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Original Article

Decreased cerebral vasomotor reactivity in patients with obstructive sleep apnea syndrome

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ABSTRACT

Objective: In obstructive sleep apnea syndrome (OSAS), any of the activated neural, vascular, hemodynamic, metabolic, inflammatory, and thrombotic mechanisms may be related to increased cerebrovascular disease and risk of death; however, the possible pathophysiological process between obstructive sleep apnea syndrome and stroke has not been clearly explained. We hypothesize that alterations in vasomotor reactivity in patients may be responsible for their altered cerebral blood flow, and may contribute to the increased risk of ischemic stroke.

Methods: A total of 30 untreated patients with severe obstructive sleep apnea and 26 control subjects were included in the study. The mean blood flow velocity and breath holding index were measured in middle cerebral artery bilaterally in both patient and control groups by using transcranial Doppler ultrasound. We compared the values between two groups.

Results: The mean blood flow velocity and breath holding indexes were significantly decreased in the patient group when compared with the control group. There were no correlations between cerebral hemodynamic parameters and polysomnographic findings in patients.

Conclusion: Our findings suggest that there was a deteriorated vasodilator response to hypercapnia in patients with OSAS. This deterioration may stem from chemoreceptors or endothelial damages that lead to vascular relaxation and vasodilatation in cerebrovascular circulation. This impaired cerebral vascular regulation may contribute to the increased risk of stroke in patients with OSAS.

1. Introduction

Obstructive sleep apnea syndrome (OSAS) is a common sleep disorder that affects individuals of both sexes; in men, it affects 10% of those 30–49 years of age and 17% of those 50–70 years of age [1]. OSAS is characterized by excessive daytime sleepiness and episodes of recurrent upper airway obstruction that occur during sleep [1]. In patients with severe OSAS, apnea can occur hundreds of times every night. It is very important for physicians to consider diagnoses of OSAS because of its strong associations with stroke, diabetes, hypertension, cardiovascular disease, decreased quality of life, as well as other metabolic abnormalities [2–6]. Although previous research has asserted that activated neural, vascular, metabolic, thrombotic, hemodynamic, and inflammatory mechanisms may be related to increased risk of death and cerebrovascular disease in individuals with OSAS, the possible pathophysiological connection between OSAS and stroke has yet to be clearly explained [5,7]. Cerebral vasomotor reactivity is considered an index of adaptation to the metabolic changes in the cerebral vessels. The impaired cerebral vascular regulation is thought to be a risk marker of cerebral infarctions [8,9]. It was shown that autoregulatory mechanisms of cerebral arteries were impaired in patients with OSAS [10,11]. In light of these findings, the following question surfaced: Are there any links between OSAS and cerebral vasomotor reactivity?

Transcranial Doppler (TCD) ultrasound is a sensitive, real-time tool that can be used to monitor cerebral hemodynamics. TCD ultrasound can also be used to measure immediate responses of

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blood flow throughout the brain [12]. Certain tests, such as the breath holding index (BHI), can evaluate intracranial hemodynamics with vasomotor reactivity. Cerebral blood flow changes due to accumulated CO_2 is used to calculate the BHI, and the cerebrovascular response capacity is then estimated [13].

We hypothesize that changes in the vasomotor reactivity of patients with OSAS may be responsible for their altered cerebral blood flow and contribute to their increased risk of ischemic stroke. Therefore, the current study aims to evaluate the cerebral hemodynamics of OSAS patients by measuring their BHI and mean blood flow velocities (MBFVs) with TCD ultrasound.

2. Methods

This cross-sectional study was performed in compliance with the Declaration of Helsinki and after approval by a local ethics committee. All subjects gave informed and written consent before participating in the study. The study group consisted of 30 untreated male patients with severe OSAS, and the control group consisted of 26 age- and sex-matched healthy subjects. All subjects were studied at Gulhane Military Medical Academy's Sleep Research Centre in the Department of Psychiatry. Recordings were made in individual bedrooms using digital polygraphs (Somnostar Alpha Series 4; SensorMedics, Yorba Linda, CA, USA) and standard recording procedures. Standard recording parameters, which included electrooculograms, electrocardiograms, electroencephalograms (C3, C4, O1, and O2) and submental electromyograms were also used. In addition, oronasal airflow, respiratory effort, finger pulse oximetry, and tibialis muscle activity were measured. Polysomnography recordings were scored using the American Academy of Sleep Medicine's Manual for the Scoring of Sleep and Related Events [14]. Apnea is scored when there is a drop in the peak signal excursion by $\geq$90% of the pre-event baseline for $\geq$10 s.

The current study included a control group and patients with severe OSAS (apnea–hypopnea index [AHI] $\geq$ 30 events/h). Based on responses given on a standardised questionnaire and information obtained from their physicians, subjects were excluded from the study if they were taking calcium channel blockers, β-blockers, or allopurinol and had known syncope, anemia, diabetes, coronary artery disease, cerebrovascular disease, or musculoskeletal abnormalities. None of the subjects with OSAS had been previously treated for the disorder.

A DWL Multi-Dop X4 (manufactured by DWL GmbH, Germany) was used to perform TCD ultrasound on all of the study participants. All subjects were submitted for TCD ultrasound between 08:00 and 09:30. The TCD ultrasound was conducted in silent rooms while the participants were lying supine. Using a 2-MHz probe, the middle cerebral arteries (MCAs) were evaluated through the windows of the temporal bone. The depth of the MCAs were approximately 45–55 mm from the surface. The mean arterial blood flow velocities of these vessels were considered to be stable during the last 3 min of the initial 10-min resting trial, which was performed after the fixation of both probes. Participants were instructed to hold their breath for 30 s after each 5-min resting interval [13]. This process was repeated three times. In the BHI study, a standard breath holding of 30 s was followed by a determination of the maximal point of average blood flow after the first inspiration. This part of the study used the equation ([Vbh–Vr]/Vr) $\times$ 100 s^{-1}, where Vbh was the MBFV of the vessel at the end of each period of breath holding, Vr was the MBFV of the vessel at rest, and s^{-1} indicated breaths held per second. This protocol was applied to the MCAs bilaterally. The data measurements were made offline.

BHI and MBFV were bilaterally measured in the MCAs of the patients and control group participants. The BHI and MBFV values were then compared between both groups. Statistical analyses and calculations were performed using Microsoft Excel 2007 (Microsoft Corporation, Redmond, WA, USA) and SPSS for Windows, version 15.0 (SPSS Inc., Chicago, IL, USA). The mean, percentage, and standard deviation (SD) were used for descriptive statistical methods. The Shapiro–Wilk test was used to evaluate the distribution of data. All of the matched data were normally distributed; therefore, an independent-sample *t* test was used to evaluate each independent group. A Pearson correlation test was used to evaluate the link between polysomnographic findings and cerebral hemodynamic parameters within the OSAS group. A p value of <0.05 was considered to be statistically significant.

3. Results

The mean age of the patients was 37.9 ± 9.5 years; the total obstructive apnea number was 377.2 ± 147.2; and the AHI was 59.9 ± 20.7. Demographic data and polysomnography (PSG) results are presented in Table 1.

The mean BFV of the MCAs was 52.5 ± 11.9 cm/s in patients with OSAS and 60.9 ± 11.6 cm/s in the control group. The BHI was 1.45 ± 0.45 in patients with OSAS and 1.6 ± 0.65 in the control group. The BHI and MBFV of the MCAs were significantly lower in the patient group ($p < 0.001$) than they were in the control group (Table 2).

In patients with severe OSAS, there were no correlations between the cerebral hemodynamic parameters and polysomnographic findings (Table 3, Fig. 1). In the control group, there was a negative correlation between non-REM2 parameters and MCA velocity and a significantly positive correlation between non-REM3 parameters and MCA velocity (Table 4).

4. Discussion

When compared with the control group, OSAS patients saw decreases in the BHI and in the MBFV of their MCAs. This impaired cerebral vascular regulation may have contributed to an increased risk of stroke in the patients with OSAS.

Depending on its regional needs, the healthy human brain is capable of regulating blood flow by changing the size of its capillaries and small arteries [15]. Vasomotor reactivity, which is closely related to autoregulation, shows the dilation potential of a vessel [16]. Cerebrovascular reactivity to hypercapnia is considered to be an index of a cerebral vessel's ability to adapt to the metabolic requests of the brain. The reduction of this property could depend on an increased susceptibility to ischemic stroke [17]. Patients who have strokes and transient ischemic attacks are more likely to have OSAS than the general population [18]. In a large observational cohort study that examined the role of OSAS in the development of first-ever strokes and death from any cause, Yaggi et al. determined that OSAS was associated with an increased incidence of both outcomes. They also concluded that the association was independent of other cardiovascular and cerebrovascular risk factors, such as hypertension [5,19].

TCD measurements performed during apnea showed that blood flow through the MCA increased toward the end of the apnea period and quickly decreased to basal levels upon inspiration [20–24]. Increases in cerebral blood flow velocity (CBFV) during apnea may be due to increases in arterial pressure and carbon dioxide concentration. However, due to the drop in CBFV at the start of inspiration, we believe that these changes are primarily associated with changes in carbon dioxide concentration [23,24]. The studies that were performed at night showed that OSAS patients had lower blood flow values than the healthy subjects, suggesting that the OSAS patients had cerebral hypoperfusion [25]. In studies