Stroke Volume Predicts Nocturnal Hypoxemia in the Acute Ischemic Stroke after Intravenous Thrombolysis

Jaana K. Huhtakangas, MD,* Tarja Saaresranta, MD, PhD,† Michaela K. Bode, MD, PhD,‡ Risto Bloigu, MSc,§ and Juha Huhtakangas, MD, PhD‖

The Goal: The aim of the study was to investigate whether stroke volume or the presence of ischemic stroke lesion on follow-up computed tomography 1 day after admission had association with sleep apnea among ischemic stroke patients undergoing thrombolysis. *Materials and Methods:* We prospectively recruited 110 consecutive ischemic stroke patients and performed computed tomography on admission and after 24 hours after intravenous thrombolysis. Stroke volume was measured from post-thrombolysis computed tomography scans. Unattended cardiorespiratory polygraphy with a 3-channel device was performed during 48 hours after admission. *Findings:* Of 110 ischemic stroke patients treated with thrombolysis 65.5% were men. Mean age was 65.8 years and body mass index 27.5 kg/m^2. The mean Epworth sleepiness scale score was 4.7. Eight patients (12.7%) with visible acute stroke after thrombolysis and none in the other group had hemorrhage as complication ($P < .001$). Sleep apnea, determined as a respiratory event index greater than or equal to 5/hour, was diagnosed in 96.4% patients. Respiratory event index greater than 15/h was found in 72.8% of patients. Both mean baseline oxygen desaturation index (23.9 versus 16.5, $P = .028$) and obstructive apneas/hour (6.2 versus 2.7, $P = .007$) were higher in visible stroke group. Stroke volume (mean 15.9 mL) correlated with proportion of time spent below saturation less than 90%, $P = .025$. *Conclusions:* Acute ischemic stroke patients treated with thrombolysis with visible stroke were more likely to have nocturnal hypoxemia than patients with not visible strokes. Stroke volume correlated with time spent below saturation of 90%.

Key Words: Thrombolysis—computed tomography—cardiorespiratory polygraphy—visible stroke—sleep apnea.

Abbreviations: AHI, apnea hypopnea index; REI, respiratory event index; ODI, oxygen desaturation index; NIHSS, National Institutes of Health Stroke Scale; BMI, body mass index; PAD, peripheral arterial disease; ESS, Epworth Sleepiness Scale; mRS, modified Rankin scale; HI, hemorrhagic infarction; PH, parenchymal hematoma; AASM, American Academy of Sleep Medicine; ODI4, oxyhemoglobin decrease of greater than or equal to 4%; SD, standard deviation; t-PA, intravenous recombinant tissue plasminogen activator

From the *Respiratory Medicine Unit, Institute of Clinical Medicine, Oulu University Hospital, MRC Oulu, Oulu, Finland; †Turku University Hospital, Division of Medicine, Department of Pulmonary Diseases and Sleep Research Centre, Department of Pulmonary Diseases and Clinical Allergology, University of Turku, Turku, Finland; ‡Oulu University Hospital, Department of Clinical Radiology, Oulu, Finland; §Medical Informatics and Statistics Research Group, University of Oulu, Oulu, Finland; and ‖Department of Neurology, Oulu University Hospital, Oulu, Finland.

Received April 13, 2019; revision received May 21, 2019; accepted June 5, 2019.

This study was supported by The Finnish Anti-Tuberculosis Association Foundation, Väinö and Laina Kivi Foundation, Tampere Tuberculosis Foundation, The Research Foundation for Respiratory Diseases, Maire Taponen Foundation, and Jalmari and Rauha Ahokas Foundation. The ApneaLink Plus (Resmed, Sydney, Australia) devices were provided by Resmed Finland.

We studied stroke volume and visible stroke association with sleep apnea among ischemic stroke patients with thrombolysis treatment in Oulu University Hospital, Department of Neurology, Finland.

Address correspondence to Jaana K. Huhtakangas, MD, Respiratory Medicine Unit, Institute of Clinical Medicine, Oulu University Hospital, Box 25, Kajaanintie 50, Oulu 90029 OYS, Finland. E-mail: jaana.huhtakangas@ppshp.fi.

1052-3057/$ - see front matter

https://doi.org/10.1016/j.jstrokecerebrovasdis.2019.06.017

Introduction

Sleep apnea is characterized by repetitive episodes of upper airway closing, decreases in oxygen saturation and increased sympathetic activation during sleep. In general population, it is present in 14% of middle-aged men and 5% of women,[1] whereas among stroke patients the prevalence estimates of sleep apnea range from 62.5% to 91.2%.[2-4] Sleep apnea may increase the risk of developing cardiovascular diseases[5] through several pathways, such as intermittent hypoxia, sleep fragmentation, chronic sympathetic activation, and systemic inflammation.[6,7]

The severity of sleep apnea is usually defined by the apnea hypopnea index (AHI) or respiratory event index (REI). Oxygen desaturation index (ODI) reflects frequency of drops in oxygen saturation and is a measure of intermittent hypoxia. The recording time spent with oxygen saturation SaO_2 less than 90% reflects the total time exposed to marked hypoxemia. After stroke 20% of patients develop oxygen desaturation within first few hours and nearly two-thirds are affected within the first 48 hours.[8] Stroke lesion can alter the central regulation of respiration, leading to sleep apnea or producing weakness of respiratory muscles.[8] Sleep apnea patients with nocturnal hypoxemia (oxygen saturation below 90%) are at risk of stroke, especially when desaturations exist more than 10% of nocturnal time.[9] A systematic review reported obstructive sleep apnea after stroke to be a risk factor for both recurrent vascular event and all-cause mortality.[10] Among stroke patients, oxygen desaturation,[11] AHI,[12] Scandinavian Stroke Scale,[12] and stroke size on admission[13] have been reported to independently predict impaired functional outcome among stroke patients.

Our study had 3 aims. First, we investigated whether stroke volume is associated with sleep apnea during the first 48 hours in ischemic stroke patients, treated with thrombolysis. Second, we examined differences in nocturnal recording results of stroke patients with or without a visible lesion in follow-up imaging. Third, we also studied the association between the measures of sleep disordered breathing and the presence of hemorrhage after thrombolysis. As far the knowledge about the association between stroke size and sleep apnea related hypoxia is limited.

Materials and Methods

We recruited 204 consecutive ischemic stroke patients of the age of 18 years or older, who were admitted to the Stroke Unit at the Department of Neurology of the Oulu University Hospital during April 2013 and January 2015. This study was performed in Oulu, Finland. Of those we included all 110 stroke patients receiving thrombolysis in this study. We classified ischemic strokes into 2 size categories: patients with (n = 63) or without (n = 47) visible acute ischemic stroke 24 hours after intravenous thrombolysis. The thrombolysis was administered within 4.5 hours from the onset of symptoms for patients who were independent, had the National Institutes of Health Stroke Scale scores (NIHSS) over 2, and did not have any contraindications for intravenous thrombolysis. The exclusion criteria for thrombolytic therapy for stroke were defined according to the Finnish Current Care Guideline for Ischemic stroke.[14] All study patients participated voluntarily and gave their written informed consent. Our study protocol was approved by the ethics committee of the Northern Ostrobothnia Hospital District (approval number 21/2013).

The demographic data included age, sex, body mass index, smoking habits, consumption of alcohol, snoring, hypertension, hypercholesterolemia, coronary artery disease, atrial fibrillation, peripheral arterial disease, hemorrhage as complication, and deaths. Smoking habits were expressed as pack years and whether a patient was a current smoker or not. Daytime sleepiness was assessed by the Epworth Sleepiness Scale (scale 0-24).[15] Stroke outcome was estimated by the modified Rankin scale (scale 0-5).[16] The stroke severity was assessed by the NIHSS (scale 0-35).[17] We classified patients into 2 groups depending if they had or did not have a visible lesion in follow-up imaging.

The experienced neuroradiologist assessed all computed tomography (CT) scans or magnetic resonance imaging (MRI) available for the acute ischemic stroke lesions and stroke volume measurements. Depending on the CT-machine, sequential technique with 5 mm axial slices or helical acquisition providing volumetric data was used, the latter being reformatted to 3-5 mm thick slices on axial plane. Area of each infarction was determined by tracing their boundaries on each slice on a clinical workstation. The obtained area was multiplied with the slice thickness, and the volume of each slice was summed. One patient had only MRI images available, and the volume was measured from diffusion weighted images in a similar manner. Multiple infarctions were combined as 1 volume. The hemorrhagic events were classified as hemorrhagic infarction types 1 and 2 and parenchymal hematoma (PH) types 1 and 2 according to previous definitions.[18]

An unattended cardiorespiratory polygraphy with portable type 4 device[19] (a 3-channel portable device, Apnea-Link Plus, Resmed, Sydney, Australia) was performed on study patients. The nocturnal recordings were scored manually (American Academy of Sleep Medicine, AASM criterion)[20] by the same scorer without blinding. We used the threshold for arterial oxyhemoglobin decreases of greater than or equal to 4% per hour (ODI4). Nocturnal recording data with minimum 4 hours successful recording were accepted for analyses. The number of apneas and hypopneas per hour of nocturnal recording was expressed by REI. Hypopnea was defined as a greater than 30% decrease of the baseline amplitude of breathing lasting greater than or equal to 10 seconds that is associated with SaO_2 drop of greater than 3%. Sleep apnea was defined as an REI greater than or equal to 5/h. Desaturation was described with measures of mean SaO_2, lowest

Table 1. *Characteristics of patients at baseline, all data were recorded on admission*

Characteristics of patients	Patients with visible acute ischemic stroke after thrombolysis treatment n = 63	Patients without visible acute ischemic stroke after thrombolysis treatment n = 47	Total n = 110	*P* value
Men, n (%)	43 (68.3)	29 (61.7)	72 (65.5)	.475
Mean age, years (SD)	64.7 (14.4)	67.4 (14.8)	65.8 (14.6)	.345
Mean BMI, kg/m^2 (SD)	27.4 (5.3)	27.5 (4.3)	27.5 (4.9)	.937
Current smoking, n (%)	13 (20.6%)	7 (14.9%)	20 (18.2)	.440
Mean pack years, years (SD)	9.5 (15.5)	7.6 (12.7)	8.7 (14.4)	.392
Alcohol users, n (%)	11 (17.5)	8 (17.0)	19 (17.3)	.952
Heavy alcohol users, ≥30 g/d, n (%)	1 (1.6)	2 (4.3)	3 (2.7)	.575
Mean neck circumference, cm (SD)	43.0 (5.9)	41.1 (4.9)	42.2 (5.6)	.084
Mean waist circumference, cm (SD)	103.4 (15.5)	103.2 (15.2)	103.3 (15.3)	.942
Snoring, n (%)	46 (73.0%)	33 (70.2)	79 (71.8)	.746
Mean ESS, score (SD)	4.5 (2.9)	5.0 (3.1)	4.7 (3.0)	.455
Mean NIHSS (scale 0-30) (SD)	8.5 (5.5)	5.2 (3.5)	7.1 (5.0)	<.001
Rankin scale (scale 0-5) n (%)				
Rankin scale 0	49 (44.5)	31 (28.2)	80 (72.7)	.081
Rankin scale 1	8 (7.3)	7 (6.4)	15 (13.6)	.085
Rankin scale 2	2 (1.8)	1 (.9)	3 (2.7)	.693
Rankin scale 3	4 (3.6)	6 (5.5)	10 (9.1)	.632
Rankin scale 4	0 (0)	2 (1.8)	2 (1.8)	.285
Rankin scale 5	0 (0)	0 (0)	0 (0)	1.000
Hypertension n (%)	36 (57.1)	29 (61.7)	65 (59.1)	.630
Hypercholesterolemia n (%)	25 (39.7)	21 (44.7)	46 (41.8)	.599
Diabetes mellitus n (%)	13 (20.6)	8 (17.0)	21 (19.1)	.633
Coronary artery disease n (%)	11 (17.5)	11 (23.4)	22 (20.0)	.441
Atrial fibrillation n (%)	3 (4.8)	2 (4.3)	5 (4.5)	1.000
PAD n (%)	3 (4.8)	2 (4.3)	5 (4.5)	1.000
Hemorrhage as complication, n (%)	8 (12.7)	0 (.0)	8 (7.3)	<.001
Death n %	3 (4.8)	1 (2.1)	4 (3.6)	.634

BMI, body mass index; ESS, Epworth sleepiness scale; PAD, peripheral arterial disease.

SaO_2, and percentage of nocturnal recording time with SaO_2 below 90%.

Demographic and nocturnal recording data are reported as means and standard deviations (SD). The chi-square test or the Fisher exact test was used to categorical variables, whereas normally distributed variables were assessed by the Student's *t*test. We used the 2-sample test of proportion to evaluate the equality of proportions for both the modified Rankin scale scores and sleep apnea severity. Group comparisons were performed using the Mann-Whitney *U* test when the data were not normally distributed. Spearman correlation coefficient was used to correlations between stroke volume and REI, ODI4, and percent of time spent below saturation 90%. *P* values of less than .05 were considered statistically significant. Statistical analyses were computed using IBM SPSS (IBM Corp. Released 2013; IBM SPSS Statistics for Windows, Version 22.0, Armonk, NY: IBM Corp.).

Results

In the entire cohort 65.5% were male, and the sex distribution did not differ between the groups as shown in Table 1. There were no between-group differences in age, body mass index, smoking, pack years, alcohol users, neck- and waist circumference, snoring, Epworth Sleepiness Scale scores, Rankin scale scores, hypertension, hypercholesterolemia, diabetes, coronary artery disease, atrial fibrillation, peripheral arterial disease and deaths. In the whole group, the mean volume of stroke was 15.9 mL (median .6 mL, SD 40.8). Patients with visible stroke had severer strokes measured by NIHHS score. Hemorrhage as complication was detected only in the group with a CT lesion (8/12.7%, $P < .001$). There were 3 (4.8%) deceased patients in the visible stroke group and 1 (2.1%) in the other group. The mean time interval from baseline to death was 67.3 (SD 51.9) days.

The results of unattended cardiorespiratory polygraphy of patients with or without a CT lesion after thrombolysis are shown in Table 2. Sleep apnea (REI ≥ 5/h) was diagnosed in 106 (96.4%) patients. At least moderate (REI > 15/h) was found in 80 (72.8%) of patients. REI per hour, central apneas and hypopneas per hour, average saturation, lowest saturation, percentage of nocturnal recording time with SaO_2 below 90% and sleep apnea severity did not differ between the groups. The patients with visible stroke had higher ODI4/h (23.9 versus 16.5, $P = .028$) and more obstructive apneas/h (6.2 versus 2.7, $P = .007$) as compared to the patients without visible stroke.

Table 2. *Unattended cardiorespiratory polygraphy results of patients with or without visible acute ischemic stroke after thrombolysis treatment*

Outcome	Patients with visible stroke n = 63	Patients without visible stroke = 47	Total n = 110	*P* value
Sleep apnea n (%)	59 (93.7)	47 (100.0)	106 (96.4)	.134
Mean REI/h (SD)	35.8 (25.1)	30.9 (20.0)	33.7 (23.1)	.257
Mean ODI4/h (SD)	23.9 (21.3)	16.5 (13.4)	20.7 (18.7)	.028
Mean OAI/h (SD)	6.2 (9.3)	2.7 (3.0)	4.7 (7.5)	.007
Mean CAI/h (SD)	4.9 (8.7)	2.5 (4.3)	3.9 (7.3)	.053
Mean MAI/h (SD)	.05 (.2)	.06 (.4)	.1 (.3)	.799
Mean hypopneas/h (SD)	24.6 (19.3)	25.6 (18.5)	25.0 (18.9)	.774
Mean average oxygen saturation (SD)	92.5 (2.0)	92.9 (2.3)	92.7 (2.1)	.362
Mean lowest oxygen saturation (SD)	79.6 (8.7)	82.3 (6.9)	80.8 (8.0)	.074
Saturation <90%, % (SD)	19.6 (22.2)	12.9 (21.6)	16.7 (22.1)	.114
Sleep apnea severity				
No sleep apnea n (%)	4 (3.6%)	0 (0)	4 (3.6)	.189
Mild (REII 5-15/h) n (%)	12 (10.9)	14 (12.7)	26 (23.6)	.771
Moderate (REI 15-30/h) n (%)	18 (16.4)	10 (9.1)	28 (25.5)	.264
Severe (REI ≥ 30/h) n (%)	29 (26.4)	23 (20.9)	52 (47.3)	.504

CAI, central apnea index; MAI, mixed apnea index; OAI, obstructive apnea index; ODI4, oxygen desaturation index 4%; REI, respiratory event index.

The infarct volume correlated positively with time spent SaO_2 below 90% ($P = .025$; Fig 1). Stroke volume did not correlate with Rankin scale score, REI or ODI4. We could not analyze if stroke size predicted sleep apnea, because 96.4% of patients had sleep apnea (AHI ≥ 5/h), and the confidence interval was too wide. There was no correlation between volume ($P = .904$) or visibility ($P = .385$) of stroke and diagnosis of sleep apnea with cut-off REI greater than or equal to 15. The stroke was located in middle cerebral artery in 60.9% of cases, 17.3% in lacunar region, and 21.7% in other region. The severity of sleep apnea in study patients, jointly with their stroke locations are illustrated in Fig 2.

Those 8 patients having hemorrhagic transformation all had sleep apnea. They had mean REI 43.5 (SD 19.8)/h, ODI4 29.1 (20.8)/h, obstructive apneas 6.6 (10.3)/h, central apneas 9.5 (11.6)/h, hypopneas 27.4 (15.7)/h, average oxygen saturation 92.5 (1.9)%, lowest oxygen saturation 81.0 (2.4)%, and saturation below 90% 22.5 (24.4)% of time.

Discussion

Our main finding was that the ischemic stroke volume and nocturnal time spent below saturation 90% correlated positively. In the study of Iranzo et al[21] the infarct volume did not differ between patients having AHI under or at least 10. Oxygen desaturation may impair brain damage because the oxygen delivery is reduced to penumbral brain tissue.[8,22,23] Previous studies have shown that nearly 20% of acute stroke patients develop intermittent hypoxia during first hours after stroke and almost two-thirds within 48 hours.[8,22,23] Kendzerska et al[24] evaluated the association between obstructive sleep apnea related variables and cardiovascular events and observed that the sleep time with SaO_2 below 90% was the strongest predictor (hazard ratio 1.50) for cardiovascular events. Previous study has shown stroke patients with more severe strokes measured by NIHHS scale and increased age to be more likely to develop oxygen desaturation.[22]

In our study, stroke patients with visible lesion on neuroimaging after thrombolysis had higher ODI4 than those without visible lesion. In the study of Turkington et al[25] the median ODI4 was even higher (33) than in our study (20.7). In an another study, the obstructive events associated with at least 4% drop in saturation and were independently associated with cardiovascular disease, suggesting that intermittent hypoxia is a matter of great importance.[26] Untreated sleep apnea causes hypoxia, sympathetic activation, systemic inflammation, oxidative stress, and endothelial dysfunction which may start atherogenesis.[27] In a study of 188 ischemic stroke patients, mean oxygen saturation below 94% for 10 minutes on admission was 1 of the positive predictive factors for mortality.[28] In this current study, stroke patients with visible stroke had fairly low mean lowest saturation (79.6%). Turkington et al[25] found that stroke severity and the minimum saturation were independently associated with disability after 6 months follow-up.

Our patients with visible stroke had significantly more obstructive apneas per hour than those without visible lesion. This is in line with previous studies,[25,29] which also showed that obstructive apneas were the most common type of apneas among stroke patients. Obstructive sleep apnea has been connected with an elevated risk of cardiovascular disease in numerous observational studies.[5,30] However, it is still unclear if sleep apnea plays a significant role in the early phase of development of vascular diseases.[30] In the Multi-Ethnic Study of Atherosclerosis with more than 6000 participants, obstructive sleep apnea associated with subclinical coronary artery disease, independent

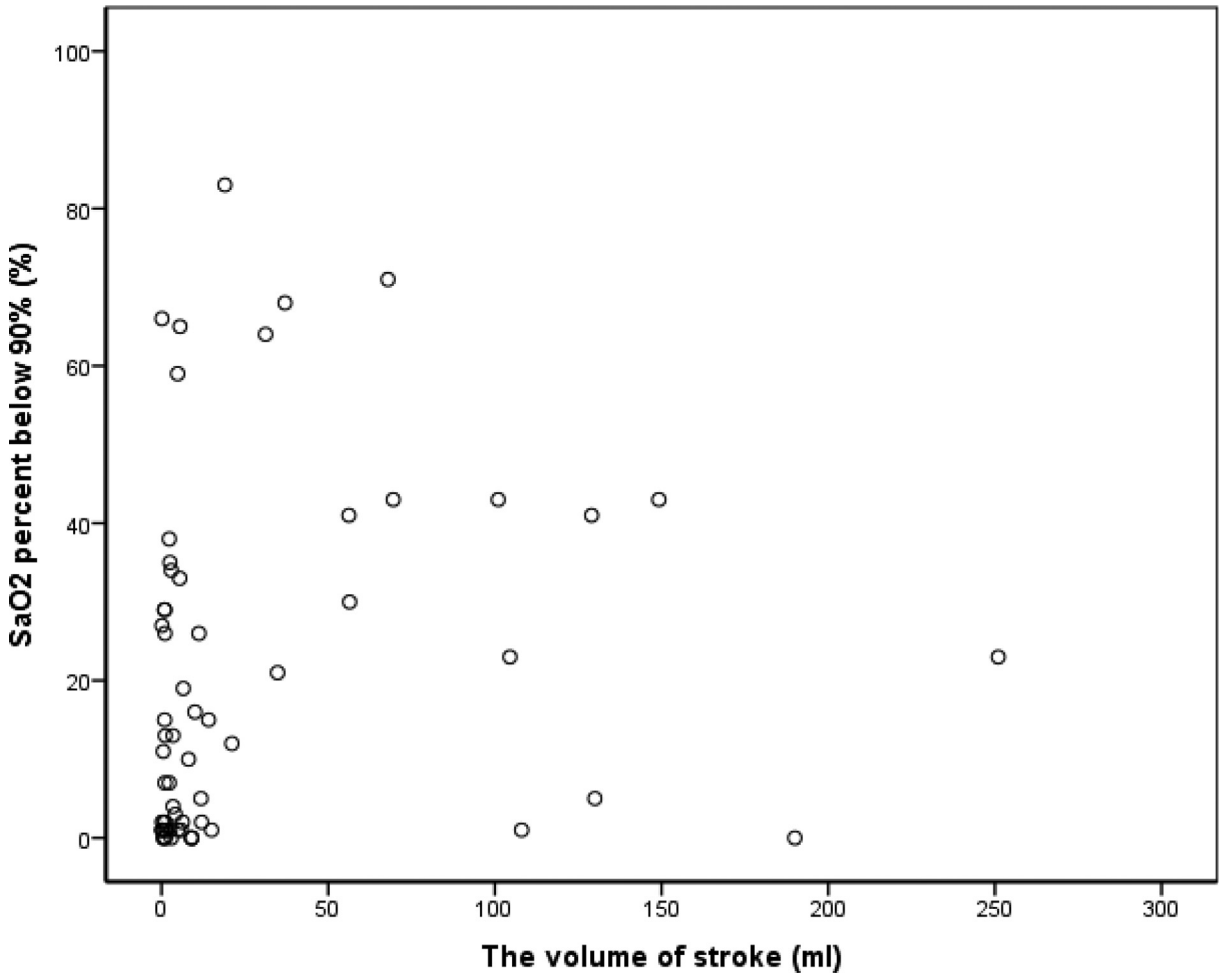

Figure 1. *Correlation between stroke volume and SaO_2 percent below 90%.*

of obesity and traditional cardiovascular risk factors.[31] Characteristics of patients were similar across the groups, with the exception of hemorrhage as complication. In previous reports, incidence of spontaneous hemorrhagic transformation (a spectrum of ischemia-related brain hemorrhage) ranged from 13% to 43% in CT studies and symptomatic hemorrhagic transformation from .6% to 20%.[32,33] The incidence of hemorrhagic event of 12.7% in our cohort fits to those previously reported ranges. Further, OSA severity among those having hemorrhage or not did not differ in our study. A significant predictor of neurological worsening and higher mortality is only PH,[34] which is defined as hemorrhagic transformation with dense blood clot(s) exceeding 30% of the infarct volume with significant space-occupying effect.[18,35] Three of our patients had PH 2 type hemorrhage. Ischemia in stroke patients is a result to inflammatory response,[36] which broke normal cerebrovascular anatomy and physiology. When ischemic area is reperfused the blood-brain-barrier is disrupted, which causes impairment of autoregulation of brain vasculature and this can lead to blood extravasation and increased inflammation.[37]

Ifergane et al[3] have reported that obstructive sleep apnea is associated with higher levels of inflammatory and coagulator biomarkers. Also the thrombolysis treatment of stroke with intravenous recombinant tissue plasminogen activator may result to reperfusion injury and intracerebral hemorrhage.[38] An experimental piece of evidence proposes that tissue plasminogen activator advances excitotoxic or ischemic neuronal death.[39]

In our previous study, we found that NIHSS was associated with sleep apnea severity in terms of REI and ODI.[4] We could not show correlation between stroke volume and diagnosis of sleep apnea and its severity. There was no correlation between Rankin scale score, ODI4, REI, and ischemic stroke volume. Only 8 patients had hemorrhagic event and the small number of patients did not allow us to analyze correlation between hemorrhage as complication and sleep apnea severity.

This is the first study evaluating the stroke size and sleep apnea among stroke patients who underwent thrombolysis. Our study population was homogeneous since all ischemic stroke patients underwent thrombolysis. Our observational real-life prospective study with consecutive patients, wide age range and high representation of females allows generalization of the results at least in the Finnish population with acute ischemic stroke and

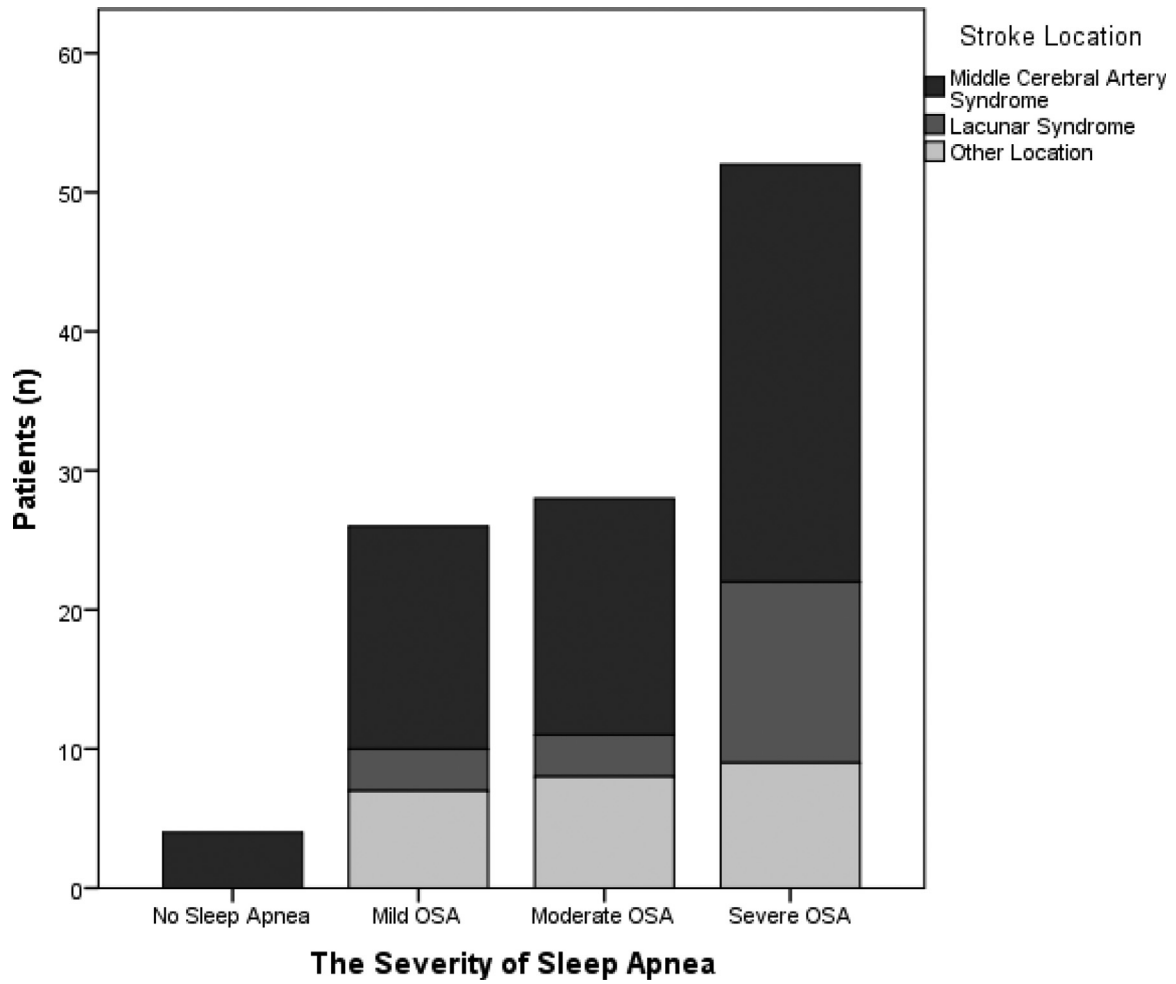

Figure 2. *Sleep apnea severity according to stroke location. Sleep apnea severity is divided to mild (REI 5-15/h), moderate (REI 15-30/h), and severe (REI ≥ 30/h) sleep apnea.*

thrombolytic treatment. However, prior studies have reported that sleep apnea prevalence varies by race among middle-aged adults,[40] and therefore our results may not represent the situation in other countries.

Brain CT was available in 109 stroke patients. Only 1 patient had only MRI images and the stroke volume was measured in a similar manner from diffusion weighted images. The volume measurements may not be accurate since they are influenced by several factors such as image quality, timing of imaging, location and shape of the lesion, and the amount of edema thus making the method prone to errors. Thus the exact stroke volume was not possible to determine for all the patients. We measured infarct volume approximately 24 hours after thrombolysis. Therefore the influence of time to edema is supposed to be the same in all patients.

We suggest considering to screen sleep apnea even during the stroke unit care in case of thrombolysis therapy if a visible new stroke CT lesion is present 24 hours after thrombolysis. The screening of sleep apnea among those suggested stroke patients leading to continuous positive airway pressure (CPAP) treatment may improve the outcome of their strokes and decrease comorbidity, although further studies are warranted.

Conclusions

In the current study, the stroke volume correlated with percent of nocturnal time spent below saturation of 90%. Time spent below saturation 90% seems to be more important factor than the conventional severity of sleep apnea defined by frequency of apneic and hypopnoeic events.

Acknowledgments: We thank the staff of the Department of Neurology and the study participants for their collaboration.

Conflict of Interest

The authors have no conflict of interest to disclose.

References

1. Peppard PE, Young T, Barnet JH, et al. Increased prevalence of sleep-disordered breathing in adults. Am J Epidemiol 2013;177:1006-1014.
2. Bassetti C, Aldrich MS. Sleep apnea in acute cerebrovascular diseases: final report on 128 patients. Sleep 1999;22:217-223.

3. Ifergane G, Ovanyan A, Toledano R, et al. Obstructive sleep apnea in acute stroke: a role for systemic inflammation. Stroke 2016;47:1207-1212.
4. Huhtakangas JK, Huhtakangas J, Bloigu R, et al. Prevalence of sleep apnea at the acute phase of ischemic stroke with or without thrombolysis. Sleep Med 2017;40:40-46.
5. Gottlieb DJ, Yenokyan G, Newman AB, et al. Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the sleep heart health study. Circulation 2010;122:352-360.
6. Leung RS, Comondore VR, Ryan CM, et al. Mechanisms of sleep-disordered breathing: causes and consequences. Pflugers Arch 2012;463:213-230.
7. Chami HA, Fontes JD, Vasan RS, et al. Vascular inflammation and sleep disordered breathing in a community-based cohort. Sleep 2013;36:768C.
8. Rowat AM, Dennis MS, Wardlaw JM. Hypoxaemia in acute stroke is frequent and worsens outcome. Cerebrovasc Dis 2006;21:166-172.
9. Stone KL, Blackwell TL, Ancoli-Israel S, et al. Osteoporotic fractures in men (MrOS) study research group. Sleep disordered breathing and risk of stroke in older community-dwelling men. Sleep 2016;39:531-540.
10. Birkbak J, Clark AJ, Rod NH. The effect of sleep disordered breathing on the outcome of stroke and transient ischemic attack: a systematic review. J Clin Sleep Med 2014;10:103-108.
11. Good DC, Henkle JQ, Gelber D, et al. Sleep-disordered breathing and poor functional outcome after stroke. Stroke 1996;27:252-259.
12. Yan-fang S, Yu-ping W. Sleep-disordered breathing: impact on functional outcome of ischemic stroke patients. Sleep Med 2009;10:717-719.
13. Bruno A, Shah N, Akinwuntan AE, et al. Stroke size correlates with functional outcome on the simplified modified Rankin scale questionnaire. J Stroke Cerebrovasc Dis 2013;22:781-783.
14. Lindsberg PJ, Sairanen T, Häppölä O. Update on current care guidelines: cerebral infarction (stroke). Duodecim 2011;127:500-501.
15. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991;14:540-545.
16. van Swieten JC, Koudstaal PJ, Visser MC, et al. Interobserver agreement for the assessment of handicap in stroke patients. Stroke 1988;19:604-607.
17. Goldstein LB, Bertels C, Davis JN. Interrater reliability of the NIH stroke scale. Arch Neurol 1989;46:660-662.
18. Wolpert SM, Bruckmann H, Greenlee R, et al. Neuroradiologic evaluation of patients with acute stroke treated with recombinant tissue plasminogen activator. The rt-PA acute stroke study group. AJNR Am J Neuroradiol 1993;14:3-13.
19. Collop NA, Tracy SL, Kapur V, et al. Obstructive sleep apnea devices for out-of-center (OOC) testing: technology evaluation. J Clin Sleep Med 2011;7:531-548.
20. Berry RB, Budhiraja R, Gottlieb DJ, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM manual for the scoring of sleep and associated events. J Clin Sleep Med 2012;8:597-619.
21. Iranzo A, Santamaría J, Berenguer J, et al. Prevalence and clinical importance of sleep apnea in the first night after cerebral infarction. Neurology 2002;58:911-916.
22. Sulter G, Elting JW, Stewart R, et al. Continuous pulse oximetry in acute hemiparetic stroke. J Neurol Sci 2000;179:65-69.
23. Siccoli MM, Valko PO, Hermann DM, et al. Central periodic breathing during sleep in 74 patients with acute ischemic stroke - neurogenic and cardiogenic factors. J Neurol 2008;255:1687-1692.
24. Kendzerska T, Gershon AS, Hawker G, et al. Obstructive sleep apnea and risk of cardiovascular events and all-cause mortality: a decade-long historical cohort study. PLoS Med 2014;11:e1001599.
25. Turkington PM, Allgar V, Bamford J, et al. Effect of upper airway obstruction in acute stroke on functional outcome at 6 months. Thorax 2004;59:367-371.
26. Punjabi NM, Newman AB, Young TB, et al. Sleep-disordered breathing and cardiovascular disease: an outcome-based definition of hypopneas. Am J Respir Crit Care Med 2008;177:1150-1155.
27. Wolk R, Kara T, Somers VK. Sleep-disordered breathing and cardiovascular disease. Circulation 2003;108:9-12.
28. Mittal SH, Goel D. Mortality in ischemic stroke score: a predictive score of mortality for acute ischemic stroke. Brain Circ 2017;3:29-34.
29. Bravata DM, McClain V, Austin C, et al. Diagnosing and managing sleep apnea in patients with chronic cerebrovascular disease: a randomized trial of a home-based strategy. Sleep Breath 2017;21:713-725.
30. Somers VK, White DP, Amin R, et al. American Heart Association Council for high blood pressure research professional education committee, council on clinical cardiology. Sleep apnea and cardiovascular disease: an American Heart Association/American College of Cardiology foundation scientific statement from the American Heart Association Council for high blood pressure research professional education committee, council on clinical cardiology, stroke council, and council on cardiovascular nursing. In collaboration with the National Heart, Lung, and Blood Institute National Center on sleep disorders research (National Institutes of Health). Circulation 2008;118:1080-1111.
31. Lutsey PL, McClelland RL, Duprez D, et al. Objectively measured sleep characteristics and prevalence of coronary artery calcification: the multi-ethnic study of atherosclerosis sleep study. Thorax 2015;70:880-887.
32. Bang OY, Saver JL, Kim SJ, et al. Collateral flow averts hemorrhagic transformation after endovascular therapy for acute ischemic stroke. Stroke 2011;42:2235-2239.
33. Jaillard A, Cornu C, Durieux A, et al. Hemorrhagic transformation in acute ischemic stroke. The MAST-E study. MAST-E group. Stroke 1999;30:1326-1332.
34. Sussman ES, Connolly Jr. ES. Hemorrhagic transformation: a review of the rate of hemorrhage in the major clinical trials of acute ischemic stroke. Front Neurol 2013;4:69.
35. Pessin MS, Del Zoppo GJ, Estol CJ. Thrombolytic agents in the treatment of stroke. Clin Neuropharmacol 1990;13:271-289.
36. Komotar RJ, Kim GH, Otten ML, et al. The role of complement in stroke therapy. Adv Exp Med Biol 2008;632:23-33.
37. Khatri R, McKinney AM, Swenson B, et al. Blood-brain barrier, reperfusion injury, and hemorrhagic transformation in acute ischemic stroke. Neurology 2012;79:S52-S57.
38. Lauderdale DS, Knutson KL, Yan LL, et al. Objectively measured sleep characteristics among early-middle-aged adults: the CARDIA study. Am J Epidemiol 2006;164:5-16.
39. Marler JR. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med 1995;333:1581-1587.
40. Macrez R, Ali C, Toutirais O, et al. Stroke and the immune system: from pathophysiology to new therapeutic strategies. Lancet Neurol 2011;10:471-480.