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Cerebrovascular pulsatility in patients with sleep-disordered breathing

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Abstract

Purpose—The aim of our study is to determine the association between the pulsatility index (PI), a surrogate of cerebral small vessel disease and sleep-disordered breathing (SDB).

Methods—We conducted a transcranial Doppler ultrasound (TCD) study of 19 consecutive patients free of stroke and cardiovascular disease, referred for the evaluation of SDB. TCD was performed by a certified technologist. Subsequent polysomnography was performed according to the practice parameters of the American Academy of Sleep Medicine. We evaluated the association between the apnea–hypopnea index (AHI), the oxygen nadir, the blood flow velocities, and the Gosling PI, for the middle cerebral artery. We performed Spearman’s rank correlation and nonparametric regression to evaluate the relationship between AHI, oxygen levels, and the PI.

Results—Median age was 48 years (range 37–83), with 52 % male sex ($n=10$), and median BMI of 29.9 (range 25–40.4). The median AHI was 16.4 (0.2–69). The median PI was 0.97 (0.72–1.89) cm/s. The PI correlated with the AHI ($\rho=0.44$; $p=0.004$) and with age ($\rho=0.57$; $p=0.001$). Nonparametric regression adjusting for age showed a positive association between the AHI and the PI (standardized estimate=0.88; $p=0.002$). There was no relation between the oxygen nadir and the PI.

Conclusion—We observed increased PI in patients with SDB during wakefulness. The PI could potentially be an estimate of cerebral small vessel disease in patients with SDB and hence allow evaluating cerebral hemodynamics during wakefulness with a clinically relevant device.

Keywords

Transcranial Doppler; Sleep-disordered breathing; Pulsatility index; Stroke; Microvascular disease

Introduction

Sleep-disordered breathing (SDB) is an independent risk factor for ischemic stroke [1], but the pathological determinants of this relation are not well defined. Cerebral small vessel disease is increasingly considered an important mechanism in the pathophysiology between SDB and stroke. A higher percentage of silent ischemic brain lesions by magnetic resonance imaging have been observed in patients with moderate to severe SDB [2].

Transcranial Doppler ultrasound (TCD) is a safe, noninvasive technique widely used in clinical practice, which enables measurement of cerebral arterial blood flow velocities in the intracranial circulation [3]. The arterial pulsatility index (PI), calculated by TCD, is considered a measure of microangiopathic changes of cerebral blood vessels and indirectly reflects microvascular damage [3]. The aim of our study is to determine the association between PI, the apnea–hypopnea index, and the oxygen nadir in patients referred to a sleep disorders center.

Methods

Population

Nineteen consecutive patients referred for SDB were recruited from the sleep disorders clinic during their initial visit between April and October of 2011. Subjects were excluded if they had a history of stroke, carotid artery disease, cardiac disease, blood dyscrasia, coagulation disorder, and pulmonary disorder; or if they were previously treated with CPAP, surgery, or an oral appliance for SDB. Subjects using stable doses of hypertensive and oral hypoglycemic medications were not excluded from the study. The study was approved by the University of Miami Miller School of Medicine Institutional Review Board, and informed consent was obtained from all participants.

Procedure

All subjects completed a structured clinical interview, a neurological examination, TCD, and baseline PSG. Demographic characteristics, medication use, lifestyle, and sleep assessments were obtained through questionnaires, physical examination, and review of medical records. The heart rate and the systolic and diastolic blood pressures were obtained during daytime TCD monitoring by using a mercury sphygmomanometer.

Nocturnal polysomnography

Subsequent polysomnography (PSG) within 1 week of the clinical assessment and TCD was performed using a standard montage, including electroencephalographic, electromyographic (EMG), and electrooculographic [4] monitoring for an in-lab overnight video-PSG. Measures of airflow were taken to detect SDB. Sleep stages, arousals, and sleep-related events, apnea–hypopnea index (AHI), and nadir of oxygen desaturations were recorded according to the established practice parameters of the American Academy of Sleep Medicine (AASM) [5]. The sleep study was performed by certified technician in an AASM-accredited sleep laboratory.

Transcranial Doppler sonography

The TCD was performed by a certified technologist (DC) using a portable microprocessor-controlled TCD system on a laptop (EMS-9U, Delica) according to the guidelines of the American Institute of Ultrasound in Medicine [6]. A low-frequency (2 MHz) pulse-waved ultrasonic signal is transmitted from the skin surface across the cranial vault to the intracerebral vessels and receives the echoes along the same path. The TCD probe is positioned over “acoustic windows” that are specific regions of skull where the cranial bone is thin, allowing examination of middle cerebral artery (MCA) and the terminal portion of the internal carotid artery. The ultrasound beam emitted from the TCD probe reflects from the erythrocytes traveling within blood flow of the insonated artery. The transducer receives the signal and converts it into an electric signal. The following TCD variables are then analyzed: (1) peak systolic velocity (PSV), (2) end-diastolic velocity (EDV), (3) mean flow velocities (MFV), and, (4) PI. The PI is calculated by the Gosling equation, $PI = (PSV - EDV) / MFV$ [3].

Data analysis

All analyses were carried out using SAS software version 9.2 (SAS Institute Inc, Cary, NC). Results are presented as median (range or interquartile range). The chi-square test was used to compare proportions, and Wilcoxon rank sum test was used for continuous nonparametric data. The Spearman’s rank correlation was used to evaluate the relation between the AHI and oxygen nadir with demographic factors (age, sex, and BMI), blood pressure parameters (systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate), and TCD measures (PI, MFV, PSV, and EDV). Nonparametric regression (Proc GAM) was used to analyze the association between the AHI and PI adjusting for age [7]. Further analysis was done by comparing the demographic, blood pressure, and TCD variables divided in two groups separated by the median AHI. Statistical significance was assumed for two-tailed p values < 0.05 .

Results

The Table 1 presents the characteristics of the sample. The median age was 48 years, with 52 % male sex ($n=10$). The BMI was in the overweight–obesity range. Nine participants had hypertension and two had diabetes. The severity of SDB ranged from primary snoring to severe OSA based on the AHI. The PI correlated with the AHI ($\rho=0.44$, $p=0.004$) and with age ($\rho=0.57$, $p=0.001$), while the oxygen nadir, sex, BMI, SBP, DBP, heart rate, and the Epworth sleepiness scale did not (data not shown). The AHI also correlated with age ($\rho=0.44$, $p=0.05$), the oxygen nadir ($\rho=-0.50$, $p=0.02$), and TCD end-diastolic velocity ($\rho=-0.59$, $p=0.007$). The AHI did not correlate with sex, BMI, Epworth sleepiness scale, and the TCD measures of MFV and PSV. The group above the median AHI was significantly older, with lower end-diastolic velocity and increased PI (Fig. 1). There was no difference in sex, BMI, blood pressure parameters, and oxygen desaturation between the groups. Nonparametric regression adjusting for age showed an association between the AHI and the PI (standardized estimate=0.88, $p=0.002$).

Discussion

In our study, increased PI during wakefulness correlated with worse AHI. An increase in PI could mean a decrease in cerebrovascular compliance and cerebral small vessel disease [8, 9]. Similar results have been described in diabetes [10], Alzheimer’s disease, and vascular dementia [8], but reports in patients with SDB are limited. In addition, increased PI is associated with white matter changes by magnetic resonance imaging (MRI), a marker of cerebral small vessel disease that predicts stroke, dementia, and disability [11].

We observed a median PI of 0.97 for the overall sample and 1.01 for the group above the median AHI. Our results are comparable to studies of microvascular complications in diabetes, where a mean PI of 0.87 was observed in the MCA of participants with complicated diabetes [10] and a mean PI of 1.05 in patients with diabetes and lacunar (small vessel) infarcts by MRI [12]. Several factors may influence the results of our study. Age and PI were correlated in our study; additionally, there was a positive correlation between age and AHI, with the group above the median AHI being significantly older. There is an increased prevalence and severity of SDB with age [13] and decreased cerebrovascular compliance associated with aging [8]. Furthermore, hypertension and diabetes can cause cerebral small vessel disease [14], but these factors did not correlate with the PI in our study. We observed an increased frequency of hypertension and a lower median score on the Epworth sleepiness scale in the group above the median AHI that did not reach statistical significance. In our clinical sample, the risk for SDB may be explained by snoring symptoms, obesity, and hypertension and less by the severity of the Epworth sleepiness scale. Our data are in agreement to findings of weak or no relationship between SDB and sleepiness score [15], but larger-sized clinical samples have correlated the degree of SDB severity to worse scores in the Epworth sleepiness scale [16]. Our findings could be partly explained by our small sample size and potential referral bias. SDB is closely related to hypertension and diabetes and may cause and/or exacerbate these vascular risk factors. Long-term exposure to hypertension and diabetes may have influenced the results of our study [17, 18]. However, when controlling for age as the main confounder in our study, the AHI was still associated with increase PI. Our findings suggest that SDB could be an independent predictor of increased PI, but future studies on the link between SDB and subclinical measures of cerebrovascular disease are needed.

In our study, lower end-diastolic velocities during wakefulness were associated with worse AHI. This is in accordance with a study describing cerebral blood flow velocities in direct relation to apneic events. Abrupt increases in the PI have been described at the end of apneas where the MFV is the lowest [9, 19]. The increased PI is primarily caused by a marked reduction in diastolic cerebral blood flow velocity. These changes follow the initial increase in systemic BP and cerebral blood flow velocities observed during the apneas, followed by a dip in end-diastolic and MFV [9, 20].

In our study, we did not detect an association between the oxygen levels and PI. Hypoxemia and hypercapnea are associated to impaired cerebrovascular reactivity to CO₂ vasodilatory response [21]. The PI as a measure of cerebrovascular resistance may not directly quantify the effects of hypoxemia in the cerebral vasculature.

The mechanism, by which cerebral hemodynamic changes (PI) persist during wake, could be related to impairment of the endothelial and myogenic response to cerebral blood pressure fluctuations during the apneas [21]. These could contribute to atherosclerotic changes disrupting the arterial wall integrity, causing endothelial dysfunction and leading to cerebral small vessel disease [22].

Several limitations should be noted. First, there might be possible bias related to patient selection and the small sample size. The cross-sectional nature of our study does not allow assessing for causality and length of exposure to SDB. Even though we excluded participants with history of carotid disease, we did not assess for extracranial stenosis with carotid ultrasound. Several studies have shown an association between snoring, SDB, and carotid disease, but these findings have not been replicated in population-based studies [14]. Also, we do not think that this was a major source of bias, as our patients were relatively young without history of cardiac disease or stroke and few vascular risk factors. Finally, we did not apply positive airway pressure while recording the TCD.

In conclusion, patients with SDB had increased PI during wakefulness. The PI could potentially be an estimate of cerebral small vessel disease in patients with SDB and hence allow evaluating cerebral hemodynamics during wakefulness with a clinically relevant device.

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Fig. 1.
Pulsatility index by the median apnea-hypopnea index

Table 1

Characteristics of the overall sample and groups divided by the median apnea–hypopnea index

<i>N</i> =19	All	AHI<16.4 <i>n</i> =9	AHI ≥ 16.4 <i>n</i> =10
Demographics			
Age, years	48.0 (37–83)	41.0(8.0)	52.0 (11.0) *
Men, <i>n</i> (%)	10 (52)	3 (33)	7 (70)
BMI, kg/m ²	29.9 (25–40)	32.1 (5.6)	28.1 (5.9)
Hypertension, <i>n</i> (%)	9 (33)	3 (33)	6 (60)
Diabetes, <i>n</i> (%)	2 (11)	–	2 (20)
Epworth sleepiness scale	8 (1–21)	10 (13)	5 (12)
Daytime blood pressure measurements			
Systolic, mm Hg	122.0 (103–154)	120.0 (14.0)	128.5 (25.0)
Diastolic, mm Hg	79.0 (65–97)	79.0(7.0)	79.5 (12.0)
Heart rate	70.0 (50–91)	71.0 (11.0)	68.5 (26.0)
Transcranial Doppler, cm/s			
Mean velocity	47.8 (32.4–68.6)	50.1 (12.3)	45.6 (11.6)
Peak systolic	80.6 (51.1–141.0)	81 (17.3)	75.0 (19.5)
End-diastolic	30.5 (19.1–47.7)	34.6 (9.0)	28.6 (7.4) *
Pulsatility	0.97 (0.72–1.89)	0.93 (0.04)	1.01 (0.31) *
Polysomnography			
AHI	16.4 (0.2–69)	9.4 (5.7)	26.8 (28.1) *
O2 Nadir	84 (70–94)	87.0(7.0)	81.5 (8.0)

Data presented as median (range or interquartile range)

*
p<0.05