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ORIGINAL ARTICLE

Cerebral blood flow in stroke patients with sleep apnea: any role of single-night positive airway pressure therapy?

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Abstract

BACKGROUND AND OBJECTIVE: Sleep-disordered breathing (SDB) is more prevalent in patients with stroke than in the population without a history of stroke. SDB is an independent risk factor for stroke. SDB impairs cerebral circulation by several mechanisms, and therefore possibly contributes to wake-up stroke. Ultrasound-tagged near-infrared spectroscopy (UT-NIRS) is a novel technology able to detect cerebral blood flow noninvasively and in real-time, displaying cerebral flow as cerebral flow index (CFI). Positive airway pressure (PAP) is the most effective approach in the treatment of SDB. We aimed to assess if single-night PAP impacts cerebral blood flow in sleep apnea patients after stroke and without a history of stroke.

MATERIALS AND METHODS: 11 stroke patients and six controls with sleep apnea were enrolled. Stroke patients underwent overnight pulse oximetry within seven days after stroke. Desaturation index ≥ 15/hour was considered a positive screening. Six weeks after stroke, patients with positive screening underwent overnight polysomnography together with cerebral blood flow monitoring using UT-NIRS (diagnostic night) and also with additional PAP therapy (therapeutic night).

RESULTS: The number of respiratory events decreased significantly in the group of stroke patients (apnea-hypopnea index [AHI] from 22.6±9.0 to 9.9±9.9) and controls (AHI from 58.1±14.9 to 7.0±9.7). CFI showed no significant changes between a diagnostic and therapeutic night in both groups.

CONCLUSION: Despite the significant reduction of respiratory events, single-night PAP therapy does not improve overall cerebral blood flow, as defined by CFI.

Abbreviations:

AHI	- Apnea-hypopnea index	PAP	- Positive airway pressure
CBF	- Cerebral blood flow	PSG	- Polysomnography
CSA	- Central sleep apnea	SDB	- Sleep-disordered breathing
CFI	- Cerebral flow index	UT-NIRS	- Ultrasound tagged near-infrared spectroscopy
NIRS	- Near infra-red spectroscopy		
OSA	- Obstructive sleep apnea	WUS	- Wake-up stroke

INTRODUCTION

The prevalence of sleep-disordered breathing (SDB) has increased over the past years, owing to the increase in obesity in particular. Its most common form, obstructive sleep apnea (OSA), defined as apnea-hypopnea index (AHI) ≥ 5/hour, is present in about 24% of men and 9% of women worldwide (Klobučníková *et al.* 2018). However, among patients with stroke or transient ischemic attack, the age-adjusted prevalence of SDB increases as high as 72% (Bassetti & Aldrich 1999; Parra *et al.* 2000). According to a 2010 meta-analysis, 93% of these SDBs are OSA (Johnson & Johnson 2010). OSA is a well-established independent risk factor for ischemic stroke contributing to overall cerebrovascular morbidity. In the long-term, OSA contributes to an increase in blood pressure, autonomic imbalance with sympathetic hyperactivity, endothelial dysfunction, metabolic changes, and pro-inflammatory state (Culebras 2014; Slouka *et al.* 2019; Sova *et al.* 2020, Šiarnik *et al.* 2014). It is pathophysiologically plausible and demonstrated by a 2012 study (Ciccone *et al.* 2012) that long OSA episodes (> 20 seconds) in combination with patent foramen ovale are associated with an almost 2-fold increased risk of an ischemic event on waking. Findings from Parra *et al.* (Parra *et al.* 2000), analyzing the time course of subtypes of apneic events in the acute and subacute phase after stroke suggest, that OSA is a condition preceding the cerebrovascular event and probably acts as a risk factor. In contrast, central sleep apnea (CSA) seems to be its consequence, confirming a known bidirectional relationship between SDB and stroke. Positive airway pressure (PAP) is the first-line therapeutic option and the most effective approach in the treatment of SDB.

Several studies have engaged near-infra-red spectroscopy (NIRS) in cerebral blood flow (CBF) monitoring, showing a decrease of oxygenation during obstructive apneas (but not hypopneas). These decreases were more pronounced in more severe OSA cases (Aries *et al.* 2012; Pizza *et al.* 2010). While NIRS shows many advantages, being noninvasive, continuous, and having an excellent temporal resolution, its disadvantage is that it measures tissue oxygenation rather than cerebral perfusion. New technology, ultrasound-tagged NIRS (UT-NIRS), combines the advantages of NIRS with ultrasound's ability to measure the movement of blood cells (corresponding to blood flow). This method was compared with the "gold standard "in cerebral perfusion measurement, Xe-SPECT, showing a perfect correlation (Schytz *et al.* 2012).

This study aimed to explore, whether single-night PAP, besides a decrease in respiratory events, also contributes to an increase in CBF, defined by the cerebral flow index (CFI), assessed by a UT-NIRS device.

MATERIALS AND METHODS

Eleven patients with ischemic stroke were enrolled in this study (one of them with a wake-up stroke [WUS]). Six controls were also enrolled: patients with OSA and no other significant disease, particularly without stroke history. The local ethical committee approved the design of this study. All participants signed informed consent before enrollment. The diagnosis of stroke was made clinically, and the location of the ischemic lesion was confirmed by computed tomography (CT) or magnetic resonance imaging (MRI).

In patients with stroke, initial SDB screening was performed within seven days after the stroke onset using overnight pulse oximetry (WristOx2 device model 3150, Nonin Medical, USA). Patients with desaturation index (number of desaturations ≥3% and >10 seconds per hour of recording) ≥15 were considered as possible PAP therapy candidates. Patients with positive screening were re-admitted six weeks after stroke for overnight polysomnography (PSG) using Alice 6 device (Philips-Respironics, Netherlands). Each patient underwent diagnostic PSG monitoring. The next night also PAP titration under PSG control was performed. CBF monitoring was performed during both PSG recordings using UT-NIRS technology: C-Flow device (Ornim medical, Israel). The device displays a cerebral flow index (CFI) as a unit-less number ranging from 0 to 100. The probe emits light at three wavelengths between 780 and 830 nm and detects the scattered light at 12 mm from the emitter. Each probe illuminates tissue of the frontal cortex with laser light and collects light scattered back. The probes also incorporate a small ultrasound transducer that provides low-power waves to induce the UT-NIRS signal, and the monitors display an indicator of the signal quality. Preparation of patients and the set-up of the device were done according to the C-Flow User Manual. A flat hairless area on the forehead on both sides was selected, cleaned with an alcohol solution, and two disposable adhesive pads (Smart Pads, supplied by Ornim) were applied, one on the right and one on the left side. Pads were secured with a headband. A small amount of ultrasound gel was then applied to the UT-NIRS probes, which were then placed onto adhesive pads (Caccioppola *et al.* 2018). The data were monitored overnight. When the probe was displaced, the sleep laboratory technician put it back on the adhesive pad. All data were acquired directly from the Ornim devices in digital format and archived.

The average CFI value of both probes was considered. Patients underwent diagnostic PSG and CBF monitoring on the first night (diagnostic night), PSG + CBF monitoring, and PAP therapy on the following night (therapeutic night). PSG was scored manually by a trained somnologist according to the standardized criteria (Iber *et al.* 2007). Biograph software (Beset, Slovakia) was used to evaluate the CBF signal and for synchronization with PSG data. Any vasoactive

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Tab. 1. Polysomnographic characteristics of patients with stroke and controls, comparing diagnostic and therapeutic night

	Diagnostic night	Therapeutic night	*p*
Strokes (n=11; Age 67.7±9.6 years, 4 females/ 7 males)			
AHI (n/h)	22.6±9.0	9.9±9.9	0.004**
Average sat (%)	94.5±2.1	94.9±2.1	0.659
Minimal sat (%)	86.3±11.7	91.6±3.2	0.157
CFI	50.3±6.4	49.0±4.5	0.602
Heart rate (n/h)	68.9±17.3	69.1±15.3	0.97
Controls (n=6, Age 43.7±14.6, 6 males)			
AHI (n/h)	58.1±14.9	7.0±9.7	<0.001***
Average sat (%)	94.6±2.0	94.7±1.9	0.943
Minimal sat (%)	79.0±10.7	91.7±2.7	0.019*
CFI	45.9±7.3	49.7±11.7	0.521
Heart rate (n/h)	63.3±6.5	66.3±6.0	0.413

CFI: cerebral flow index, AHI: apnea-hypopnea index, sat: nocturnal saturation of blood with oxygen, *: $p<0.05$, **: $p<0.01$, ***: $p<0.001$

medication was avoided 12 hours before monitoring. 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. For group comparison, the Student t-test and Mann-Whitney test were used for particular variables. *P* values < 0.05 were considered statistically significant.

RESULTS

The mean age of stroke patients (n=11) was 67.7±9.6 years; four of them were females. The mean age of controls (n=6) was 43.7±14.6 years. None of the control group patients was a smoker, and 8 (72.7%) patients of the stroke group were non-smokers, other 3 (27.3%) were mild smokers (occasional smoking in one patient and up to 10 cigarettes/day in other two subjects). In the stroke group, three patients were using their chronic medication, which might be potentially vasoactive (doxazosin in 2 patients, urapidil in one patient). No other vasoactive treatment was given to any patient from neither stroke nor control group. The results of stroke patients and controls are in table 1. The number of respiratory events significantly decreased in the group of stroke patients (AHI from 22.6±9.0 to 9.9±9.9) and controls (AHI from 58.1±14.9 to 7.0±9.7) when comparing diagnostic and therapeutic night, respectively. CFI showed no significant changes between a diagnostic and therapeutic night in both groups. See table 1 for details.

DISCUSSION

Our study failed to find any significant CFI changes (representing CBF) when evaluating the effect of single-night PAP therapy. Several factors could explain this.

First, there were not enough data to compare CFI in "awake stroke" patients to WUS patients. Above three-fold increased prevalence of WUS were reported among patients with OSA compared to non-OSA patients (Mohammad *et al.* 2019). Šiarnik *et al.* reported a higher prevalence of moderate to severe OSA types among WUS patients than among non-WUS and higher AHI in the WUS population (Šiarnik *et al.* 2016). The CBF autoregulation is impaired in patients with recurrent intermittent hypoxia, as is seen in chronic obstructive pulmonary disease and OSA, and cerebral vasculature responds poorly to hypoxia (Beaudin *et al.* 2017). It seems that noninvasive ventilatory correction improves short-term neurological disability, according to a 2017 meta-analysis (Tsivgoulis *et al.* 2017). Therefore we suppose that more significant differences in CFI might be found in the group of WUS patients.

Second, in this study, we compared the average CFI between diagnostic and therapeutic night, which showed no significant differences in both groups. However, it might be more appropriate to examine relatively temporary excursions of CFI in time correlation with the specific respiratory event (i.e., apnea or desaturation). It has been shown by several studies that patients with OSA have an inadequate response to cerebral hypoxia, and their autoregulation fails to adjust to a hypoxic state by vasodilatation. This response even decreased with higher severity of OSA (Beaudin *et al.* 2017). Moreover, another study (Gregori-Pla *et al.* 2019) has found that bilateral CBF fluctuations occurred in close time relationship to apneic and/or hypopneic events (time window between -5 to 35 sec. from the start of the event). Future studies should focus on the association of particular respiratory events with CBF swings.

Finally, in our study, patients underwent only one therapeutic night with PAP therapy, whereas long-term

treatment might be necessary for change in cerebrovascular reactivity. In studies examining cerebral vasoreactivity among patients after stroke, patients with OSA had worse vasodilator response to hypoxia, which, however, returned to normal after 4-12 weeks of PAP treatment (Gregori-Pla *et al.* 2019; Reichmuth *et al.* 2009). Vasodilator response was defined by mean velocity in the middle cerebral artery, hence not corresponding to CBF *per se*. However, it was demonstrated before that microcirculatory changes (Gregori-Pla *et al.* 2019; Zirak *et al.* 2018) mirror those of macrocirculation (Alex *et al.* 2014), both showing an increase (velocity in middle cerebral artery or blood flow index, BFI) with the peak occurring toward the end or shortly after cessation of OSA episode, followed by a sudden subnormal decrease after the episode.

The main limitations of our study are a small study population, particularly that of WUS patients. It is necessary to admit, that our study did not focus on the time relationship of apneic events with CFI changes, which could confound the effect of sleep apnea on CBF. To the best of our knowledge, this is the first study using C-Flow for CBF monitoring during sleep, so physiological values of CFI and physiological changes of CFI during sleep are unknown. Similarly, no studies are describing the effect of ischemic brain lesions on CFI change. We have to admit that CFI in our study assesses only CBF in a small volume of the frontal cerebral cortex, which is another important limitation. Future prospective CBF studies in stroke subjects with SDB should take all of these limitations into consideration.

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COMPLIANCE WITH ETHICAL STANDARDS

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Conflict of Interest

All authors declare that they have no conflict of interest.

Ethical approval

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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All authors have seen and approved the manuscript.

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