Sleep Medicine 10 (2009) 875–881

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

Cerebral vasoreactivity decreases overnight in severe obstructive sleep apnea syndrome: A study of cerebral hemodynamics

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ARTICLE INFO

Article history:
Received 16 June 2008
Received in revised form 11 September 2008
Accepted 27 September 2008
Available online 5 February 2009

Keywords:
Obstructive sleep apnea syndrome
Cerebral hemodynamics
Transcranial Doppler sonography
Pulse transit time
Cerebrovascular reactivity
Polysomnography

ABSTRACT

Background: OSAS has been associated with surrogate markers of atherosclerosis and is a known risk factor for stroke. However, there is limited data on the effects of recurring apneas in severe OSAS on cerebral circulation and their consequences on cerebrovascular reactivity and compliance.
Objective: To evaluate cerebral blood flow velocity (CBFV) changes and vascular compliance in patients with severe obstructive sleep apnea syndrome (OSAS) using transcranial Doppler sonography (TCD) and cerebral pulse transit time (PTT).
Methods: Seven patients (1 woman, 6 men, mean age 57.4 years) with severe OSAS underwent polysomnography at the sleep laboratory of the Neurology Department of Innsbruck Medical University. TCD was performed continuously during the whole night using a pulsed wave probe and was co-registered with routine polysomnography. Cerebrovascular reactivity was assessed by calculation of apnea and hypopnea-related CBFV changes. Arterial compliance was characterized by PTT derived from phase difference analysis between ECG and TCD signals. Sleep time was dichotomized into periods with high density of consecutive respiratory events (CRE) vs. periods with low density of consecutive respiratory events (non-CRE).
Methods: TCD measurements of CBFV showed a regular, undulating pattern with flow minima immediately before apneas or hypopneas and maxima closely after their termination, reciprocally to peripheral O_2 saturation. CBFV reactivity was significantly diminished in CRE compared to non-CRE periods. PTT phase differences were reduced in non-CRE, and even more so in CRE periods, compared to initial wake phases.
Conclusion: We found severe disturbances of cerebrovascular reactivity in OSAS patients. Our data demonstrate loss of vasoreactivity and increase of arterial stiffness, indicated by CBF hyporeactivity and PTT reduction, especially during CRE periods. These changes are likely to impair cerebral circulation and may be detrimental to the endothelium.

1. Introduction

Obstructive sleep apnea syndrome (OSAS) is independently associated with increased risk for ischemic stroke [1–3] and with surrogate markers for atherosclerosis, most notably carotid intima media thickness, and with already manifest carotid artery stenosis [4,5]. The pathogenetic mechanisms causing these associations, however, remain elusive, although recurrent hypoxia and rapid hemodynamic changes resulting in vascular stress have been suggested as key factors.

Transcranial Doppler sonography (TCD) is a non-invasive technique for real-time assessment of cerebral blood flow (CBF) and its dynamic changes and has been applied to assess sleep in healthy controls [6–8] and in patients with Cheyne–Stokes respiration [9] or OSAS [10–18]. However, the effects on CBF of multiple apneas or hypopneas occurring in rapid succession (which is a typical finding in severe OSAS), have not been comprehensively investigated. The pulse transit time (PTT) is an indicator of vascular stiffness influenced by blood pressure, age, and atherosclerosis. PTT is defined as the speed of the pulse wave travelling from the heart to the periphery and is calculated from the time difference between R-waves of the electrocardiogram and the peripheral pulse wave [19].

In the present study, we investigated changes in CBF reactivity in patients with severe OSAS measured by TCD over periods with

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doi:10.1016/j.sleep.2008.09.011

frequent, repetitive apneas compared to periods with fewer respiratory events and stage wake before sleep onset. Secondly, we assessed vascular compliance in the supra-aortal vessels using PTT derived from ECGs and middle cerebral artery (MCA) flow signals.

2. Patients and methods

2.1. Study subjects

Consecutive patients with severe OSAS who underwent 8-h polysomnography (PSG) at the sleep laboratory of the Department of Neurology of Innsbruck Medical University between December 2003 and June 2004 were included in this study. OSAS was diagnosed according to ICSD-1 criteria [20]. Severe OSAS was indicated by an apnea/hypopnea index (AHI) > 30/h according to published recommendations of the AASM [21]. Exclusion criteria were a history of cerebral infarction, stenosis or occlusion of extracranial or intracranial arteries on duplex ultrasound performed prior to PSG, and absence of a temporal bone window sufficient for whole-night TCD. Overall, 7 patients (6 men, 1 woman) were included in this study. Each patient gave written informed consent before inclusion.

2.2. Polysomnographic registration

All patients underwent nocturnal 8-h video-polysomnography for two consecutive nights. The first night was used for adaptation; during the second night, TCD signals of the right MCA were registered and saved to the hard drive of the sleep laboratory system database.

Polysomnography was performed with a digital polygraph (Brainlab 3.30, Schwarzer Inc., Munich, Germany). A standard montage was used including C3, C4, O1, O2, A1 and A2 electrodes, vertical and horizontal electrooculography and electromyography of mental, submental and both tibialis anterior muscles. Cardiorespiratory monitoring included electrocardiography, nasal airflow, nasal pressure cannula, tracheal microphone, thoracic and abdominal respiratory effort, and oxygen saturation. Sleep was scored according to Rechtschaffen and Kales [22]. Obstructive apneas were defined as complete cessation of airflow with duration of at least 10 s but ongoing respiratory effort. Hypopneas were defined as a 50% decline of flow signal independent of an additional desaturation of at least 10 s. The initial wake phase registered on PSG (until occurrence of sleep stage I) was used as a baseline measurement for cerebral blood flow velocity (CBFV) and PTT. In order to define prolonged "clusters" of consecutive respiratory events (CRE) for further examination, we applied filtering criteria of a minimum of 15 consecutive apneas or hypopneas covering at least 50% of the time span measured from the first to the last of these respiratory events. Sleep periods fulfilling the above-mentioned criteria were analyzed in comparison to periods not fulfilling them. Dichotomization of PSG recordings into CRE and non-CRE periods was automatized using Matlab (The Mathworks, Germany) applications.

2.3. Transcranial Doppler ultrasound and vascular parameters (TCD apnea score, PTT breath holding index)

TCD tracings of the right MCAs were recorded after localisation of the optimal signal using a 2-MHz pulsed wave Doppler system (MultiDop X-2, DWL, Germany) and a customized head holder (Aheadset, USA). In the case of artifacts, probe position was manually readjusted during the night by an investigator (M.F.). MCA blood flow raw data were co-registered with the other polysomnographic tracings on the hard disk of a personal computer.

Cerebral vasoreactivity was calculated using the TCD apnea score described by Klingelhoefer et al., which was defined as the percentage rise of baseline flow velocity before an apnea or hypopnea (respiratory event, RE) to peak flow velocity after a RE divided by RE duration (%/s) [14].

PTT for the cerebral vasculature was calculated as follows: (1) when comparing CRE with non-CRE sleep periods, PTT values were calculated continuously as the differences between the phase position of ECG and TCD signals during REs divided by RE duration (PTT unit: rad/s). (2) For comparison of PTT during the initial wake phases vs. sleep periods (CRE and non-CRE), PTT was analyzed separately for every pulse wave (i.e., the R-waves detected in the ECG) and the corresponding TCD flow peaks (PTT unit: rad).

The breath holding index (BHI) is a measure of cerebrovascular reactivity with hypercapnia due to breath holding as the vasodilatory stimulus. In order to investigate potential BHI changes already at daytime in longstanding patients with OSAS, baseline BHI was acquired for each patient at 5:00 PM before baseline registration using the method described by Markus and Harrison [23]. BHI was computed as the mean of two consecutive measurements. Normal BHI values were taken from the publication by Silvestrini and coworkers [24].

All mathematical transformations and calculations concerning CBF changes or phase differences were performed with specific applications programmed using the Matlab software (MS). Phase differences were computed using three different approaches to exclude artifacts: (1) evaluation of the phase difference between the detrended ECG and the detrended CBFV without any other filtering; (2) stroboscopic evaluation of the phase of the cerebral blood flow velocity at the time of the R waves (with high pass filtering); (3) evaluation of the phase difference between the rhythm of the R–R intervals and the spectrally low-pass filtered CBFV (>0.1 Hz truncated in order to eliminate pulsatile trends) during time intervals of high apnea density (CREs). This method was not applicable outside CRE areas which did not exhibit oscillatory behaviour.

2.4. Statistical evaluation

For analyses of CBF and PTT changes during respiratory events in CRE vs. non-CRE periods, measurements of all patients were combined. To ensure statistical comparability, only relative measurements, i.e., CBF changes and PTT changes over time, were analyzed together. For calculation of differences between wake PTT vs. sleep PTT (CRE and non-CRE) each patient was assessed separately because these measurements could not be standardized since they are affected by individual characteristics (e.g., body height, BMI).

Differences of vascular parameters for respiratory events (CBF and PTT) between CRE and non-CRE periods and differences between PTT during the initial wake phase and during sleep (CRE and non-CRE periods) were analyzed using the two-sided Kruskal–Wallis test with Bonferroni correction for multiple testing.

Values given are means and SD, if not otherwise indicated. *p*-Values below 0.05 were considered significant (if not otherwise indicated after Bonferroni correction for multiple comparisons).

3. Results

3.1. Characteristics of study participants

Demographics and clinical characteristics of the patients (6 men, 1 woman) are presented in Table 1. The mean age was 57.4 ± 6.5 years. Mean AHI was 73.4 ± 18.3/h, with a mean oxygen desaturation index of 51.7 ± 15.7/h. BHI values at 5:00 PM before baseline registration were within the normal range. Detailed data are given in Table 1.