Doppler Measurement of Blood Flow Velocities in Extraocular Orbital Vessels in Patients with Obstructive Sleep Apnea Syndrome

C. Zuhal Erdem, MD,[1] Remzi Altin, MD,[2] L. Oktay Erdem, MD,[1] Sebnem Kargi, MD,[3] Levent Kart, MD,[2] Fikret Cinar, MD,[4] Ferruh Ayoglu, MD[5]

[1] Department of Radiology, Zonguldak Karaelmas University School of Medicine, Kozlu 67600, Zonguldak, Turkey
[2] Department of Chest Disease, Zonguldak Karaelmas University School of Medicine, Kozlu 67600, Zonguldak, Turkey
[3] Department of Ophthalmology, Zonguldak Karaelmas University School of Medicine, Kozlu 67600, Zonguldak, Turkey
[4] Department of Ear, Nose, and Throat, Zonguldak Karaelmas University School of Medicine, Kozlu 67600, Zonguldak, Turkey
[5] Department of Public Health, Zonguldak Karaelmas University School of Medicine, Kozlu 67600, Zonguldak, Turkey

Received 26 August 2002; accepted 2 February 2003

ABSTRACT: *Purpose.* We used color Doppler sonography to determine blood flow velocities in the extraocular orbital vessels of patients with obstructive sleep apnea syndrome (OSAS) and compared the results with those of healthy control subjects without OSAS.

Methods. Patients with OSAS were classified according to the apnea-hypopnea index (AHI) as having mild OSAS (AHI < 20) or severe OSAS (AHI ≥ 20). The peak systolic velocity (PSV), end-diastolic velocity (EDV), and resistance index were measured in the ophthalmic artery (OA), central retinal artery (CRA), lateral short posterior ciliary artery, and medial short posterior ciliary artery using color Doppler sonography. Only 1 eye was measured in each study participant, and right and left eyes were chosen randomly. The blood flow velocities of patients with OSAS and those of control subjects were compared with the Kruskal-Wallis test and Wilcoxon's rank-sum test.

Results. The study comprised 30 patients (15 with mild and 15 with severe OSAS) and 20 healthy control subjects. Blood flow velocities were higher in most measured vessels in patients with OSAS than they were in the control subjects. Among patients with mild OSAS, the PSVs and EDVs in the posterior ciliary arteries were statistically significantly higher than those of the control group ($p < 0.05$), but those in the OA and CRA did not differ significantly between the mild OSAS group and the control group ($p > 0.05$). However, as the severity of OSAS increased, the PSVs and EDVs of the OA and CRA were also affected ($p < 0.05$).

Conclusions. Color Doppler sonographic measurements of blood flow parameters in the orbital vessels may differ significantly between patients with OSAS and those without the syndrome. Therefore, OSAS should be considered in addition to other conditions when interpreting the results of color Doppler sonography of the extraocular orbital vessels if the clinical history points toward such a diagnosis. © 2003 Wiley Periodicals, Inc. *J Clin Ultrasound* **31**:250–257, 2003; Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/jcu.10171

Keywords: obstructive sleep apnea syndrome; color Doppler ultrasonography; orbital blood flow

Sleep apnea is a condition in which breathing ceases during sleep.[1] The most common type, obstructive sleep apnea syndrome (OSAS), or hypopnea, results from a complete or partial pha-

Correspondence to: C. Z. Erdem

ryngeal occlusion during sleep.[2] It occurs more frequently in middle-aged obese men, some of whom have arterial hypertension, than in other patients.[3–5]

The pathophysiology of OSAS is complex and not completely understood. The individual apneic episodes in OSAS have a considerable hemodynamic effect that is mediated by a complicated sequence of physiologic events. Several important regulatory mechanisms in cardiovascular homeostasis seem to be affected in patients with OSAS, and it is increasingly being linked to vascular disease.[6] The health consequences of sleep apnea are especially evident in the cardiovascular system: direct and deleterious effects of OSAS on the cardiovascular system may contribute to the initiation or progression of systemic and pulmonary hypertension, congestive heart failure, coronary artery disease, idiopathic cardiomyopathy, and cerebrovascular disease.[6,7] Although the effects of OSAS on other vascular systems have been studied, to the best of our knowledge, little is known about the hemodynamic effects of OSAS on the ocular circulation.

Color Doppler sonography (CDUS) can be used to estimate the velocity of blood flow in the orbital vessels behind the eye. This in turn permits deductions to be made about blood flow to the eye through the ophthalmic artery (OA), the central retinal artery (CRA), and the posterior ciliary arteries (PCAs).[8–10] In this prospective study, we aimed to compare findings on CDUS among patients with OSAS with those of control subjects without OSAS to assess the effects of OSAS on vessels supplying the eye.

PATIENTS AND METHODS

Potential study participants were recruited from patients who attended a sleep disorders clinic. Before their enrollment, all candidates underwent general physical examination, blood pressure measurement, complete blood count, blood chemistry profile, and neurologic examination to detect any underlying systemic disease. If the candidates had no underlying disease, they also underwent an overnight sleep study in a sleep laboratory between 10:30 p.m. and 6:00 a.m. under the observation of a technician. Participants were monitored using a Poly-Mesam cardiorespiratory diagnostics system (MAP Medizin-Technologie; Martinsried, Germany) consisting of a flow sensor for nasal and oral breath flow, a laryngeal microphone, a 3-channel electrocardiograph, 1 stress-sensitive belt each for the thorax and the abdomen, a positional sensor for determination of body movement, and a periodic leg–movement sensor. The data were stored on a computer, and the software used (Poly-Mesam version 1.42; MAP) automatically calculated the apnea-hypopnea index (AHI), apnea index, hypopnea index, O_2 desaturation index, heart rate variation index, and movement index. The AHI is defined as the sum of the number of episodes of apnea and hypopnea per hour of sleep; the other indices are calculated similarly. Both automated and hand-scored data analyses were provided and evaluated.

A reduction in O_2 was recorded for O_2 desaturations of at least 4% independent of the simultaneous occurrence of apnea or hypopnea. Apnea was defined as cessation of airflow lasting at least 10 seconds, and hypopnea was defined as a 50% reduction in thoracic excursion for at least 10 seconds. The mean O_2 saturation (the mean of the O_2 saturation levels recorded during the night) level and the lowest O_2 saturation level were obtained for each patient.

In our study, the presence of clinical symptoms and an AHI of 5 or greater were accepted as evidence of OSAS. Patients with OSAS were classified into group I (mild OSAS, AHI < 20) or group II (severe OSAS, AHI $\geq$ 20). Although patients with an AHI of 5 or greater are considered to have OSAS, morbidity and mortality rates are substantially higher among patients with an AHI of 20 or greater than they are in those with an AHI of less than 20.[11]

Control subjects exhibited no clinical findings of OSAS (snoring, apnea, or daytime sleepiness) and did not show evidence of OSAS during the sleep study. At the time of the sonographic examination, the sleep study results were unknown to the sonographer.

The CDUS measurements were all taken by the same examiner, using an HDI 5000 ultrasound scanner (Advanced Technology Laboratories, Bothell, WA) with a 7.5-MHz linear-array transducer. Measurements were taken in the morning, with the patient in the supine position, after the overnight sleep study was completed. Ultrasound gel was applied to the external surface of the eyelids without any pressure on the eye. Only 1 eye per participant was measured. In a previous study of 15 patients who were not included in the current study, we had found no statistically significant differences between right and left eyes, so we chose at random which eye to study. Three consecutive measurements were taken for each vessel studied, and the mean mea-

surement was recorded. During the approximately 40-minute examination, arterial blood pressure was measured every 10 minutes.

The OA, CRA, lateral short PCA (LPCA), and medial short PCA (MPCA) were examined. The OA can be traced nasally from the optic nerve after it crosses the optic nerve; strong signals are routinely detectable at this site. When the right OA was being measured, participants were asked to look to the left, and for the left OA, they were asked to look to the right. The CRA was examined at the retrobulbar region on the optic nerve trace and 10 mm behind the globe. The PCAs were examined temporally and nasally to the optic nerve although characteristic Doppler spectra can be obtained from PCAs with higher diastolic flow velocities because of the low resistance in the choroid, which they supply. When the vessels were seen in color Doppler mode, the Doppler cursor was placed on the lumen. When a signal was detected, a 1-mm sample volume was used to obtain the Doppler spectral waveforms. The proximal and distal portions of the vessel were imaged to determine vessel direction and to adjust the Doppler angle, which was always less than 60°. The peak systolic velocity (PSV), end-diastolic velocity (EDV), and resistance index (RI) were measured in all arteries (Figures 1–4).

Statistical analyses were performed using SPSS for Windows version 11.0 (SPSS, Chicago, IL). Mean values and standard deviations were calculated for PSV, EDV, and RI in the arteries. Differences in blood flow velocity between groups were compared with the Kruskal-Wallis test, and Wilcoxon's rank-sum test was used if a between-group difference was detected. The relationships between the mean O_2 saturation values of patients with OSAS and the blood flow velocities and RIs were analyzed with Pearson's correlation test. The level of statistical significance was set at $p < 0.05$.

The study protocol and the participants' consent form were approved by our institutional ethical committee. Each patient and healthy control subject provided written informed consent to participate in the study.

RESULTS

In total, we enrolled 30 patients with OSAS and 20 healthy control subjects. Fifteen patients had mild OSAS, and 15 had severe OSAS. All patients and control subjects were men, and they had no systemic diseases, including hypertension. The participants' characteristics are summarized in Table 1. When the mean and lowest O_2 saturation levels were compared, the mean values were statistically significantly lower among patients with severe OSAS than among those with mild OSAS and those in the control group.

Table 2 summarizes the comparisons of blood flow velocities in all vessels in patients with OSAS and control subjects. Most mean values in the OAs, CRAs, and PCAs were higher in patients with OSAS than they were in control subjects. The PSVs and EDVs in the OA and CRA were higher in group I than in the control group, but the difference was not statistically significant ($p >$

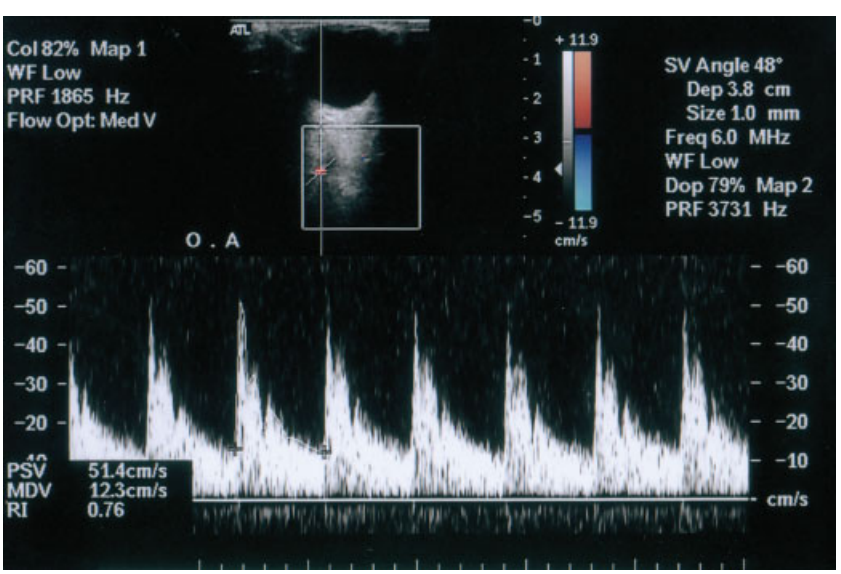

FIGURE 1. Color duplex sonogram of an ophthalmic artery (OA) in a patient with obstructive sleep apnea syndrome shows a peak systolic velocity (PSV) of 51.4 cm/second and a resistance index (RI) of 0.76.

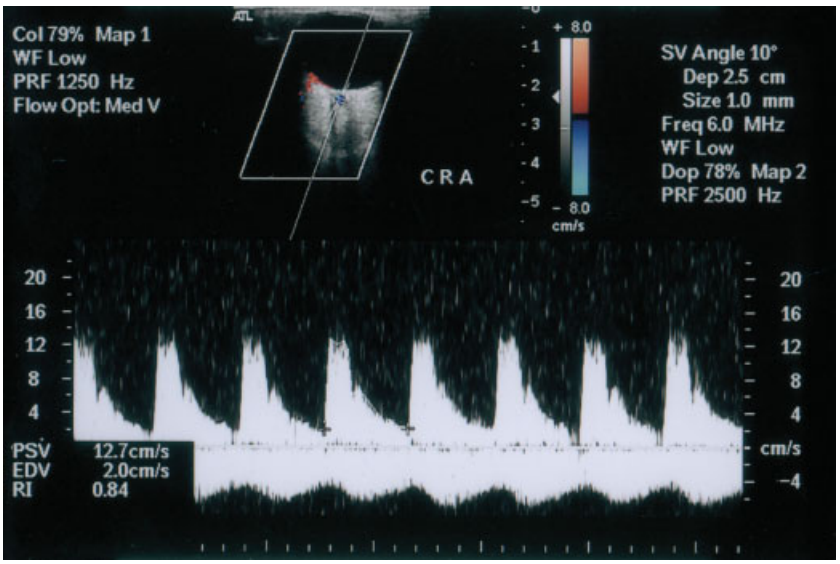

FIGURE 2. Color duplex sonogram of a central retinal artery (CRA) in a patient with obstructive sleep apnea syndrome shows a peak systolic velocity (PSV) of 12.7 cm/second and a resistance index (RI) of 0.84.

0.05). However, the velocities in the OA and CRA were statistically significantly higher among patients in group II than they were in the control group ($p < 0.05$). The RIs in both arteries were the same or slightly lower among patients with OSAS than they were in control subjects ($p > 0.05$).

The PSVs and EDVs in the OA were statistically significantly higher in group II than they were in group I ($p < 0.05$). The velocities in the CRA were also higher in group II than in group I, but the difference was not statistically significant ($p > 0.05$) (Figures 5 and 6).

When group I and the control group were compared, the PSVs and EDVs in the PCAs were statistically significantly higher in group I ($p < 0.05$), but the PSVs in the MPCAs were not statistically significantly higher than in the control group ($p > 0.05$). These velocities in both the LPCAs and the MPCAs also were statistically significantly higher in patients in group II than in control subjects ($p < 0.05$). The velocities in the PCAs were also statistically significantly higher in group II than in group I ($p < 0.05$). However, the RIs in both these arteries were the same or slightly

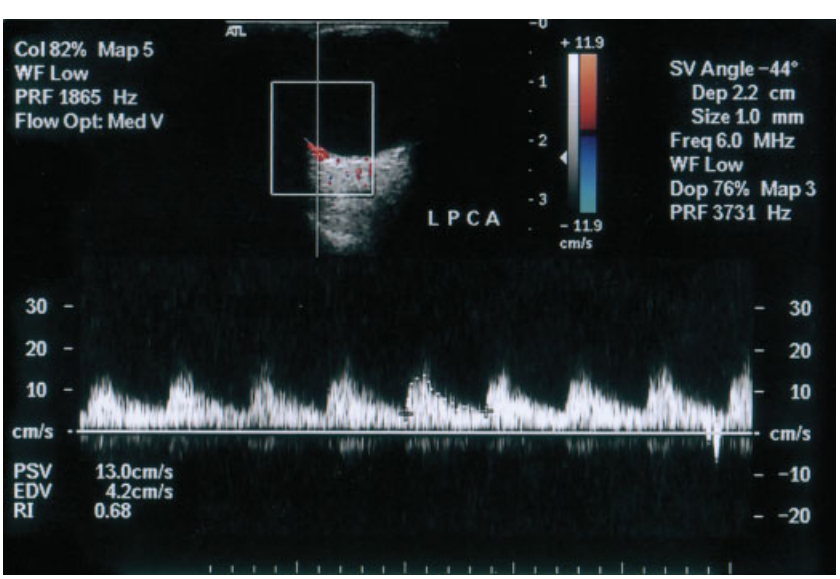

FIGURE 3. Color duplex sonogram of a lateral posterior ciliary artery (LPCA) in a patient with obstructive sleep apnea syndrome shows a peak systolic velocity (PSV) of 13.0 cm/second and a resistance index (RI) of 0.68.

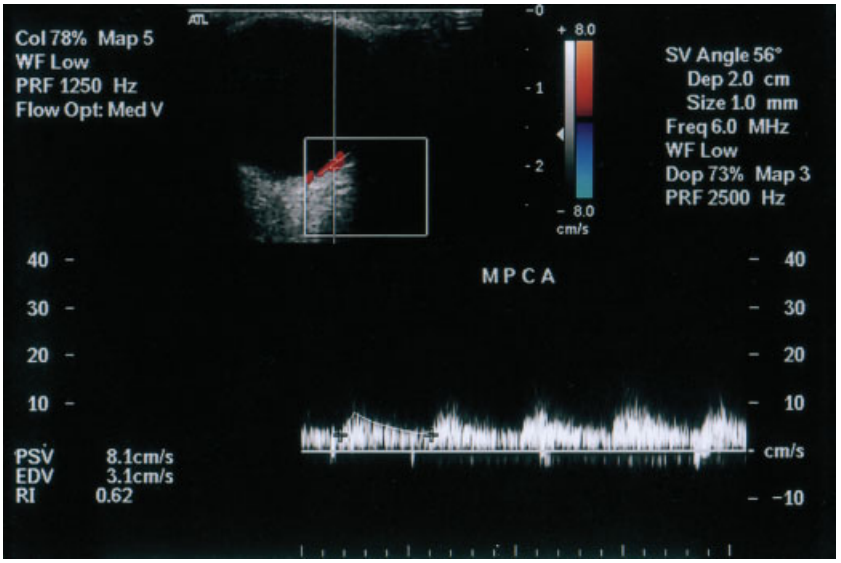

FIGURE 4. Color duplex sonogram of a medial posterior ciliary artery (MPCA) in a patient with obstructive sleep apnea syndrome shows a peak systolic velocity (PSV) of 8.1 cm/second and a resistance index (RI) of 0.62.

TABLE 1
Characteristics of Patients with Obstructive Sleep Apnea Syndrome (OSAS) and Healthy Control Subjects*

Characteristic	Patients with OSAS: Group I, AHI < 20 (n = 15)	Patients with OSAS: Group II, AHI ≥ 20 (n = 15)	Control Subjects (n = 20)
Age, years	45 ± 6	44 ± 1	41 ± 6
Mean oxygen saturation level, %	94 ± 2	90 ± 5	96 ± 1
Lowest oxygen saturation level, %	83 ± 5	66 ± 14	89 ± 2

Abbreviation: AHI, apnea-hypopnea index.
*Values are means ± standard deviations.

TABLE 2
Mean Blood Flow Velocities in Patients with Obstructive Sleep Apnea Syndrome and in Healthy Control Subjects

Vessel	Mean (SD) Values: Group I Patients* (n = 15)	Mean (SD) Values: Group II Patients* (n = 15)	Mean (SD) Values: Control Subjects (n = 20)	p Value†	p Values for Between-Group Comparisons‡: Group I vs. Control Group	Group II vs. Control Group	Group I vs. Group II
Ophthalmic artery							
PSV, cm/second	45.7 (5.8)	49.2 (5.0)	41.9 (8.9)	0.03	0.41	0.02	0.03
EDV, cm/second	11.1 (1.4)	13.6 (3.4)	10.5 (2.8)	0.02	0.16	0.01	0.03
RI	0.74 (0.09)	0.74 (0.05)	0.76 (0.05)	0.2	0.2	0.6	0.08
Central retinal artery							
PSV, cm/second	11.0 (4.1)	11.3 (1.5)	9.9 (2.0)	0.2	0.4	0.03	0.8
EDV, cm/second	4.0 (1.7)	4.6 (1.8)	3.3 (1.1)	0.01	0.3	0.02	0.4
RI	0.71 (0.01)	0.71 (0.08)	0.74 (0.06)	0.6	0.3	0.5	0.9
Lateral posterior ciliary artery							
PSV, cm/second	9.3 (2.6)	12.7 (2.7)	7.9 (2.1)	0.001	0.02	0.001	0.004
EDV, cm/second	4.9 (2.3)	6.5 (1.5)	3.5 (2.1)	0.001	0.03	0.001	0.04
RI	0.69 (0.07)	0.67 (0.09)	0.70 (0.05)	0.8	0.6	0.6	0.9
Medial posterior ciliary artery							
PSV, cm/second	8.7 (2.0)	12.6 (3.0)	7.7 (1.9)	0.001	0.17	0.001	0.001
EDV, cm/second	4.1 (1.6)	6.5 (1.6)	2.7 (1.1)	0.001	0.015	0.001	0.002
RI	0.63 (0.08)	0.65 (0.09)	0.66 (0.08)	0.7	0.4	0.9	0.61

Abbreviations: SD, standard deviation; vs., versus; PSV, peak systolic velocity; EDV, end-diastolic velocity; RI, resistance index.
*Group I patients had mild obstructive sleep apnea syndrome (OSAS), with an apnea-hypopnea index (AHI) of less than 20; group II patients had severe OSAS, with an AHI of 20 or greater.
†Differences in blood flow velocities between all groups compared with the Kruskal-Wallis test.
‡Differences in blood flow velocities between paired groups compared with Wilcoxon's rank-sum test.

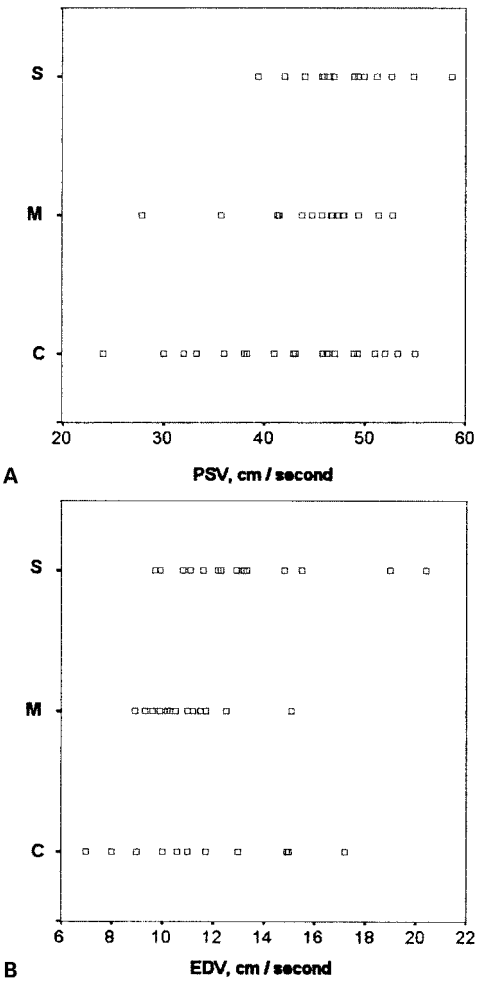

FIGURE 5. Scattergrams show **(A)** the peak systolic velocity (PSV) and **(B)** the end-diastolic velocity (EDV) in the ophthalmic arteries in patients with severe (S) and mild (M) obstructive sleep apnea syndrome and in control subjects (C).

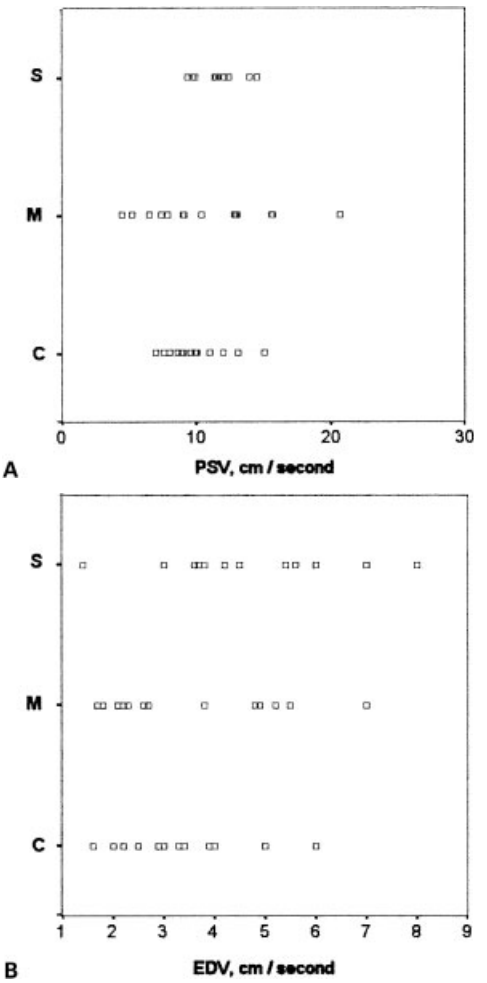

FIGURE 6. Scattergrams show **(A)** the peak systolic velocity (PSV) and **(B)** the end-diastolic velocity (EDV) in the central retinal arteries in patients with severe (S) and mild (M) obstructive sleep apnea syndrome and in control subjects (C).

lower among patients with OSAS than among control subjects ($p > 0.05$) (Figures 7 and 8).

We investigated the relationship between the mean O_2 saturation values in patients with OSAS and the blood flow velocities and RI. Statistically significant correlations were found for the PSVs and EDVs in the LPCAs ($r = -0.356$, $p = 0.045$ and $r = -0.378$, $p = 0.004$, respectively) and in the MPCAs ($r = -0.611$, $p = 0.001$ and $r = -0.640$, $p = 0.001$, respectively), whereas no significant correlation was found for any of these parameters in the OAs or the CRAs.

DISCUSSION

OSAS is now recognized as an important risk factor for cardiovascular and neurovascular diseases.[12] Even seemingly healthy patients with OSAS who have no overt vascular disease have subtle but noteworthy abnormalities in vascular regulation at several levels, including the neural, humoral, and endothelial levels. Statistically significantly higher diastolic blood pressures, both at night and during the day, were observed in the patients with OSAS, compared with the control subjects.

During sleep, repetitive episodes of airway occlusion, with consequent hypoxemia, hypercapnia, and dramatic changes in intrathoracic pressure, elicit a wide variety of autonomic, hemodynamic, humoral, and neuroendocrine responses.[13] Compared with wakefulness, sleeping is associated with a reduction in minute ventilation, breath volume, and the ventilatory responses to hypoxia and hypercapnia, resulting in a decreased partial pressure of O_2 and an increased partial pressure of CO_2.[14]

The cardiovascular responses to hypoxemia are

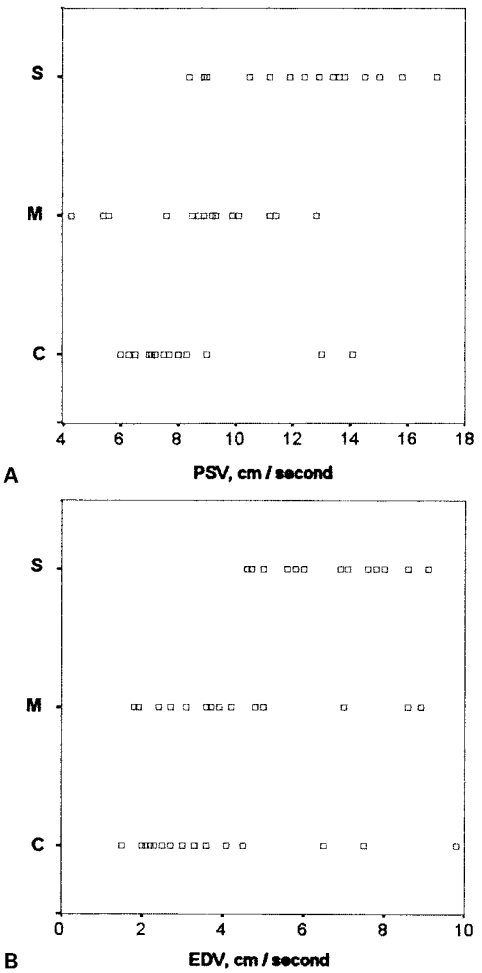

FIGURE 7. Scattergrams show **(A)** the peak systolic velocity (PSV) and **(B)** the end-diastolic velocity (EDV) in the lateral posterior ciliary arteries in patients with severe (S) and mild (M) obstructive sleep apnea syndrome and in control subjects (C).

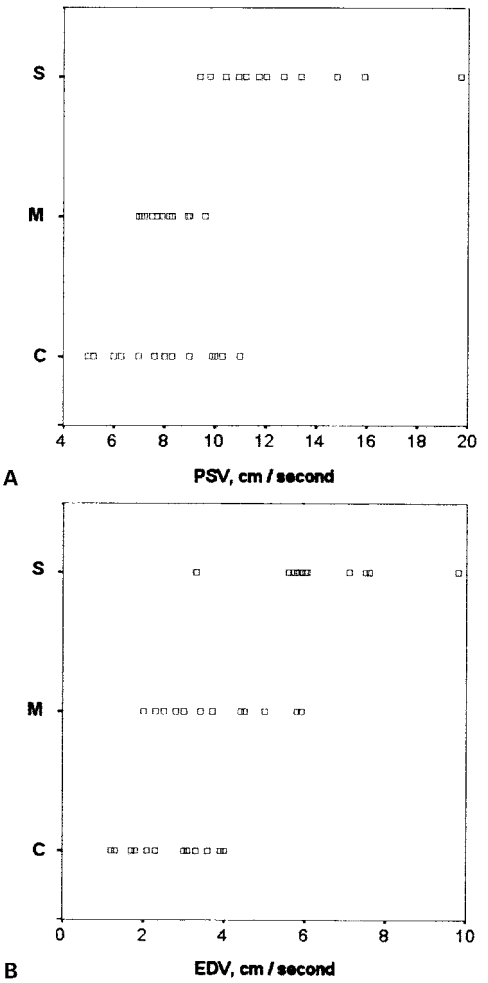

FIGURE 8. Scattergrams show **(A)** the peak systolic velocity (PSV) and **(B)** the end-diastolic velocity (EDV) in the medial posterior ciliary arteries in patients with severe (S) and mild (M) obstructive sleep apnea syndrome and in control subjects (C).

complex, and they differ depending on whether hypoxemia develops during apnea, with hypercapnia, or during hyperventilation, with hypocapnia. In the latter situation, the systemic circulation responds to the hypoxemia with vasodilation and increased heart rate and cardiac output to maintain the blood pressure and O_2 delivery to the peripheral tissues. In contrast, voluntary breath holding or apnea results in peripheral vasoconstriction, bradycardia, and decreased cardiac output, with regional vasodilatation in the cerebral and myocardial circulations to preserve O_2 delivery to these critical organs. Ocular blood flow is part of the cerebral circulation, and our results indicated regional downstream vasodilatation and increased blood flow velocity in the measured vessels as a response to systemic vasoconstriction.[15]

Oxygen and CO_2 concentrations play the greatest roles in modulating cerebrovascular resistance, with CO_2 being the more important factor. For instance, if the brain requires more O_2 than is being supplied, it produces more CO_2, which causes vasodilation and increases the blood flow until enough O_2 has been supplied to reduce the CO_2 concentration. This effect can occur either globally or locally.[16] In our study, blood flow velocities were higher in most of the measured vessels in patients with OSAS than they were in the control subjects; this effect was more pronounced in the PCAs than in the other vessels.

During changes in CO_2 concentrations, the relationship between flow velocity and flow volume within a large cerebral artery is linear, provided that the CO_2 concentration does not directly affect the diameter of the large proximal arterial segments.[17,18] The CO_2 dilatory effect is restricted primarily to the peripheral arterial vascular bed and in particular to the small vessels.[19]

According to our results, when group I and the control group were compared, the PSVs and EDVs in the PCAs were statistically significantly higher in group I, but the blood flow velocities in the OAs and CRAs were not. The PCAs are smaller vessels than the OAs and CRAs are, so the CO_2 level probably affected these small arteries first. As the severity of OSAS increased, the PSVs and EDVs in the OAs and CRAs were also affected ($p < 0.05$). However, the RIs, a measure of vascular resistance, were not increased. In fact, in some vessels, the RIs were even decreased in patients with OSAS compared with those in control subjects, although the differences were not statistically significant. This finding also supports the finding of vasodilatation of these vessels.

To show the effect of hypoxemia, we measured O_2 saturation levels at night. The delay between the saturation measurement and the Doppler examination was not considered important because the effects of OSAS are not limited to the nighttime; they are also apparent during the day.[20] We found statistically significant correlation between the mean O_2 saturation values and the blood flow velocities in the PCAs. The mean O_2 saturation indirectly reflects hypoxemia, and hypoxemia, in turn, induces hypercapnia. We believe that the vasodilatory response to hypercapnia, 1 of the most important consequences of OSAS, is more pronounced in these small vessels than it is in the general cerebral circulation. Because the orbital blood flow is a continuation of the cerebral blood flow, this finding is not surprising.

In summary, OSAS is widely prevalent and is increasingly being linked to cardiac and vascular diseases. CDUS measurements of blood flow parameters in the extraocular orbital vessels may differ significantly between patients with OSAS and those without the syndrome. When interpreting the results of CDUS of the orbital vessels, OSAS should be 1 of the conditions considered to explain such differences in blood flow, if the clinical history points toward a diagnosis of OSAS.

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