) and lower mean blood oxygen saturation (95.1% ± 1.5% vs. 95.8% ± 1.3%, p = 0.046) than the patients with NWUS. Limited sleep study was used to diagnose SDB. No EEG recording was used to detect the sleep state, so total sleep time, as well as arousals, could have not been evaluated. No significant differences in clinical characteristics (age, gender, obesity, hypertension, diabetes mellitus, dyslipidemia, AF, smoking, severity and etiology of stroke) were found in this study.[17] Results of our study are consistent with previous studies. We observed significantly higher values of AHI and DI among the population of WUS. We emphasize the importance of significantly higher frequency of moderate-to-severe SAS among WUS population (68.8% vs. 29.2%), as this population is indicated for positive airway pressure therapy. Use of full polysomnography additionally allowed us to discover significantly higher AI among the population of WUS. Although AI did not remain an independent variable significantly associated with WUS in the binary logistic regression model, WUS seem to have more disruptions of sleep. All causes of arousals, including non-respiratory, were included in our study. We suggest that most of the arousals due to respiratory events and movement disorders leading to disruption of sleep might be present in stroke patients. More studies are needed to elucidate their impact.[20,21]

Apart from SDB parameters, we found among WUS population significantly higher values of diastolic BP and TG levels, and significantly lower levels of D-dimer. Moreover, DI and

TG remained as the only independent variables significantly associated with WUS in the regression model. We suppose that these differences in WUS and NWUS could be linked to SDB. Several mechanisms might link SDB with ischemic stroke.[7–11] Multiple changes during respiratory events including cardiac arrhythmias, BP swings, inflammatory changes, and coagulation changes may be responsible for stroke onset during sleep in patients with SDB.[22] Previous studies described changes of coagulation in SDB patients including increased blood fibrinogen and platelet aggregation.[23,24] Our study found nonsignificant differences in fibrinogen levels in WUS and NWUS populations. Discovery of significantly lower D-dimer levels in WUS population suggests the minor importance of thrombotism in WUS onset. Despite detailed search for AF, we also failed to find any significant differences in frequency of AF between populations. We also did not find any significant difference in inflammation status represented by leucocyte count and CRP level.

To assess BP swings during sleep, we used a parameter of PTT drop. PTT is the time between the R-wave on the ECG (representing ventricular contraction and start of ejection) and the subsequent arrival of the pulse wave in the pulse oximeter clipped on the subject's finger. BP changes can be recorded by monitoring changes in PTT.[25] A sudden increase in BP increases the vascular tone, which results in an increase of arterial wall rigidity and shorter PTT.[26] Although there was a higher number of PTT drops in WUS, the difference was not statistically significant. On admission, we found significantly higher levels of diastolic BP in WUS, supporting the role of BP changes in WUS onset. We must admit that use of Holter BP monitoring (a reference technique for diagnosis of arterial hypertension) could bring more consistent findings in future studies.[27]

Several publications suggest that SDB is associated with metabolic changes including impaired glucose tolerance, insulin resistance, and dyslipidemia.[28,29] Despite no significant differences in glycaemia, total cholesterol, LDL, and HDL levels, we found significantly higher TG levels among WUS population. Moreover, TG remained as the independent variable significantly associated with WUS in the regression model. TG are considered a biomarker of vascular diseases, although there is no strong evidence that TG are directly involved in the process of atherogenesis.[30] The available data from prospective cohort studies and case-control studies are inconsistent. Five of 12 case-control studies identified a positive relationship between ischemic stroke risk and elevated fasting TG. Meta-analysis of 1,996 ischemic stroke cases revealed an odds ratio of 1.15 (95% CI 1.08–1.21). The association between TG levels and ischemic stroke, especially WUS, needs further investigation.[31] We suppose that higher TG levels in WUS population might also relate to the higher burden of other vascular risk factors in WUS population (trend towards higher BMI, BP, smoking habit). Our results suggest that there seems to be no superior pathomechanism linking SDB with WUS onset. However, other mechanisms including reduction of cerebral blood flow, decreased cardiac output, and baroreceptor and endothelial dysfunction should be investigated in the future prospective studies.[9,10,22,32,33]

Selection bias seems to be the main limitation of our study, because we enrolled only subjects with minor (NIHSS: 1–4) to moderate stroke (NIHSS: 5–15). The population of our study most likely differs from representative sample population with acute cerebral ischemia due to absenting patients with severe cardioembolic strokes. The population of small vessel strokes with generally milder severity may be more representative. On the contrary, recent population-based study has shown that clinical features including stroke severity in WUS and NWUS do not differ, and therefore the extent of selection bias should be similar among both populations.[1]

CONCLUSIONS

Although the design of our study does not prove the causal relationship between SDB and WUS onset, higher severity of SDB parameters in WUS supports this hypothesis. We emphasize the importance of significantly higher frequency of moderate-to-severe SAS in WUS population, as this population is indicated for positive airway pressure therapy. Multiple mechanisms might link SDB with WUS, including coagulation changes, BP surges, inflammatory overactivity, increased arterial stiffness, or the development of cardiac arrhythmias. Our results suggest that there seems to be no superior pathomechanism linking SDB with WUS onset. Several other potential mechanisms including reduction of cerebral blood flow, decreased cardiac output, paradoxical embolization, and baroreceptor and endothelial dysfunction, as well as the association between TG levels and WUS should be investigated in future prospective studies.

ABBREVIATIONS

AF, atrial fibrillation
AHI, apnea-hypopnea index
AI, arousal index
BMI, body mass index
BP, blood pressure
CPAP, continuous positive airway pressure
CRP, C-reactive protein
CSA, central sleep apnea
CT, computed tomography
DI, desaturation index
ECG, electrocardiogram
EEG, electroencephalogram
ESS, Epworth Sleepiness Scale
HDL, high density lipoproteins
IQR, interquartile range
LDL, low density lipoproteins
MRI, magnetic resonance imaging
mRS, modified Rankin Scale
NIHSS, National Institutes of Health Stroke Scale
NWUS, non-wake-up stroke
OSA, obstructive sleep apnea
PTT, pulse transit time
SAS, sleep apnea syndrome

SDB, sleep disordered breathing
TG, triglycerides
TOAST, Trial of Org 10172 in Acute Treatment
TST, total sleep time
WUS, wake-up stroke

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