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Original Article

Obstructive sleep apnea syndrome and blood flow to the eyes

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Abstract. To evaluate the pulsatile ocular blood flow (POBF) in patients with obstructive sleep apnea syndrome (OSAS). Forty-one newly diagnosed OSAS patients without comorbidities and 17 healthy control subjects were included to the study. Subjects were classified into groups of control, mild- moderate OSAS and severe OSAS, based on apnea–hypopnea index (AHI) values as control [AHI=<5 h(-1)), mild-moderate [AHI= 5-30 h(-1)], and severe [AHI >30 h(-1)]. For each eye, the Ocular Blood Flow Analyzer was used to obtain measurements of POBF. This study included 41 patients (10 female, 31 male) and 17 controls (6 female, 11 male). Cases and controls were comparable in body mass index, sex, and age. No statistical difference was found between the groups of patients with OSAS and healthy control subjects in age, BMI, sex, ocular axial length, IOP and mean blood pressure. There was no significant difference between control and OSAS patients in terms of POBF (T-test; p>0.05). There was no significant difference between groups in terms of POBF (one way ANOVA; p=0.3). In severe OSAS group, no statistically significant correlation was found between AHI and POBF(r= 0.09, p=0.5). These data show that the OSAS patients exhibit no significant difference in POBF compared to control group.

Key words: Intraocular pressure, obstructive sleep apnea syndrome, ocular blood flow, pulsatile ocular blood flow

1. Introduction

Obstructive sleep apnea syndrome (OSAS) is a common disorder that affects 3% to 7% of general population (1). OSAS is characterized by upper airway collapses during sleep and by the persistence of inspiratory effort during the interruptions of airflow (2). The cessation or substantial reduction in airflow is associated with hypoxia and hypercapnia which detrimentally stimulates the cardiovascular system. Obstructive sleep apnea syndrome has been shown to generate arterial hypertension, atherosclerosis, endothelial dysfunction, and autonomic dysfunction, all of which may interact with ocular vascular regulation (3-5). The clinical importance of these outcomes arises from the fact that reduced ocular blood flow represents a potential threat for the health of the eye, which is likely to increase its susceptibility to ocular pathologies such as glaucoma.

Recent research indicates that OSAS may have neurophthalmological consequences. Floppy eyelid syndrome (6), keratoconus (7), papilledema (8), optic neuropathy, visual field defects (9), decrease in retinal nerve fiber layer thickness (10), and a high prevalence of glaucoma have been described in patients with OSAS (11). Vascular dysfunction, as an explanation for some of these consequences, was considered among the possible causes since OSAS impacts on macro vasculature and autonomic function and may therefore interfere with ocular microvascular regulation (12-14). However in one study concerning ophthalmic blood velocity at rest, no difference was found between patients with OSAS and healthy control

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subjects (14). Moreover, in a recent study, using ocular blood flow analyser showed unimpaired pulsatile ocular blood flow (POBF) in patients with OSAS (15).

Pulsatile ocular blood flow can be derived from the intraocular pressure (IOP) variation according to cardiac rhythm. It measures the pulsatile component of arterial ocular inflow, particularly choroidal perfusion (16). The pulsatile ocular blood flow analyser is a modified pneumotonometer interfaced with a microcomputer. The technique is characterised by excellent reproducibility (17). In this study, we hypothesized that POBF was altered in patients with OSAS compared to control subjects.

2. Methods

The study included 17 healthy controls and 41 patients with OSAS and they have no other associated comorbidities. All the subjects were aware of their right to withdraw from the study at any time for any reason of their choosing, and gave written informed consent for all the test procedures that complied with Uludag University's ethics committee for human research. All aspects of testing are conformed to the Declaration of Helsinki regarding the use of humans in research.

The inclusion criterias were absence of any suggestive history of ocular trauma and ocular diseases (including retinal disease, ametropia > 3 diopters, optic neuropathy and glaucoma). To eliminate the confounding effect of myopia, we excluded all patients with axial length greater than 24 mm. The right eye of each subject was included in the study, if it was found to be eligible. Systemic diseases and drugs likely affect ocular blood flow, such as chronic steroid use, use of anti-glaucoma medications, cardiovascular treatment (vasoconstrictors, vasodilators, β- and α-receptor agonists or antagonists, nitric-derived medication), theophylline, sildenafil, immunosuppressors, neuroleptics, nonsteroidal antiinflammatory agents, estroprogestative treatment, hypnotics (benzodiazepines) and uncontrolled high blood pressure (>150/90 mmHg) were excluded from the study. Subjects comparable for body mass index (BMI), sex, age and ocular axial length were enrolled as a control group. The control group was recruited from those attending our sleep disorders clinic for polysomnography who had sleep-related symptoms (i.e. snoring, witnessed sleep apnoeas and excessive daytime sleepiness) and without any sleep disorder. Self reported health was good for them and there was no history of systemic or ocular disease.

2. 1. Ophthalmic Examination

All patients and healthy subjects received ophthalmologic evaluation, including best-corrected visual acuity, slit-lamp examination, and fundus examination after pupil dilation. The axial length was measured with IOLMaster (Zeiss Humphrey, Zeiss Meditec, Jena, Germany). The ophthalmologic examination was performed within one week after the polysomnography and before the beginning of OSAS therapy. Ocular examination of all patients with OSAS and healthy subjects was normal.

2. 2. Polysomnography

Full Polysomnography was performed in all subjects (Compumedics P-series Sleep System; Compumedics Sleep; Melbourne, Australia). Participants come to the sleep laboratory at 8:30 pm, and polysomnography was initiated at 10:30 pm. Polysomnographic recordings included two electrooculogram channels, two EEG channels (C3/A2 and O2/A1), one ECG channel, and one sub mental electromyogram channel. Ventilatory monitoring included hemoglobin oxygen saturation by pulse oximetry (oxygen saturation measured via a fingeroximeter), recording of oronasal airflow (with an oronasal thermistor), respiratory movement (with an inductive plethysmography) including chest and abdomen, and body position. Sleep staging was scored according to the standard criteria of Rechtschaffen and Kales (1968). To assess the ventilation during sleep, nasal airflow was analyzed. Apnea was defined as episodes lasting at least 10 second with airflow cessation. Hypopnea was defined as episodes lasting at least 10 second with a decrease in thermistor signal amplitude by at least 50% and associated fall of at least 3% in oxygen saturation or an arousal. The apnea-hypopnea index (AHI) was the sum of the number of apneas and hypopneas per hour of sleep. Subjects with AHI > 5 were considered to have OSAS. Subjects with AHI< 5 were included in the control group. When the AHI was between 5 and 30, OSAS was regarded as "mild-moderate'' (Group 1) and when it was over 30 it was regarded as "severe'' (Group 2).

2.3. Pulsatile Ocular Blood-Flow Measurements

Ocular pulsatility was assessed with an ocular blood flow analyser (OBFA; Paradigm Medical instruments Inc., Salt Lake City, UT, USA), based on the principle of pneumotonometry (18). . The Ocular Blood Flow Analyzer reports output parameters including IOP (mmHg), pulse amplitude (mmHg), POBF (μL/min), pulse rate and a number of flow related measures. The

instrument produces a detailed report, which provides the time, date and a graphic representation of the patient's test results. Pulsatile ocular blood flow was measured with the subjects in the sitting position. After anesthetizing the cornea with Alcain (Alcon Laboratories, Fort Worth, Tex.) and lubricated with a commercially available artificial tear solution to minimize any corneal insult resulting from repeated IOP measurements, average IOP and POBF measurements were automatically calculated from one continuous IOP recording (approximate recording time 5–10 seconds) that was sufficient to encapsulate five similar IOP pulses. A built-in processor analyses different characteristics of the IOP pulse waves and selects the five most representative pulses for the calculation of POBF. Ocular pressure rises and falls with each heartbeat. This pressure waveform is created when the bolus of blood from each heartbeat passes through the ocular choroid. The systolic increase and diastolic decrease in intraocular pressure caused by the POBF is accurately recorded by the OBFA. In this study IOP, POBF, pulse rate and pulse amplitude were included in the analyses. Systemic blood pressure (BP) measurements were obtained just before OBFA measurements. Mean BP was calculated as diastolic BP +1/3 (systolic BP-diastolic BP). The ocular perfusion pressure (OPP) is the pressure that forces blood to flow through the ocular vascular bed and is equal to the difference between the mean arterial pressure and the venous pressure at the exit point. The venous pressure in the eye is approximately equal to the IOP. The OPP was calculated based on IOP, systolic blood pressure (SBP), and diastolic blood pressure (DBP), according to ophthalmodynamometric studies (subtracting the IOP from two thirds of the mean BP).

2. 4. Statistical Analysis

Mean and standard deviation were calculated in the groups. Kolmogorov-Smirnov tests were used with Lilliefor's correction to assess normality of distribution for each variable. One-way ANOVA and unpaired T- test were used to test the significant difference among the groups. The Pearson correlation coefficient for normally distributed variables is reported at the eye level. Chi square was used when appropriate. Differences were considered significant at $p< 0.05$. The statistical power was calculated by using the PS software (http://biostat.mc.vanderbilt.edu/twiki/bin/view/Main/PowerSampleSize) based on the 5% alpha error level for comparison of POBF in control versus patients with OSAS. All statistical analyses were carried out using statistical software (SPSS, version 16.0 for Windows, SPSS Inc., Chicago, IL, USA) and MS Excel.

3. Results

Forty-one patients (10 female, 31 male) and 17 controls (6 female, 11 male) were included in the study. A total of 58 eyes were appropriate according to the inclusion criterias. No statistical difference was found between the groups of patients with OSAS and healthy control subjects in age, BMI, sex, ocular axial length, IOP and mean blood pressure (Table 1).

The mean value of POBF in overall OSAS patients was 786.7±114.8. There was no significant difference between control and OSAS patients in terms of POBF (Unpaired T test, p= 0.3). Observed power was 0.66 for POBF. The mean value of POBF in control, mild-moderate and severe OSAS groups were respectively 864±118 µL/min (range 592-1102), 781±159 µL/min (range 482-1468) and 790±127µL /min (range 500-1156) (Figure). There was no significant difference between groups in terms of POBF (One way ANOVA, p= 0.5).

The mean value of IOP in overall OSAS patients was 15.5±3.0. There was no significant difference between control and OSAS patients in terms of IOP (Unpaired T test, p= 0.1). Observed power was 0.74 for IOP. The mean value of IOP in control, mild-moderate and severe OSAS groups were respectively, 13.5±1.7 mmHg (range 9.3-17.8), 15.5±3.2 mmHg (range 7.7-22.4) and 15.6±3.9 mmHg (range 9.9-23.4). There was no significant difference between groups in terms of IOP (One way ANOVA, $p> 0.05$). No significant correlation was seen between IOP and POBF in each group ($p> 0.05$).

When a correlation analysis was performed in the control subjects, no statistically significant correlation was found between AHI and POBF($r=0.3$. $p=0.07$). In mild-moderate OSAS group, no statistically significant correlation was found between AHI and POBF($r=-0.05$, $p=0.7$). In severe OSAS group, no statistically significant correlation was found between AHI and POBF($r=0.09$, $p=0.5$).

When the correlation analysis was performed in the control subjects, no statistically significant correlation was found between POBF and age ($r=0.3$. $p=0.08$). In mild-moderate OSAS group and severe OSAS group, no statistically significant correlation was found between POBF and age ($r=-0.21$, $p=0.21$; $r=-0.01$, $p=0.9$ respectively).

Table 1. Data of OSAS Patients Versus Control Group Subjects

	Control Group	Mild-Moderate OSAS patients (Group 1)	Severe OSAS Patients (Group 2)	p
Number	17	18	23	N/A
Sex (m;f)	11;6	14;4	17;6	n.s.
Age (year)	49.5± 5	52.6±9.6	50.5±11.5	n.s.
BMI (kg/m^2)	25.6±0.3	26.6±0.6	26.3±0.4	n.s.
Systolic BP(mm Hg)	122±15,1	123±18,1	126±17.3	n.s.
MAP(mmHg)	93.9±13.5	97.2±14.7	94.7±16.4	n.s.
Axial Length (mm)	22.6±1.2	22.7±0.9	23±0.9	n.s.
PaO^2 (mmHg)	85±4	82.5± 5	79.6±10	<0,001
$PaCO^2$ (mmHg)	39±3	40±4	42±3	<0,05
Mean SaO_2(%)	95.9±1.3	91.7±2.0	89.6±4.3	<0,001
IOP (mmHg)	13.5±1.7	15.5±3.2	15.6±3.9	n.s.
POBF(µL/min)	864±118	781±159	790±127	n.s.
OPP (mmHg)	50.3±8.4	49.3±9.1	49.7±10.2	n.s.
PA (mmHg)	3.9±1.3	3.2±1.3	3.5 ±1.2	n.s.
PR (/min)	73.8±17.8	84.1±23	75.5±18.8	n.s.
AHI (events/h)	1.3±1.1	18.4±6.4	62.9±15.5	<0,001

OSAS= obstructive sleep apnea syndrome; m= male; f= female; y=years; BP= blood pressure; MAP= mean arterial pressure; IOP= intraocular pressure; POBF= pulsatile ocular blood flow; OPP = ocular perfusion pressure; PA= pulse amplitude; PR= pulse rate; AHI= apnea-hypopnea index; N/A= not applicable; n.s.= statistically not significant. Data presented as mean ± SD.

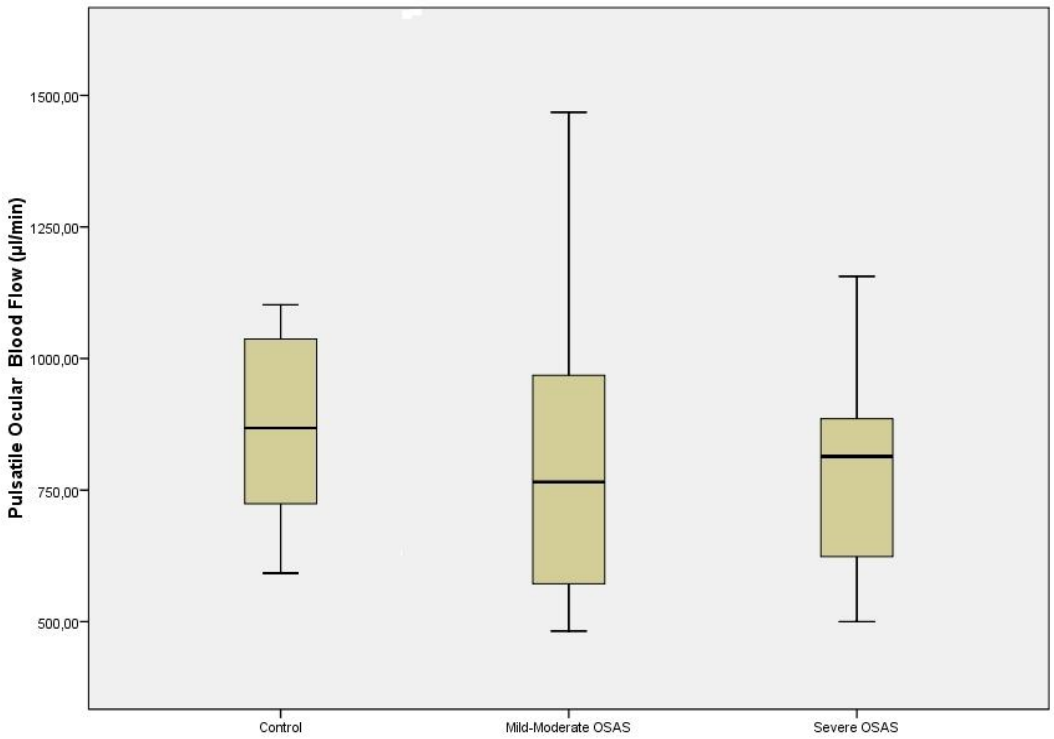

Fig. Distribution of mean pulsatile ocular blood flow (POBF) among the eyes in obstructive sleep apnea syndrome (OSAS) patients and control group (One-way ANOVA, p>0.05).

4. Discussion

This prospective case-controlled study investigated POBF in patients with OSAS. Our data demonstrated that POBF in patients with OSAS was similar to the control subjects.

The retinal circulation accounts for approximately 15% of total ocular blood flow. Uveal blood flow comprises the remaining 85%, including flow to the choroid, ciliary body and iris (19). Because most of the blood flow into the eye is within the choroidal circulation, it is presumed that POBF primarily measures the pulsatile component of choroidal perfusion, independent from the retinal circulation (16).

Obstructive sleep apnea syndrome related hypoxia and systemic inflammation might be associated with the progression of atherosclerosis 20 in which a reduction in ocular blood flow may be expected. Obstructive sleep apnea syndrome related apnea and hypoxia may result in endothelial damage (21). The repetitive hypoxia and reoxygenation episodes that are characteristic of the OSAS result in the increased production of reactive oxygen species that leads to vascular events (22). Chronic hypoxic stress results in irreversible remodeling of the vasculature and surrounding tissues, with smooth muscle proliferation and fibrosis (23). In addition, decreased plasma levels of NO derivatives (24) and abnormal endothelium-dependent and -independent vasodilatation (25) have been reported in patients with OSAS. Eventually, plaque deposits or fibrosis can make the artery narrow and less flexible. This makes it harder for blood to flow. Hovewer in published studies, one concerning POBF and the other ophthalmic blood velocity found no difference between patients with OSAS and healthy control subjects (14,15). Absence of pathologic POBF in OSAS is unexpected, given the autonomic regulation of the choroid (26), the known reduction in vascular response to α- and β-adrenergic receptors in OSAS (27), and an increased sympathetic activation secondary to the repetitive hypoxia and reoxygenation episodes (28).

The techniques used to evaluate POBF assumes a constant ocular rigidity that is influenced by age. Lam et al. (29) investigated the effect of age on POBF; and found that the reduction in POBF with age was significant. Ravalico et al. (30) found that POBF decreased in normal subjects with increasing age. On the contrary, Agarwal et al. (31) found no significant relation between age and POBF, because of a limitation of their dataset (subjects of at least 40 years old were selected to participate). In our study, we have determined the relation between POBF and age and there was no significant correlation in both control and patient groups. A probable reason could be that our study population was older (mean 51.0±9.5) and all other independent variables were standardized, thus reducing possible counteracting effects.

Another factor that may have affected our results was the negative relation that has been shown to exist between ocular axial length and POBF (16). This is because the pulse wave depends on the relationship between volume and pressure changes and the volume of choroidal vascular bed in the individual eye. A similar volume of blood entering the eye will thus produce greater pressure change in smaller eyes than in larger eyes. In this study, we had excluded the patients with refractive error of greater than ± 4D and axial length of greater than 24 mm. This was probably the reason that we did not find an association of this parameter associated with POBF.

Kiekens et al. (32) reported that patients with OSAS demonstrated significant 24-hour IOP fluctuations, with the highest values at night. Since the highest IOPs were found at night, single IOP measurements during office hours, do not permit the identification of patients who may present nyctohemeral IOP spikes. Pulsatile ocular blood flow measurements were taken between 8:00 a.m and 4:00 p.m. We did not take diurnal variation into consideration since the study was designed to determine blood flow changes for making inter-individual comparisons (single measurement for diagnosis) rather than intra-individual blood flow changes (e.g., before and after medication). In addition, as reported by Kiel and Shepherd (33), less significant variations in IOP are not often associated with a measurable change in ocular blood flow, due to the stabilizing effect of the autoregulatory response. Therefore, diurnal variation was not controlled.

Study limitations

To make the method as rigorous as possible, we tried to eliminate any possible source of error although it was impossible to completely eliminate these counteracting factors. Understanding these limitations is essential to proper study design and data interpretation. Especially having an OSAS and matched control group is very difficult, however, to find obese middle-aged patients without the presence of comorbidities which act as confounding factors and would potentially influence POBF measurements performed in the study. In this pilot study, although statistical power is modest (0.66) to formally confirm unimpaired POBF, the

impaired ocular blood flow in OSAS seems less likely. However, since the POBF measurement using POBF tonometer has a strong reliability as proved in other studies (34,35), it will be meaningful if variation from the above factors can be controlled or taken into account. An additional weakness, common to all sleep studies, is that the measurements have been performed in the sitting position, while OSAS as such presents in the supine position at night.

5. Conclusion

We report that POBF is unimpaired during the daytime in otherwise healthy patients with OSAS. Investigations of POBF in OSAS should however be performed with care taking into account the impact of factors contributing to the hemodynamics, posture, treatment and nyctohemeral effects.

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