Retinal Sensitivity Is Reduced in Patients With Obstructive Sleep Apnea

Blanca Ferrandez,[1] Antonio Ferreras,[1,2] Pilar Calvo,[1] Beatriz Abadia,[1] Paolo Fogagnolo,[3] Yaowu Wang,[4] Jose M. Marin,[5] and Michele Iester[6]

[1]Department of Ophthalmology, Miguel Servet University Hospital, Aragon Health Sciences Institute, Zaragoza, Spain
[2]University of Zaragoza, Spain
[3]G.B. Bietti Foundation-Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Rome, Italy
[4]Faculty of Medicine, University of Toronto, Canada
[5]Department of Pneumology, Miguel Servet University Hospital, Zaragoza, Spain
[6]University of Genoa, Genoa, Italy

Correspondence: Antonio Ferreras, Department of Ophthalmology, Miguel Servet University Hospital, Isabel la Catolica 1-3, 50009 Zaragoza, Spain;
aferreras@msn.com.

PURPOSE. To evaluate the outcomes of standard automated perimetry (SAP) in patients with obstructive sleep apnea (OSA).

METHODS. Eighty OSA patients and 111 age-matched controls were consecutively and prospectively enrolled. One eye per subject was randomly selected. All participants underwent at least one reliable SAP (24-2 SITA Standard algorithm). The peripapillary retinal nerve fiber layer thickness (RNFL) was measured with spectral-domain optical coherence tomography (OCT). Patients with OSA were classified into three groups according to the apnea/hypopnea index: mild, moderate, or severe OSA. Parameters of SAP and OCT were compared between healthy controls and OSA patients. Correlation of apnea/hypopnea index with OCT and SAP measurements were calculated.

RESULTS. Mean age, best-corrected visual acuity, and central corneal thickness were similar between groups. Intraocular pressure, however, was lower in the OSA group. Mean deviation of SAP was -0.23 ± 0.8 dB in the control group and -1.74 ± 2.8 dB in the OSA group ($P < 0.001$). Thickness of RNFL measured with OCT did not differ significantly between groups. Patients with OSA showed reduced sensitivity at most points tested by white-on-white perimetry compared with healthy individuals. The threshold values were more depressed in the peripheral visual field. The apnea/hypopnea index was related to the SAP indices: Pearson correlations were -0.432 with mean deviation, 0.467 with pattern standard deviation, and -0.416 with the visual field index ($P < 0.001$).

CONCLUSIONS. Patients with OSA exhibited reduced retinal sensitivity measured with SAP compared with healthy controls.

Keywords: obstructive sleep apnea, visual field, optical coherence tomography, retinal nerve fiber layer, optic disc

Obstructive sleep apnea (OSA) syndrome is a disorder characterized by recurrent partial (hypopnea) or complete (apnea) cessation of breathing during sleep. When the apnea/hypopnea index (AHI) is at least five events per hour, OSA is considered a clinical entity. Obstructive sleep apnea has a reported prevalence of more than 20% in the general population[1,2] and is associated with cardiovascular, neurologic, and endocrine disease.[3–10] Sympathetic activation, oxidative stress, and systemic inflammation are the main intermediary mechanisms associated with sleep apnea and intermittent hypoxia.[11]

Retinal ganglion cells provide a peripheral but accessible window to central nervous system neurons that could be subject to neuronal damage in association with OSA. Hypoxia and oxidative stress are risk factors for neuronal death in retinal diseases such as diabetic retinopathy and glaucoma.[12,13] This neuronal injury may result in thinning of the retinal nerve fiber layer (RNFL) or reduced visual field (VF) sensitivity.

Noninvasive imaging technologies, such as spectral domain optical coherence tomography (OCT), provide quantitative and reproducible measurements for assessing RNFL thickness. Numerous studies have confirmed the ability of OCT to detect and monitor glaucoma,[14–19] as well as to diagnose and follow-up other disorders that affect the optic nerve head (ONH), such as Parkinson disease, multiple sclerosis, and Alzheimer disease.[20–25]

The purpose of the present study was to compare the VF and OCT parameters between healthy individuals and OSA patients.

MATERIALS AND METHODS

The study design adhered to the tenets of the Declaration of Helsinki and was approved by the Clinical Research Ethics Committee of Aragon. Healthy eyes were recruited from the hospital staff or relatives, and patients referred for refraction

TABLE 1. Clinical Characteristics of the Study Population

| | Control | | OSA | | |
	Mean	SD	Mean	SD	P*
Age, y	50.78	9.46	48.83	11.52	0.20
BCVA, logMAR	0.04	0.05	0.02	0.05	0.02
Pachymetry, μm	551.66	35.60	560.01	30.12	0.10
IOP, mm Hg	17.09	2.46	13.99	2.60	**<0.001**
MD SAP, dB	−0.23	0.82	−1.74	2.77	**<0.001**
PSD SAP	1.42	0.23	1.98	1.05	**<0.001**
VFI SAP	99.52	0.70	97.51	4.83	**<0.001**
SAP test duration, s	319.90	39.31	331.40	45.52	0.06
Fixation losses SAP, %	3.79	3.38	4.23	4.17	0.42
False positive rate SAP, %	1.07	1.25	1.05	0.98	0.90
False negative rate SAP, %	0.61	0.98	0.72	0.95	0.44
Systolic pressure, mm Hg	118.98	12.32	124.11	14.76	0.01
Diastolic pressure, mm Hg	75.83	8.82	78.74	9.78	0.03
BMI, kg/m^2	24.25	4.78	27.82	7.21	**<0.001**
n	111		80		

* Student's *t*-test. Significant differences ($P \leq 0.001$) are highlighted in bold font.

that underwent routine examination without abnormal ocular findings, obesity, or history of symptoms related to OSA (sleepiness, fatigue, snoring, adenoid facies, etc.). The group with OSA was selected from among patients at the Respiratory Unit of the Miguel Servet University Hospital in Zaragoza, Spain. The group with OSA had no significant ophthalmic disease and was not followed more frequently than the healthy group. All individuals who met the inclusion criteria and provided written informed consent were consecutively and prospectively enrolled from January 2011 to December 2012.

All patients with OSA underwent an overnight sleep study in the hospital for evaluation and diagnosis of OSA syndrome. The diagnosis of OSA was based on a polysomnographic evaluation comprising electroencephalography, electromyography, electrocardiography, respiratory movements, and pulse oximetry measurements. These tests were performed over a minimum of 6 hours in the electrophysiology department of our hospital. Dual respiratory inductance plethysmography belt signals (thorax and abdomen) were used for scoring apnea and hypopnea. Sleep and respiratory events in each patient were recorded according to standard criteria.[26] An apnea event was defined as a decrease in the peak signal excursion ≥90% for at least 10 seconds. A hypopnea event was defined as a decrease in the peak signal excursion ≥ 30% (and <90%) from the pre-event baseline for at least 10 seconds, and ≥3% oxygen desaturation from the pre-event baseline, or an event associated with arousal. Individuals with an AHI of at least five events/h were considered to have OSA. Severity of OSA was classified according to the AHI as follows: mild OSA when the AHI was between 5 and 14 events/h, moderate OSA when the AHI ranged from 15 to 19 events/h, and severe OSA when the AHI was higher than 19 events/h.

Inclusion criteria were best-corrected visual acuity of 20/40 or better, refractive error within ± 5.00 diopters (D) equivalent sphere, and ±2 D astigmatism; transparent ocular media (nuclear color and opalescence, cortical or posterior subcapsular lens opacity < 1) according to the Lens Opacities Classification System III system[27]; and open anterior chamber angle. Exclusion criteria were previous intraocular surgery, diabetes, history of any ocular or neurologic disease, and any treatment with oxygen therapy or noninvasive mechanical ventilation. Patients with glaucomatous standard automated perimetry (SAP) defects, glaucomatous optic disc morphology,

or intraocular pressure (IOP) > 20 mm Hg were also excluded from the study. A total of 80 patients with OSA and 111 healthy subjects were included in the statistical analysis.

Study Protocol

All examinations were performed within 6 weeks of the subject's date of enrollment into the study. Participants underwent a comprehensive ophthalmologic examination: clinical history, best corrected visual acuity (BCVA), slit-lamp biomicroscopy of the anterior segment, gonioscopy, Goldmann applanation tonometry, central corneal ultrasonic pachymetry (OcuScan RxP; Alcon Laboratories, Inc., Irvine, CA, USA), and ophthalmoscopy of the posterior segment.

Two SAPs were performed using a Humphrey field analyzer (model 750i; Zeiss Humphrey Systems, Dublin, CA, USA), with the 24-2 SITA Standard strategy. Subjects completed the perimetry tests before undergoing any clinical examination or structural test, and each test was performed at least 3 days apart to avoid a fatigue effect. All participants had a reliable SAP (false positives and negatives < 15%, fixation losses < 20%) in the second attempt. The data from the last perimetry test were used for the statistical analysis to minimize the learning effect.

Peripapillary RNFL thickness was measured using the Optic Disc Cube 200 × 200 acquisition protocol of the OCT device (Cirrus HD, software version 6.2; Carl Zeiss Meditec, Dublin, CA, USA). This protocol scanned a 6 × 6 mm^2 area centered on the optic disc. A 3.46-mm diameter circular scan, containing 256 A-scans, was automatically targeted around the optic disc to provide the RNFL thicknesses of the four quadrants and at each of the 12 clock-hour positions. Left eyes were converted to a right eye format. All images were obtained by the same experienced technician with a signal/strength ratio greater than 6/10.

Statistical Analysis

Statistical analyses were performed using statistical software (IBM SPSS, version 21.0; IBM Corporation, Somers, NY, USA). When both eyes fulfilled the inclusion criteria, only one eye per subject was randomly selected for the study. All study variables had a normal distribution as verified with the Kolmogorov-Smirnov test (K-S of 1 sample). Demographics, SAP, and OCT parameters were compared between groups with Student's *t*-tests. The Bonferroni correction for multiple comparisons was applied, resulting in a significance level of $P < 0.002$. Pearson correlations were calculated between the AHI and VF indices.

RESULTS

The clinical characteristics of the study sample are detailed in Table 1. A total of 111 healthy controls and 80 OSA patients were included in the statistical analysis. Mean age was 50.78 ± 9.4 years in the control group and 48.8 ± 11.5 years in the OSA group ($P = 0.19$). Central corneal thickness was similar in both groups (551.66 ± 35.6 μm in healthy subjects and 560.01 ± 30.1 μm in OSA patients; $P = 0.09$), but intraocular pressure was significantly lower in the OSA group (17.09 ± 2.5 mm Hg in healthy subjects and 13.99 ± 2.6 mm Hg in OSA patients; $P < 0.001$).

Main SAP indices differed significantly between the groups. Mean deviation (MD) was lower in the OSA group (−0.23 ± 0.8 dB vs. −1.74 ± 2.8 dB; $P < 0.001$), pattern standard deviation (PSD) was higher in the OSA group (1.42 ± 0.2 vs. 1.98 ± 1.1; $P < 0.001$), and the visual field index (VFI) was lower in the

TABLE 2. Differences in Sensitivity Threshold Values (dB) of Tested VF Points in SAP Between Control and OSA Groups

	Control Group		OSA Group		
	Mean	SD	Mean	SD	P*
SAP 1	27.24	2.22	25.59	3.79	<0.001
SAP 2	28.06	2.16	26.04	4.48	<0.001
SAP 3	27.33	1.98	25.11	4.83	<0.001
SAP 4	27.18	2.63	24.78	5.34	<0.001
SAP 5	28.62	2.24	27.04	3.40	<0.001
SAP 6	29.70	1.59	28.26	2.76	<0.001
SAP 7	29.71	1.44	28.16	3.09	<0.001
SAP 8	29.27	1.61	26.99	4.72	<0.001
SAP 9	29.39	2.01	28.08	3.17	0.001
SAP 10	29.13	2.27	26.75	5.33	<0.001
SAP 11	28.46	2.26	26.41	4.40	<0.001
SAP 12	30.43	1.42	29.18	2.60	<0.001
SAP 13	31.61	1.27	29.93	4.54	<0.001
SAP 14	31.51	1.40	30.51	2.89	0.002
SAP 15	31.05	1.37	29.60	3.06	<0.001
SAP 16	30.32	1.65	28.85	3.31	<0.001
SAP 17	30.20	1.92	28.68	3.81	<0.001
SAP 18	28.68	2.22	26.69	4.93	<0.001
SAP 19	26.86	2.61	25.06	5.16	0.002
SAP 20	29.00	1.68	27.53	3.73	<0.001
SAP 21	31.30	1.35	29.90	3.15	<0.001
SAP 22	32.38	1.14	30.74	4.00	<0.001
SAP 23	32.68	1.24	31.38	3.34	<0.001
SAP 24	32.42	1.35	30.90	3.43	<0.001
SAP 25	31.41	1.52	30.09	3.44	<0.001
SAP 26	29.84	2.03	27.64	4.72	<0.001
SAP 27	26.89	2.66	24.81	5.71	0.001
SAP 28	29.38	1.68	27.61	4.04	<0.001
SAP 29	31.60	1.47	30.36	2.84	<0.001
SAP 30	32.50	1.15	31.23	3.05	0.001
SAP 31	32.66	1.27	31.87	2.39	0.004
SAP 32	32.66	1.39	31.66	2.66	0.001
SAP 33	31.76	1.49	30.41	2.76	<0.001
SAP 34	30.25	2.04	28.64	3.77	<0.001
SAP 35	28.82	1.96	27.33	3.65	<0.001
SAP 36	30.75	1.44	29.70	3.23	0.003
SAP 37	32.22	1.34	31.26	2.87	0.002
SAP 38	31.91	1.33	30.91	2.52	<0.001
SAP 39	32.07	1.20	31.00	2.77	<0.001
SAP 40	31.61	1.79	30.68	3.06	0.009
SAP 41	30.68	1.72	29.83	3.33	0.02
SAP 42	29.68	2.09	28.13	4.12	0.001
SAP 43	30.05	1.97	28.49	3.80	<0.001
SAP 44	30.62	1.43	29.68	2.84	0.003
SAP 45	30.95	1.57	29.54	3.37	<0.001
SAP 46	30.77	1.61	29.53	3.15	<0.001
SAP 47	30.93	1.49	29.85	3.45	0.004
SAP 48	30.92	1.69	28.85	4.39	<0.001
SAP 49	28.92	2.20	27.16	4.25	<0.001
SAP 50	29.16	1.95	27.31	5.16	0.001
SAP 51	29.93	1.88	28.14	4.20	<0.001
SAP 52	30.00	2.05	28.10	4.90	<0.001

* Student's *t*-test. Significant differences ($P \leq 0.001$) are highlighted in bold font.

OSA patients (99.52 ± 0.7 vs. 97.51 ± 1.1; $P < 0.001$). Reliability indices of SAP and test time were similar between groups. Systolic and diastolic blood pressure did not differ between groups, but body mass index (BMI) was higher in the OSA group.

Table 2 shows the VF threshold values at each of the 52 VF points tested by the grid of the 24-2 SITA Standard strategy (Fig. 1). Most of these points were depressed in OSA patients compared with healthy controls (Figs. 2, 3). The measurements of OCT revealed that the two groups were not different in peripapillary RNFL thickness at each of the 12 clock-hour positions, in the four quadrants, or in the average thickness (Table 3). Moreover, OSA patients grade 2 (moderate) and grade 3 (severe) combined or grade 3 alone had RNFL thicknesses similar to those in the control group (Table 4).

The VF indices of the SAP correlated moderately with the AHI: the Pearson correlation coefficients between AHI and MD, PSD, and VFI were −0.432, 0.467, and −0.416, respectively ($P < 0.001$).

DISCUSSION

The pathogenesis of neurodegeneration in OSA syndrome is unclear. Intermittent upper airway obstruction in OSA patients during sleep can increase carbon dioxide levels while decreasing oxygen levels, thereby reducing the oxygen saturation during a variable period of sleep. These alterations induce oxidative stress, and lead to increased vascular resistance and endothelial dysfunction. Hypoxia and hypercapnia episodes cause autonomic, hemodynamic, and neurorendocrine changes.[28,29] Obstructive sleep apnea syndrome is associated with neurovascular disease, cardiovascular disease, arterial hypertension, pulmonary hypertension, arrhythmia, and other systemic disorders.[30]

The oxygenation-reoxygenation process in OSA syndrome can compromise normal vascularization and perfusion of the ONH similar to glaucoma, based on the vascular theory proposed by Anderson.[31] This theory suggests that the damage to the ONH in glaucoma is caused, at least in part, by persistent or temporary ischemia. Failure of the blood supply from the posterior ciliary arteries to the short posterior ciliary arteries could lead to nonperfusion of the anterior part of the ONH and neuronal ischemia. The affected ONH microcirculation would interfere with axonal nutrition and axoplasmic flow. Calvo et al.[32] reported that abnormal retrobulbar blood flow velocities measured by color Doppler ultrasound may be a risk factor for conversion to glaucoma. On the other hand, Lin et al.[33] recently suggested that OSA is associated with an increased risk of a subsequent diagnosis of open-angle glaucoma during a 5-year follow-up period after the diagnosis of OSA.

We hypothesized that these vascular phenomena could affect VF and ONH morphology in OSA patients and that such changes could be measured by SAP and OCT, respectively. Retinal sensitivity was reduced in OSA patients compared with the control group, although we detected no significant differences in the RNFL thickness measurements. The topographic correspondence between VF regions and RNFL thickness in humans is moderate in glaucoma patients due to the high variability of normal human ONH morphology and the intertest variability of SAP.[34–36] The agreement between the SAP and OCT results in OSA patients is expected to be similar to that in healthy individuals.[34–38]

Previous studies using different imaging techniques to measure RNFL thickness in OSA patients described contradictory results.[39–44] Some studies reported decreased RNFL thickness in OSA patients, in contrast to the present results,[39,40,42] whereas others found no correlation between RNFL thickness and AHI.[42] Still others observed a significant decrease in the RNFL thickness in patients with severe OSA.[44] All of these findings, however, were based on different imaging technologies than used in the present study. We measured the RNFL thickness with a spectral-domain OCT (Cirrus), whereas
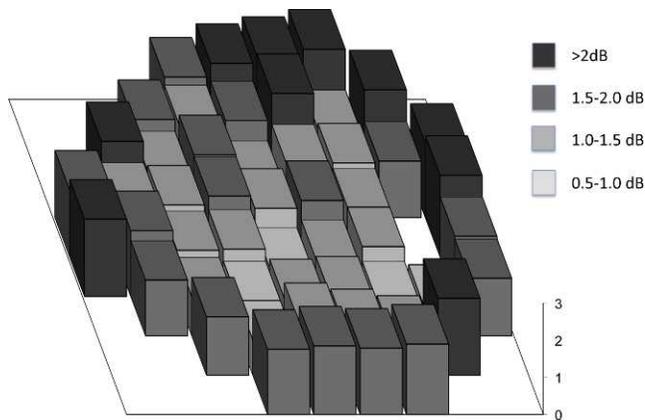
OD   OS

FIGURE 1. Grid of visual field points tested by the 24-2 SITA Standard algorithm of SAP. These locations were numbered as shown based on the side of the eye.

time-domain OCT[40,41,43] or scanning laser polarimetry[39,42] were used in the previous studies.

If outcomes of VF or OCT differed between groups, these parameters could potentially be used as biomarkers for neuronal damage in OSA patients. Although we detected no changes in the peripapillary RNFL thickness measured by OCT, there were differences in the retinal sensitivity and VF indices. Patients with OSA exhibited diffuse decreased retinal sensitivity without localized VF defects typical of other pathologies such as glaucoma. This generalized reduction of the threshold values, particularly in the peripheral VF, could be explained by diffuse vascular damage to the retinal ganglion cells, causing axonal loss and VF depression. This injury to the retinal ganglion cells may lead to dysfunction of the visual pathway that could be identified by a functional test, such as SAP, while the anatomy is relatively unaffected and therefore undetected by a structural test, such as OCT. Moreover, OSA patients (especially those with more advanced disease) may have experienced at least one apnea/hypopnea event during the VF examination, which could decrease attention and impair testing ability, resulting in reduced retinal sensitivity, even

when the SAP reliability criteria were maintained within normal limits.

Quantitative variables MD, PSD, and VFI could be used to monitor the progression of the disease, treatment with oxygen therapy, or noninvasive mechanical ventilation.[45] The main criterion to begin treatment with continuous positive airway pressure (CPAP) is a graduated severity of OSA syndrome (moderate and severe). Thus, any changes detected in the VF could help to support the decision to begin CPAP in OSA patients.

Huseyinoglu et al.[44] also reported worse MD and PSD (Octopus perimetry) in OSA subgroups compared to a control group. Lin et al.,[40] however, found no differences in the MD of SAP (30-2 strategy) between OSA patients and healthy controls. Different study designs and populations, inclusion and exclusion criteria, tests performed, and the level of OSA damage make it difficult to compare the results among several studies.

A limitation of the present study was that the control group did not undergo an overnight sleep study and we assumed that they had no apnea/hypopnea events per hour. Ideally, they

FIGURE 2. Mean SAP sensitivity threshold values (dB) in the control group (*left graph*) and the OSA group (*right graph*) for a right eye. The group with OSA had reduced sensitivity at most points tested by white-on-white perimetry compared with the control group, mainly in the peripheral visual field.

FIGURE 3. Differences in mean SAP sensitivity threshold values (dB) of the right eye between the control group and the OSA group. The *grayscale* represents the mean difference in decibels.

should have also undergone a polysomnographic evaluation for one night, but this evaluation is costly and we could not justify its inclusion in the study protocol because the criteria used to select the control group minimized the possibility of including an OSA patient by chance (exclusion criteria for the control group: obesity and symptoms related to OSA). Nevertheless, if all controls were chosen according to a strictly normal sleep study, we would have selected a "super-healthy" control group. In addition to the effect size (difference between groups), these factors would probably lead to a larger retinal sensitivity reduction than the one observed.

In the present study, OCT did not demonstrate neurodegenerative changes in OSA patients, but retinal sensitivity was significantly reduced in OSA patients compared with healthy subjects. Given the issues related with subjective perimetry, studies employing objective functional testing (e.g., electro-

TABLE 3. Differences in Peripapillary RNFL Thickness Measured by OCT Between the Control and OSA Groups

	Control Group				OSA Patients				
	Min	Max	Mean	SD	Min	Max	Mean	SD	P*
H1	58	164	108.86	21.62	30	163	110.24	22.52	0.67
H2	52	139	92.82	18.21	61	160	92.29	19.04	0.84
H3	40	83	62.22	9.89	45	89	60.30	8.82	0.16
H4	41	115	70.05	13.87	30	112	69.45	14.38	0.77
H5	61	162	107.18	21.74	77	210	112.58	27.07	0.13
H6	78	211	144.75	25.70	71	213	147.10	25.19	0.53
H7	81	207	140.91	22.84	92	181	135.13	20.15	0.07
H8	39	119	67.19	13.19	41	113	65.86	12.83	0.49
H9	34	73	50.40	7.77	36	88	52.74	7.72	0.04
H10	55	144	77.88	13.85	43	100	75.21	11.35	0.16
H11	90	184	133.41	17.63	10	709	133.30	69.77	0.99
H12	65	195	121.76	26.97	39	183	127.49	27.71	0.15
Superior	93	169	121.39	15.65	55	155	120.93	17.16	0.86
Inferior	42	165	130.04	17.13	96	171	131.11	15.68	0.66
Nasal	38	110	74.90	11.61	52	148	76.06	15.38	0.55
Temporal	47	104	65.12	9.55	30	88	64.49	8.70	0.64
Average thickness	80	120	98.04	8.21	61	120	97.15	9.71	0.50
n			111				80		

H, RNFL thickness at every clock-hour position for a right eye; Min, minimum; Max, maximum.
* Student's *t*-test.

TABLE 4. Analysis of Peripapillary RNFL Thickness Measurements by OCT in Healthy Controls Versus OSA Grade 2 and 3 Patients

	Control Group		Grades 2 And 3 OSA Patients			Grade 3 OSA Patients		
	Mean	SD	Mean	SD	P*	Mean	SD	P†
H1	108.86	21.62	111.16	20.67	0.48	110.52	20.32	0.64
H2	92.82	18.21	92.35	19.09	0.87	91.04	18.65	0.56
H3	62.22	9.89	59.87	8.87	0.22	59.71	8.13	0.22
H4	70.05	13.87	70.44	14.71	0.87	70.90	13.82	0.72
H5	107.18	21.74	109.57	24.45	0.50	104.75	21.69	0.51
H6	144.75	25.70	144.10	24.11	0.87	141.40	23.57	0.43
H7	140.91	22.84	136.57	20.12	0.20	136.77	18.84	0.26
H8	67.19	13.19	66.69	12.95	0.81	68.10	12.12	0.68
H9	50.40	7.77	53.09	8.18	0.03	53.75	8.50	0.01
H10	77.88	13.85	75.26	11.93	0.20	75.44	11.37	0.27
H11	133.41	17.63	135.34	75.16	0.80	136.25	85.53	0.74
H12	121.76	26.97	128.68	27.16	0.10	125.96	27.09	0.36
Superior	121.39	15.65	121.87	16.43	0.85	120.38	16.80	0.71
Inferior	130.04	17.13	129.51	15.51	0.84	127.52	14.74	0.36
Nasal	74.90	11.61	76.51	16.06	0.44	73.52	11.58	0.48
Temporal	65.12	9.55	65.41	8.06	0.83	66.23	7.87	0.46
Average thickness	98.04	8.21	97.03	10.20	0.47	96.90	9.09	0.43
n	111		68			52		

* Student's *t*-test between grade 2 and 3 OSA patients and the control group.
† Student's *t*-test between grade 3 OSA patients and the control group.

physiology test) are warranted, as well as further prospective longitudinal studies to clarify the role of VF and OCT as a neurodegenerative marker in OSA syndrome.

Clinicians should be aware that OSA patients may have nonglaucomatous VF defects, which should be differentiated from true glaucomatous optic neuropathy.

References

1. Duran J, Esnaola S, Rubio R, Iztueta A. Obstructive sleep apnea-hypopnea and related clinical features in a population-based sample of subjects aged 30 to 70 yr. *Am J Respir Crit Care Med*. 2001;163:685–689.
2. Young T, Peppard P, Palta M, et al. Population-based study of sleep-disordered breathing as a risk factor for hypertension. *Arch Intern Med*. 1997;157:1746–1752.
3. Peker Y, Kraiczi H, Hedner J, et al. An independent association between obstructive sleep apnoea and coronary artery disease. *Eur Respir J*. 1999;14:179–184.
4. Tsai JC. Neurological and neurobehavioral sequelae of obstructive sleep apnea. *NeuroRehabilitation*. 2010;26:85–94.
5. Zhang X, Ma L, Li S, Wang Y, Wang L. A functional MRI evaluation of frontal dysfunction in patients with severe obstructive sleep apnea. *Sleep Med*. 2011;12:335–340.

Investigative Ophthalmology & Visual Science

6. Bajpai S, Im KB, Dyken ME, Sodhi SK, Fiedorowicz JG. Obstructive sleep apnea and risk for late-life depression. *Ann Clin Psychiatry*. 2014;26:E1–E8.

7. Aurora RN, Punjabi NM. Obstructive sleep apnoea and type 2 diabetes mellitus: a bidirectional association. *Lancet Respir Med*. 2013;1:329–338.

8. Nannapaneni S, Ramar K, Surani S. Effect of obstructive sleep apnea on type 2 diabetes mellitus: a comprehensive literature review. *World J Diabetes*. 2013;4:238–244.

9. Morgenstern M, Wang J, Beatty N, Batemarco T, Sica AL, Greenberg H. Obstructive sleep apnea: an unexpected cause of insulin resistance and diabetes. *Endocrinol Metab Clin North Am*. 2014;43:187–204.

10. Surani SR. Diabetes, sleep apnea, obesity and cardiovascular disease: Why not address them together? *World J Diabetes*. 2014;5:381–384.

11. Levy P, Tamisier R, Arnaud C, et al. Sleep deprivation, sleep apnea and cardiovascular diseases. *Front Biosci (Elite Ed)*. 2012;4:2007–2021.

12. Gozal D, Kheirandish-Gozal L. Cardiovascular morbidity in obstructive sleep apnea: oxidative stress, inflammation, and much more. *Am J Respir Crit Care Med*. 2008;177:369–375.

13. Stoohs R, Guilleminault C. Cardiovascular changes associated with obstructive sleep apnea syndrome. *J Appl Physiol*. 1992;72:583–589.

14. Sihota R, Sony P, Gupta V, et al. Diagnostic capability of optical coherence tomography in evaluating the degree of glaucomatous retinal nerve fiber damage. *Invest Ophthalmol Vis Sci*. 2006;47:2006–2010.

15. Ferreras A, Pablo LE, Pajarín AB, Larrosa J, Polo V, Honrubia FM. Logistic regression analysis for early glaucoma diagnosis using optical coherence tomography. *Archives Ophthalmol*. 2008;126:465–470.

16. Mwanza JC, Oakley JD, Budenz DL, Anderson DR; Cirrus Optical Coherence Tomography Normative Database Study Group. Ability of cirrus HD-OCT optic nerve head parameters to discriminate normal from glaucomatous eyes. *Ophthalmology*. 2011;118:241–248.

17. Mwanza JC, Oakley JD, Budenz DL, Chang RT, Knight OJ, Feuer WJ. Macular ganglion cell-inner plexiform layer: automated detection and thickness reproducibility with spectral domain-optical coherence tomography in glaucoma. *Invest Ophthalmol Vis Sci*. 2011;52:8323–8329.

18. Hwang YH, Kim YY. Glaucoma diagnostic ability of quadrant and clock-hour neuroretinal rim assessment using cirrus HD optical coherence tomography. *Invest Ophthalmol Vis Sci*. 2012;53:2226–2234.

19. Hwang YH, Kim YY, Kim HK, Sohn YH. Ability of Cirrus high-definition spectral-domain optical coherence tomography clock-hour, deviation, and thickness maps in detecting photographic retinal nerve fiber layer abnormalities. *Ophthalmology*. 2013;120:1380–1387.

20. Tian T, Zhu XH, Liu YH. Potential role of retina as a biomarker for progression of Parkinson's disease. *Int J Ophthalmol*. 2011;4:433–438.

21. Adam CR, Shrier E, Ding Y, Glazman S, Bodis-Wollner I. Correlation of inner retinal thickness evaluated by spectral-domain optical coherence tomography and contrast sensitivity in Parkinson disease. *J Neuroophthalmol*. 2013;33:137–142.

22. Fjeldstad AS, Carlson NG, Rose JW. Optical coherence tomography as a biomarker in multiple sclerosis. *Expert Opin Med Diagn*. 2012;6:593–604.

23. Fernandes DB, Raza AS, Nogueira RG, et al. Evaluation of inner retinal layers in patients with multiple sclerosis or neuromyelitis optica using optical coherence tomography. *Ophthalmology*. 2013;120:387–394.

24. Kesler A, Vakhapova V, Korczyn AD, Naftaliev E, Neudorfer M. Retinal thickness in patients with mild cognitive impairment and Alzheimer's disease. *Clin Neurol Neurosurg*. 2011;113:523–526.

25. Marziani E, Pomati S, Ramolfo P, et al. Evaluation of retinal nerve fiber layer and ganglion cell layer thickness in Alzheimer's disease using spectral-domain optical coherence tomography. *Invest Ophthalmol Vis Sci*. 2013;54:5953–5958.

26. Berry RB, Budhiraja R, Gottlieb DJ, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. *J Clin Sleep Med*. 2012;8:597–619.

27. Chylack LT Jr, Wolfe JK, Singer DM, et al. The Lens Opacities Classification System III. The Longitudinal Study of Cataract Study Group. *Arch Ophthalmol*. 1993;111:831–836.

28. Calvo P, Ferrández B, Ferreras A, Marín JM. Retinal nerve fiber layer thickness alterations in patients with obstructive sleep apnea. *Arch Soc Esp Oftalmol*. 2012;87:1–2.

29. Karaca Z, Ismailogullari S, Korkmaz S, et al. Obstructive sleep apnoea syndrome is associated with relative hypocortisolemia and decreased hypothalamo-pituitary-adrenal axis response to 1 and 250µg ACTH and glucagon stimulation tests. *Sleep Med*. 2013;14:160–164.

30. Shahar E, Whitney CW, Redline S, et al. Sleep-disordered breathing and cardiovascular disease: crosssectional results of the Sleep Heart Health Study. *Am J Respir Crit Care Med*. 2001;163:19–25.

31. Anderson DR. Glaucoma, capillaries and pericytes. 1. Blood flow regulation. *Ophthalmologica*. 1996;210:257–262.

32. Calvo P, Ferreras A, Polo V, et al. Predictive value of retrobulbar blood flow velocities in glaucoma suspects. *Invest Ophthalmol Vis Sci*. 2012;53:3875–3884.

33. Lin CC, Hu CC, Ho JD, Chiu HW, Lin HC. Obstructive sleep apnea and increased risk of glaucoma: a population-based matched-cohort study. *Ophthalmology*. 2013;8:1559–1564.

34. Garway-Heath DF, Poinoosawmy D, Fitzke FW, Hitchings RA. Mapping the visual field to the optic disc in normal tension glaucoma eyes. *Ophthalmology*. 2000;107:1809–1815.

35. Ferreras A, Pablo LE, Garway-Heath DF, Fogagnolo P, García-Feijoo J. Mapping standard automated perimetry to the peripapillary retinal nerve fiber layer in glaucoma. *Invest Ophthalmol Vis Sci*. 2008;49:3018–3025.

36. Lamparter J, Russell RA, Zhu H, et al. The influence of intersubject variability in ocular anatomical variables on the mapping of retinal locations to the retinal nerve fiber layer and optic nerve head. *Invest Ophthalmol Vis Sci*. 2013;54:6074–6082.

37. Lopez-Pena MJ, Ferreras A, Polo V, et al. Relationship between standard automated perimetry and HRT, OCT and GDx in normal, ocular hypertensive and glaucomatous subjects. *Arch Soc Esp Oftalmol*. 2007;82:197–208.

38. Lopez-Pena MJ, Ferreras A, Larrosa JM, et al. Relationship between standard automated perimetry and retinal nerve fiber layer parameters obtained with optical coherence tomography. *J Glaucoma*. 2011;20:422–432.

39. Kargi SH, Altin R, Koksal M, et al. Retinal nerve fiber layer measurements are reduced in patients with obstructive sleep apnea syndrome. *Eye*. 2005;19:575–579.

40. Lin PW, Friedman M, Lin HC, Chang HW, Pulver TM, Chin CH. Decreased retinal nerve fiber layer thickness in patients with obstructive sleep apnea/hypopnea syndrome. *Graefes Arch Clin Exp Ophthalmol*. 2011;249:585–593.

41. Casas P, Ascaso FJ, Vicente E, Tejero-Garcés G, Adiego MI, Cristóbal JA. Retinal and optic nerve evaluation by optical coherence tomography in adults with obstructive sleep apnea-

hypopnea syndrome (OSAHS). *Graefes Arch Clin Exp Ophthalmol*. 2013;251:1625–1634.

42. Moghimi S, Ahmadraji A, Sotoodeh H, et al. Retinal nerve fiber thickness is reduced in sleep apnea syndrome. *Sleep Med*. 2013;14:53–57.

43. Sagiv O, Fishelson-Arev T, Buckman G, et al. Retinal nerve fiber layer thickness measurements by optical coherence tomography in patients with sleep apnea syndrome. *Clin Experiment Ophthalmol*. 2014;42:132–138.

44. Huseyinoglu N, Ekinci M, Ozben S, Buyukuysal C, Kale MY, Sanivar HS. Optic disc and retinal nerve fiber layer parameters as indicators of neurodegenerative brain changes in patients with obstructive sleep apnea syndrome. *Sleep Breath*. 2014; 18:95–102.

45. Benbir G, Karadeniz D. A pilot study of the effects of non-invasive mechanical ventilation on the prognosis of ischemic cerebrovascular events in patients with obstructive sleep apnea syndrome. *Neurol Sci*. 2012;33:811–818.

Investigative Ophthalmology & Visual Science