



Parafoveal and optic disc vessel density in patients with obstructive sleep apnea syndrome: an optical coherence tomography angiography study

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Abstract

Aims To compare optic disc perfusion, radial peripapillary capillaries (RPC) and macular vascular density, between normal subjects and subjects with obstructive sleep apnea syndrome (OSAS) using spectral-domain OCT angiography (OCTA).

Methods Sixteen eyes of patients with mild OSAS, 17 eyes with moderate OSAS, 20 eyes with severe OSAS on polygraphy and 28 controls were evaluated with OCTA RT XR Avanti (AngioVue software, Optovue Inc., Fremont, CA). Optic nerve head (ONH), RPC and macular vessel density were measured. Clinical data, visual field parameters, and Spectral Domain OCT evaluation (retinal nerve fiber layer (RNFL) thickness and ganglion cell complex (GCC) thickness) were recorded for all patients.

Results ONH vascular flow ($p = 0,396$), RPC vascular density (automatized data “whole” $p = 0,913$, “peripapillary” $p = 0,539$, and segmented analysis with a topographic grid) and macular vascular density (foveal $p = 0,484$, parafoveal $p = 0,491$) were not significantly different between the four groups. FDT-Matrix™ and Humphrey 24/2 mean deviation were significantly lower in eyes with severe OSAS and were correlated to the apnea-hypopnea index. Retinal nerve fiber layer (RNFL) thickness, Cup/Disc ratio, rim area, and ganglion cell complex (GCC) were not significantly modified.

Conclusions OCTA did not detect reduced ONH, RPC, neither macular blood vessel density in eyes with OSAS. The precise mechanisms that link OSAS with optic nerve pathologies remain unclear: our study was not able to demonstrate a vascular impact by OCTA examination.

Keywords Obstructive sleep apnea syndrome · Optic nerve · OCT angiography · Vascularization; perimetry · FDT-Matrix

Introduction

Obstructive sleep apnea syndrome (OSAS) is a disorder characterized by repetitive complete or partial obstructions of the upper airway during sleep causing nocturnal recurrent oxygen desaturations [1]. Studies have suggested that OSAS was associated with anterior ischemic optic

neuropathy [2], retinal venous occlusion [3], more severe and resistant [4] maculopathy and more frequent and severe retinopathy in diabetic patients with OSAS.

Recently, meta-analysis [5–8] found a significant association between OSAS and glaucoma. Nevertheless, the mechanisms that link OSAS with glaucoma or other optic neuropathies are not established yet.

Blood is driven to the ONH from two major sources: the central retinal artery in superficial layers and the posterior ciliary artery in deeper ones [9]. The inner retinal vascular network is composed of three distinct layers of vessels and capillaries, all originating from the central retinal artery, including the radial peripapillary plexus in the nerve fiber layer, the superficial and the deep vascular plexus.

The purpose of this study was to investigate microcirculation in the ONH, the peripapillary retinal capillaries and macular superficial network changes in patients with OSAS. To the best of our knowledge, there is only one

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other study [10] using OCT angiography (OCTA) to explore a series of OSAS patients.

Material and methods

Patients

This retrospective observational study was conducted at the Quinze-Vingts National Ophthalmology Hospital, Paris, France, from July to November 2016. Sleep investigations were conducted at the Foch Hospital, Suresnes, France, and at the Centre Medical Veille Sommeil, Paris, France. The study adhered to the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of the French Society of Ophthalmology. Informed consent was obtained from all subjects.

Inclusion criteria for patients with OSAS were as follows: age above 18, an apnea-hypopnea index (AHI), calculated as the total number of apneas and hypopneas per hour of sleep, greater than 5 found on a polysomnography level 1 or 3; for all patients, it was their first sleep investigation and no one had a known history of OSAS. Apnea was defined as a cessation of airflow for at least 10 s with effort to breathe. Hypopnea was defined as a minimum of 30% reduction of airflow when compared to the baseline, lasting at least 10 s, and an oxygen desaturation more than 3% or a “micro-arousal” on polysomnography level 1 [11]. OSAS severity was classified as mild for an AHI between 5 and 15, moderate for an AHI greater than 15 and less than 30, and severe for an AHI greater than 30. Oxygen saturation was measured by pulse oxymetry. All sleep studies were scored and read by a one board-certified physician who was unaware of the study. Inclusion criteria for controls were as follows: age above 18, AHI < 5 or a Berlin Questionnaire score equal to zero, and without any known ophthalmologic affection history. Patients with glaucoma, diabetes, history of retinal disease or surgery, ONH congenital affection or poor quality of OCTA images were excluded.

For all patients, the following data were recorded: age, gender, familial history of glaucoma, body mass index (BMI), best corrected visual acuity (BCVA, logMAR), spherical equivalent (SE), IOP using the Goldmann applanation tonometer (mmHg), central corneal thickness (CCT) with an optic pachymeter (Haag-Streit international, Koeniz, Switzerland) (μm), and gonioscopy. The mean retinal nerve fiber layer (RNFL) thickness, mean cup/disc (c/d) ratio, rim area, and mean ganglion cell complex (GCC) thickness were evaluated by the OCT Spectral Domain RT XR Avanti (Optovue Inc., Fremont, CA, USA).

Perimetry

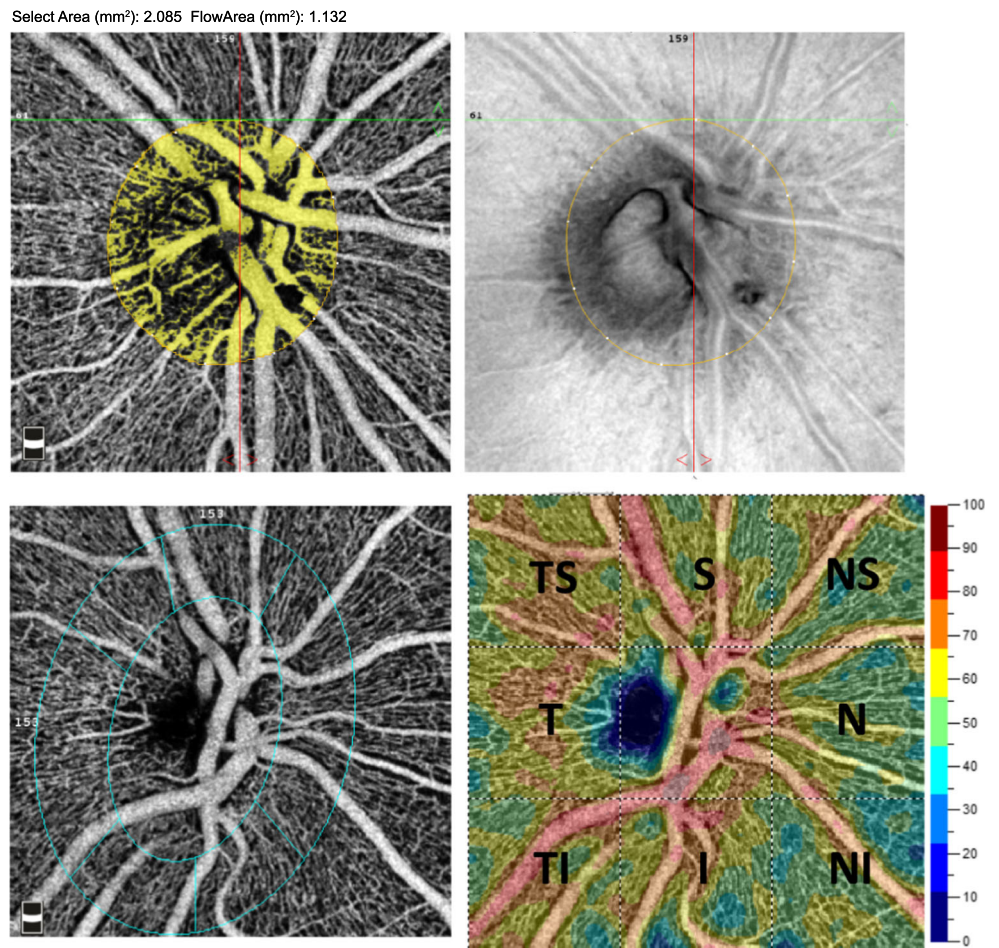
Frequency Doubling Technology (FDT)-perimetry (Humphrey FDT 710 Perimeter Visual Field Analyzer, Carl Zeiss Meditec, Inc., USA) set for a 24-2 threshold test was performed for all patients to collect mean deviation (MD) and pattern standard deviation (PSD). Results were analyzed in accordance to OHTS criteria [12], and standard automated perimetry (SAP) was performed if FDT was abnormal. SAP were performed with a Humphrey Field Analyzer II (Humphrey Field Analyzer II, Carl Zeiss Meditec Inc., USA) set for 24-2.

Optical coherence tomography angiography data acquisition and processing

The OCTA images were acquired using an 840-nm superluminescent diode at an A-scan rate of 70,000 scans per second: the RT XR Avanti scanner (Optovue Inc., Fremont, CA, USA) with the Angiovue software. It detects blood flow in an acquired volume using the split-spectrum amplitude-decorrelation angiography (SSADA) [13]. Each of the acquired optic disc cubes ($3 \times 3 \text{ mm}$) consisted of 304 clusters of 2 repeat B-scans containing 304 A-scans each. SSADA algorithm was employed to improve the signal-to-noise ratio by splitting the spectrum to generate multiple repeat OCT frames from the 2 original repeat OCT frames. En face angiogram images of the retinal circulation were obtained from the maximum flow projections from the analyzed volumes.

The optic disc boundary was determined based on the scanning laser ophthalmoscopy (SLO) images, on the “Angio disc” acquisitions to quantify the vessels densities in the peripapillary retina and optic disc. Vessel density (VD) was defined by the percentage of area occupied by vessels, measured using the intensity-based thresholding feature of the Angiovue software (Optovue). On the “Nerve Head” layer, we manually calculated the VD of the ONH by dividing ONH flow area over the optic disc surface (Fig. 1). On the “RPC” layer, we studied the eight peripapillary regions of the software grill which divides the en face projection in nine 1-mm side squares (Fig. 1). We also noted the automatic variables of the software qualified by “whole”, “peripapillary”, and “inside disc”. In the macular region, we analyzed the superficial vascular layer, extended from 3 μm below the internal limiting membrane to 15 μm below the inner plexiform layer. VD was calculated over two regions of interest: the foveal and parafoveal regions. Poor quality images with a signal strength index (SSI) < 50 or image sets with remaining motion artifacts were excluded from the study analysis.

Fig. 1 Optic nerve head OCT angiography acquisition. Up: vessel density in ONH calculated as flow index/ ONH area. Down: RPC vascular density map. Image is divided in nine equal size squares. TS, temporal superior; S, superior; NS, nasal superior; T, temporal; N, nasal; TI, temporal inferior; I, inferior; NI, nasal inferior



Reproducibility and repeatability

The coefficient of variation (CV) was used to evaluate between-day reproducibility and within-day repeatability. Intra-visit reproducibility was calculated for all subjects with two sets of scans performed in a single visit and CV and interclass correlation coefficient (ICC) were calculated by comparing two measurements obtained by a single examiner. An imaging session was repeated once during the study period. The measurements of VD were performed by two independent examiners.

Statistical analysis

Quantitative data are presented as mean with standard deviation. Qualitative data are given as proportions. Kruskal-Wallis tests were used to compare the data between the four groups (“mild OSAS” group, “moderate OSAS” group, “severe OSAS” group and controls), whereas Mann-Whitney tests were used to compare data between two groups. When *p* was inferior to 0.05, Mann-Whitney tests were performed between the different groups. Linear regression analysis was used to investigate for correlation

for the statistically different variables. A *p* value < 0.05 was considered statistically significant.

Results

Eighty-one eyes were included: 16 in the “mild OSAS” group, 17 in the “moderate OSAS”, 20 in the “severe OSAS” and 28 controls. Six eyes were excluded (1 with retinal detachment history, 1 with optic nerve coloboma and 2 diabetics, and 2 because of poor images quality with amblyopic eye or high myopia). There was no significant difference between the four groups concerning age, ethnic origin, visual acuity, IOP, and CCT (Table 1).

Mean AHI and SD was 10/h (±2.9) in “mild OSAS” group, 23/h (±4.4) in “moderate OSAS”, and 56/h in (±21.1) “severe OSAS”. Oxygenation desaturation index (ODI) was 7/h (±2.6), 20/h (±5.4), and 49/h (±24.1) respectively. When we separated apneic patients in a “non-desaturating OSAS” group with ODI less than 20/h (corresponding to the median of our population) and a “desaturating OSAS” group with ODI more than 20/h, mean ODI was 10.1/h (±4.3) and 43.4/h (±22.5) respectively.

Table 1 Qualitative and quantitative demographic data

	Mild OSAS (<i>n</i> = 16)	Moderate OSAS (<i>n</i> = 17)	Severe OSAS (<i>n</i> = 20)	Controls (<i>n</i> = 28)	<i>p</i> value
Age	50.4 ± 11.9	53.2 ± 12.7	54.4 ± 12.1	48.9 ± 15.5	0.34
Gender					
Male	14 (87.5)	15 (88.2)	16 (80)	15 (53.6)	
Female	2 (12.5)	2 (11.7)	4 (20)	13 (46.4)	
Eye					
Right	8 (50)	8 (47)	10 (50)	15 (53.6)	
Left	8 (50)	9 (53)	10 (50)	13 (46.4)	
Family history of glaucoma	4 (25)	0 (0)	2 (10)	2 (7.1)	
Ethnic origin					
Caucasian	16 (100)	15 (88.2)	20 (100)	24 (85.7)	
Asian	0 (0)	2 (11.7)	0 (0)	0 (0)	
Afro-American	0 (0)	0 (0)	0 (0)	4 (14.3)	
VA (logMAR)	0 ± 0	0 ± 0	0 ± 0	0 ± 0	
SE (dioptries)	−0.19 ± 1.77	−0.35 ± 1.4	−0.43 ± 3.47	−1 ± 3.02	0.63
IOP (mmHg)	14.6 ± 1.9	14.4 ± 2.9	14.4 ± 2.56	13.9 ± 3.07	0.55
CCT (μm)	549.4 ± 26.9	547.1 ± 41.7	550.7 ± 28.1	546.5 ± 35.5	0.83
Gonioscopy					
Open	16 (100)	17 (100)	18 (90)	28 (100)	
Close	0 (0)	0 (0)	2 (10)	0 (0)	
BMI (kg/m ²)	26.3 ± 4.7	25.8 ± 3.8	28.5 ± 9	24.8 ± 3.7	
Tobacco <i>n</i> (%)	8 (50)	2 (11.7)	6 (30)	5 (17.9)	

OSAS obstructive sleep apnea syndrome, VA visual acuity, SE spherical equivalent, IOP intraocular pressure, CCT central corneal thickness, BMI body mass index

Perimetry and OCT

We did not find any significant difference concerning FDT MD between the 4 groups ($p = 0.139$), but FDT PSD was statistically altered in OSAS patients ($p = 0.009$) different from controls. For apneic patients with SAP, median MD was statistically different too ($p = 0.014$). Patients with abnormal visual field data did not have any clinical signs of glaucoma associated.

Anatomic data were not significantly modified ($p = 0.362$, $p = 0.278$, $p = 0.333$, and $p = 0.125$) (Table 2). There was no significant difference for anatomic data comparing all OSAS patients versus controls either.

OCTA

In ONH, we did not find any statistically significant difference of VD between the 4 groups ($p = 0.396$). Concerning RPC network, “whole” VD of the 3 × 3 mm acquisition square, “inside disc” and “peripapillary” automatical VD were not significantly different in OSAS patients ($p = 0.913$, $p = 0.473$, $p = 0.539$, respectively). VD was not significantly altered on foveal and parafoveal superficial capillary networks ($p = 0.484$ and $p = 0.491$) (Table 2 and Fig. 2).

When we analyzed our results comparing non-desaturating OSAS versus desaturating OSAS, we found same results concerning perimetric and tomographic data. But, this time, OCTA revealed VD significantly lower in inferior RPC in desaturating OSAS (inferior RPC VD was 64.2 ± 6.3 versus 67.6 ± 3.6 and 66.9 ± 3.7 in non-desaturating OSAS and controls, $p = 0.046$; Mann-Whitney test between “desaturating” and “non-desaturating” $p = 0.01$). RPC VD was also significantly lower in temporal-inferior area (Table 3).

When we analyzed results comparing all OSAS patients versus controls, we did not find any significant difference either concerning OCTA data.

Linear regression analysis showed a statistical correlation between 24/2 VF MD and PSD with AHI ($p = 0.0028$, $r = -0.54$ IC_{95%}[-0.76; -0.21], $p = 0.0026$, $r = 0.54$ IC_{95%}[0.22; 0.76]). We also found a significant correlation between 24/2 VF MD and PSD with ODI ($p = 0.0028$, $r = -0.54$ IC_{95%}[-0.76; -0.21], $p = 0.017$, $r = 0.446$ IC_{95%}[0.09; 0.71]). A statistical correlation also existed between ODI and positional OSAS ($p = 0.03$, $r = -0.29$ IC_{95%}[-0.52; -0.03]).

Coefficient of variation (CV) values were 0.68 and 3.1% for intravisit and intervisit repeatability respectively. Interobserver intrasession ICC values were 0.95 for the vessel densities, and intraobserver intersession reproducibility ICC values were 0.87.

Table 2 Perimetric, tomographic and OCT angiography results (Mean ± Standard deviation)

	Mild OSAS (<i>n</i> = 16)	Moderate OSAS (<i>n</i> = 17)	Severe OSAS (<i>n</i> = 20)	Controls (<i>n</i> = 28)	<i>p</i> value
VF					
FDT					
MD	0.63 ± 2.94	− 0.51 ± 3.06	− 0.51 ± 3.26	0.97 ± 2.68	0.31
PSD	2.67 ± 0.63	2.85 ± 0.68	2.9 ± 0.46	2.49 ± 0.48	0.009
24-2 VF					
VFI	99.14 ± 0.9	99.14 ± 1.22	97.75 ± 1.17		0.046
MD	0.56 ± 0.9	− 0.004 ± 1.94	− 1.98 ± 1.39		0.014
PSD	1.53 ± 0.32	1.63 ± 0.47	2.06 ± 0.48		0.072
OCT					
RNFL					
Mean	99.75 ± 4	98.06 ± 6.52	98.85 ± 10.57	96.04 ± 10.17	0.362
Superior	122.81 ± 3.54	118.53 ± 7.63	119.2 ± 15.32	117.93 ± 13.02	0.156
Nasal	78.81 ± 7.61	79.59 ± 7.46	80.15 ± 12.71	76.9 ± 13.24	0.611
Inferior	122 ± 6.67	120.29 ± 18.1	120.8 ± 15.55	118.96 ± 12.86	0.585
Temporal	75 ± 6.81	73.47 ± 5.68	74.9 ± 10.43	71.04 ± 10.97	0.645
Rim	1.4 ± 0.28	1.24 ± 0.38	1.37 ± 0.47	1.37 ± 0.34	0.278
C/D	0.35 ± 0.1	0.37 ± 0.16	0.3 ± 0.16	0.31 ± 0.14	0.333
GCC					
Mean	97.53 ± 3.63	95.07 ± 6.36	99.12 ± 8.72	94.72 ± 7.65	0.125
Superior	96.77 ± 4.6	94.4 ± 6.33	99.6 ± 7.97	94.18 ± 7.32	0.06
Inferior	98.3 ± 3.17	95.75 ± 7.92	98.67 ± 9.9	95.27 ± 8.26	0.327
ANGIO DISC					
SSI	78 ± 4.3	76 ± 6.5	75 ± 8	76 ± 7	
ONH					
Flow index	1.26 ± 0.24	1.09 ± 0.16	1.06 ± 0.27	1.1 ± 0.18	0.057
ONH area	2.2 ± 0.33	1.93 ± 0.22	1.97 ± 0.44	1.97 ± 0.32	0.093
Vessel density	0.57 ± 0.05	0.56 ± 0.05	0.54 ± 0.07	0.56 ± 0.03	0.396
RPC					
“Whole”	59.76 ± 2.36	59.24 ± 1.79	59 ± 3.9	59.41 ± 3.2	0.913
“Inside disc”	46.39 ± 6.02	45.21 ± 7.99	47.4 ± 9.25	47.73 ± 9.78	0.473
“Peripapillary”	67.69 ± 2.02	67.83 ± 2.09	66.19 ± 3.33	67 ± 2.72	0.539
RPC TS	66.64 ± 3.26	66.13 ± 2.96	64.97 ± 4.3	65.21 ± 4.2	0.350
S	64.72 ± 3.69	64.94 ± 3.71	63.99 ± 3.92	64.49 ± 3.27	0.916
NS	62.93 ± 3.55	60.36 ± 3.89	59.78 ± 4.2	60 ± 4.98	0.054
T	59.77 ± 7.42	57.14 ± 7.73	58.37 ± 5.48	58.48 ± 4.98	0.6
N	59.63 ± 4.57	59.27 ± 3.2	59.61 ± 4.96	59.12 ± 3.5	0.278
TI	65.11 ± 3.61	65.17 ± 3.81	62.86 ± 5.56	64.76 ± 4.04	0.533
I	67.33 ± 3.73	66.25 ± 4.75	64.33 ± 6.69	66.89 ± 3.71	0.342
NI	60.4 ± 3.8	58.52 ± 3.68	58.26 ± 4.37	56.93 ± 5.54	0.078
ANGIO RETINA					
SSI	73 ± 6.6	73 ± 6	73 ± 6	76 ± 7.3	
Fovea	32.74 ± 7.04	31.38 ± 4.88	31.05 ± 5.89	33.79 ± 5.89	0.484
Parafovea	55.49 ± 2.9	54.58 ± 2.9	55.33 ± 3.01	55.99 ± 2.31	0.491

OSAS obstructive sleep apnea syndrome, VF visual field, FDT frequency doubling technology perimetry FDT-Matrix™, MD mean deviation, PSD pattern standard deviation, VFI visual field index, OCT optical coherence tomography, RNFL retinal nerve fiber layers, Rim rim area, C/D cup/disc ratio, GCC ganglion cell complex, SSI strength signal index, ONH optic nerve head, RPC radial peripapillary capillary network, TS temporal superior, S superior, NS nasal superior, T temporal, N nasal, TI temporal inferior, I inferior, NI nasal inferior

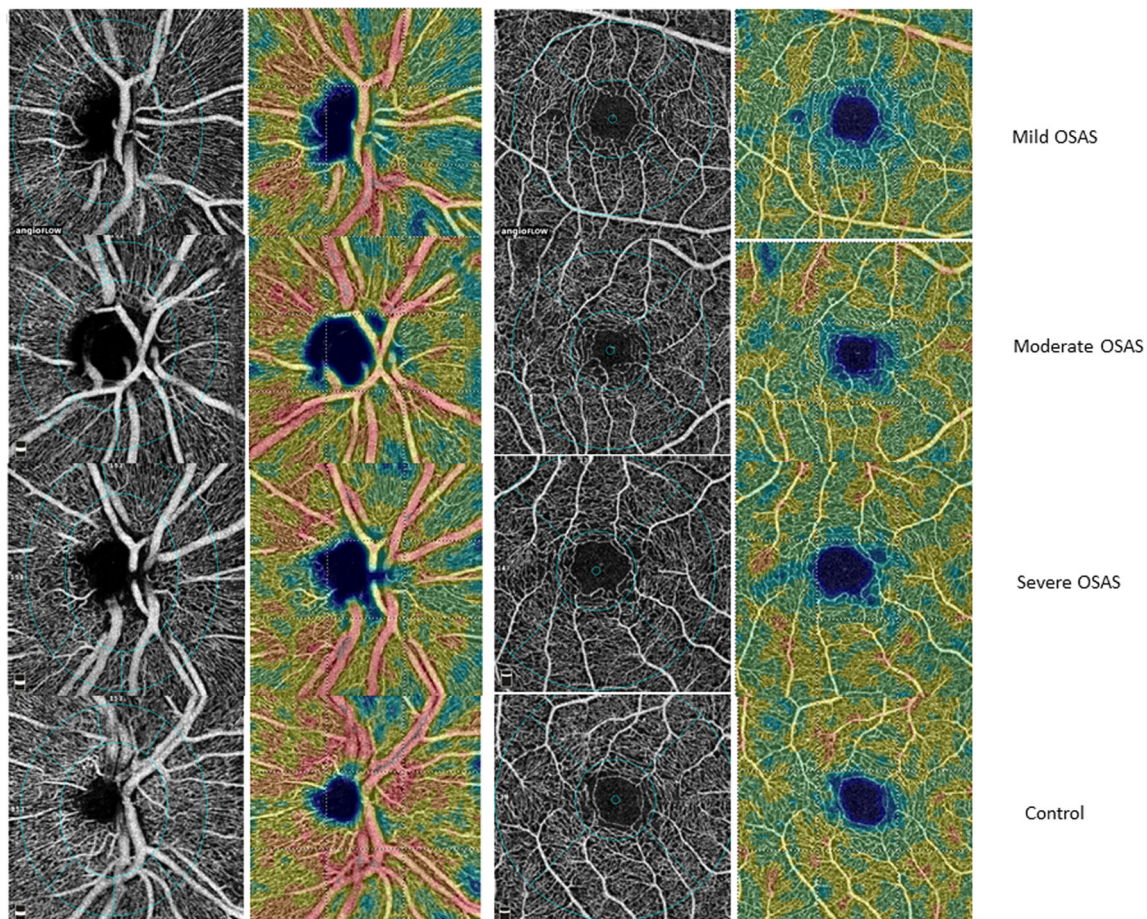


Fig. 2 OCT angiography images and vessel density maps. Up to down: patient with mild obstructive sleep apnea syndrome (OSAS), patient with moderate OSAS, severe OSAS and control. Left: radial peripapillary

capillary network OCT angiograms. Right: superficial macular capillary network. OCT RT XR Avanti images with AngioVue software, Grid Analysis (Optovue Inc., Fremont, CA)

Discussion

Functionally, patients with severe OSAS had statistically significant altered MD and PSD, on FDT-Matrix as well as on SAP. We did not find any significant difference concerning ONH, RPC, and macular VD in OSAS patients when comparing to controls using OCTA. Anatomically, we did not either find significant difference between apneic and non-apneic patients. IOP and clinical data were also comparable.

Patients with untreated OSAS are at higher cardiovascular risks for hypertension, stroke, heart failure, and myocardial infarction [14], but vascular impact of OSAS on retina and optic nerve remains unclear. Choroidal blood flow is not altered in OSAS patients when measured with laser Doppler flowmetry [15] compared to healthy patients, even though choroidal thickness was found thinner in OSAS patients using Enhanced Depth Imaging–OCT [16].

The underlying etiological mechanisms for the relationship between optic neuropathies and OSAS remain unknown, although there are several possible explanations. Among the vascular factors, it has been postulated that there may be

insufficient blood supply to nourish the retinal nerve fiber layer (RNFL) and/or optic nerve [5–7, 17]. But we did not find in the literature direct papillary or retinal microvascularization study in OSAS. Nevertheless, in regard to our study, this theory does not seem realistic. We did not find ONH, RPC, neither macular vascular rarefaction in apneic patients compared to controls, using OCTA.

Another theory seems more plausible; the upper airway collapse during sleep in OSAS patients would lead to repeated or prolonged episodes of hypoxia, which may reduce the oxygen supply to the optic nerve, and subsequently lead to optic neuropathy [18, 19]. Indeed, we found a significantly lower oxygen arterial saturation in apneic patients than in controls, statistically correlated to AHI ($p < 0.001$; $r = 51$). Hypoxia in OSAS may lead to ischemia around the optic nerve through following mechanisms: direct lack of oxygenation with lower oxygen saturation, platelet activation and aggregation, polycythemia with blood hypercoagulability (which could be linked to glaucoma progression [20]), and endothelial dysfunction [21]. Indeed, hypoxia may be responsible for endothelial dysfunction with a decreased synthesis of nitric oxide

Table 3 Non-desaturating OSAS versus desaturating OSAS comparison (Mean ± Standard deviation)

	Non-desaturating OSAS (n = 26)	Desaturating OSAS (n = 27)	Controls (n = 28)	p value
ANGIO DISC				
ONH				0.98
Flow index	1.15 ± 0.26	1.10 ± 0.23	1.1 ± 0.18	
ONH area	2.06 ± 0.36	2.00 ± 0.36	1.97 ± 0.32	
Vessel density	0.56 ± 0.05	0.55 ± 0.06	0.56 ± 0.03	
ANGIO DISC				
RPC				
Whole	59.6 ± 2.4	59.0 ± 3.3	59.4 ± 3.2	0.83
Inside disc	46.6 ± 7.7	46.2 ± 8.2	47.7 ± 9.8	0.68
Peripapillary	67.6 ± 2.4	66.8 ± 2.9	67.0 ± 2.7	0.59
RPC TS	66.3 ± 3.8	65.4 ± 3.5	65.2 ± 4.2	0.39
S	64.4 ± 4.2	64.6 ± 3.4	64.5 ± 3.3	0.94
NS	61.2 ± 5.1	60.7 ± 2.9	60.0 ± 5.0	0.23
T	57.4 ± 7.6	59.4 ± 5.9	58.5 ± 5.0	0.54
N	59.6 ± 3.9	59.4 ± 4.6	59.1 ± 3.5	0.51
TI	64.3 ± 4.9	64.2 ± 4.3	64.8 ± 4.0	0.95
I	67.6 ± 3.6	64.2 ± 6.3	66.9 ± 3.7	0.046
NI	59.9 ± 4.3	56.9 ± 5.5	58.1 ± 3.6	0.018
ANGIO RETINA				
Fovea	31.5 ± 6.2	31.8 ± 5.7	33.8 ± 5.9	0.32
Parafovea	55.3 ± 3.0	55.0 ± 2.9	56.0 ± 2.3	0.42
VF				
FDT				
MD	-0.51 ± 3.35	0.22 ± 2.78	0.97 ± 2.68	0.25
PSD	2.76 ± 0.62	2.85 ± 0.56	2.49 ± 0.48	0.049
24-2 VF				
MD	0.43 ± 1.33	-1.53 ± 1.43		0.005
OCT				
RNFL				
Mean	99.6 ± 4.8	98.2 ± 9.8	96.0 ± 10.2	0.17
Superior	119.8 ± 6.3	120.4 ± 13.5	117.9 ± 13.0	0.52
Nasal	79.6 ± 7.2	79.5 ± 11.7	76.9 ± 13.2	0.42
Inferior	124.3 ± 11.1	117.9 ± 16.3	119.0 ± 12.9	0.33
Temporal	74.3 ± 6.5	74.7 ± 9.3	71.0 ± 11.0	0.23
Rim	1.34 ± 0.37	1.34 ± 0.43	1.37 ± 0.34	0.68
C/D	0.35 ± 0.13	0.33 ± 0.16	0.31 ± 0.14	0.48
GCC				
Mean	97.5 ± 5.3	97.2 ± 8.1	94.7 ± 7.6	0.46
Superior	96.9 ± 6.0	97.3 ± 7.6	94.2 ± 7.3	0.39
Inferior	98.2 ± 5.2	97.0 ± 9.6	95.3 ± 8.3	0.41

OSAS obstructive sleep apnea syndrome, *SSI* strength signal index, *ONH* optic nerve head, *RPC* radial peripapillary capillary network, *TS* temporal superior, *S* superior, *NS* nasal superior, *T* temporal, *N* nasal, *TI* temporal inferior, *I* inferior, *NI* nasal inferior

(NO), a vasodilator factor. Moreover, increased concentrations of endothelin-1, a powerful vasoconstrictor, were found in both OSAS [21] and in normal-tension glaucoma [22]. This hypoxia-mediated imbalance between NO and endothelin would lead to vascular dysregulation in the optic nerve in

OSAS patients. Hypoxia might be more implicated than a possible simple vascular involvement in evolution and aggravation of glaucomatous neuropathy.

Other theories, including inflammation and oxidative stress have also been suggested to explain the implication

of OSAS on the optic nerve [23]. Additionally, OSAS, through sympathetic tone activation, results in renin-angiotensin-aldosterone system activation, and then to a higher systolic blood pressure [24].

From our results, OSAS does not seem to lead to direct quantitative ONH vascular damages, but OCTA cannot lead to a meaningful conclusion at this time; moreover, we are not able to exclude the possible implication of hypoxia and its consequences. Indeed, when we separated OSAS patients in the non-desaturating OSAS group versus desaturating OSAS group, we found decreased vessel density in inferior RPC in patients with desaturating OSAS.

Nevertheless, Yu et al. [10] recently found different results; they observed, using the same OCTA RT XR Avanti (Optovue Inc., Fremont, CA, USA) on 69 patients, that in OSAS subjects, the vessel densities in the peripapillary and parafoveal areas decreased with greater disease severity and that the decrease was more prominent in the peripapillary area. These differences might be due to different populations and ethnicity. They also have more coherent sample of severe OSAS than ours, which could have induced a bias in our statistical study.

One case report of a 56-year-old man with OSAS is also available in the literature [25]. Vascular perfusion maps were also obtained using the same OCTA; the superficial and deep capillary plexivascular perfusion maps revealed patchy areas of reduced flow, whereas the choriocapillaris maps were normal, associated with a retinal vascular tortuosity in both arteries and veins in the superficial capillary plexus. They only performed a qualitative analysis without any quantitative data.

About our anatomical data, we did not find significant difference concerning RNFL thickness, rim area, C/D ratio, GCC thickness, and IOP between the four groups. In the literature, multiple significant negative correlations were found between AHI and RNFL [19]. Lin et al. [19] also found significant positive correlation between SaO₂ and RNFL, supporting the “hypoxia-mediated” optic neuropathy hypothesis. Several studies also revealed higher IOP values in OSAS patients compared to controls [17, 19], but we did not find such results in our patients.

About functional data, in our study, severe OSAS patients had significant altered visual fields MD and PSD, with a negative correlation with AHI. These results are coherent with other studies also finding correlation between AHI and MD and PSD [18]. Patients with abnormal visual fields data did not have any clinical signs of glaucoma associated. Defects were not clearly systematized. It might just be an incidental finding, or a lack of concentration due to their OSAS with the learning curve phenomenon, or an indirect consequence of optic nerve hypoxia.

Our study has some limitations. Our sample size might be responsible for a lack of power to reveal debutant papillary or retinal vascular lesions in patients with OSAS. This number of subjects is too small to draw a meaningful conclusion with our

statistical analysis. Moreover, we did not perform any qualitative analysis of vascular densities maps, which induce subjectivity. We chose to rely on only quantitative aspect and objective measures given by the software. OSAS patients were young with a first diagnosis of the disease (from their first sleep investigation), without any precise knowledge of their OSAS evolution. Although we can consider that OSAS duration might be a prognostic factor on papillary and retinal vessel density. Moreover, the studied OCTA area of 3×3 mm around optic nerve and fovea, corresponding to 10° of visual field, might be too small to find significant anomalies. We did not objectively measure SaO₂ during sleep in our control patients. They all had a Berlin Questionnaire scale of zero that does not indicate the necessity of proceeding to a sleep study [11]. Additionally, OCTA is an exam that we cannot perform in supine position and that needs patient cooperation, making it impossible to perform on sleeping patients. It also presents some interpretation limitations; OCT angiogram images of retinal vessels are obtained from reconstructions of many projections, thanks to SSADA algorithm, giving quantitative data from vascular flow. Qualitative vascular aspect as vascular caliber or resistance cannot be precisely studied. Despite recent advances in technology, OCTA studies are still in its early phase, and it is not possible to draw a meaningful conclusion concerning vascularization and physiopathology. Then, there are quite different systems of OCTA on the market that have different peculiarities.

OCTA did not detect reduced optic nerve head, radial peripapillary capillaries, neither macular blood VD in eyes with OSAS. The precise mechanisms that link OSAS with optic nerve pathologies remain unclear: our study was not able to demonstrate a vascular impact through OCTA examination. Further studies would be helpful to investigate repercussion of OSAS on optic nerve microcirculation.

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Compliance with ethical standards

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Ethics Committee of the French Society of Ophthalmology) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

- White DP (1995) Sleep-related breathing disorder. 2. Pathophysiology of obstructive sleep apnoea. *Thorax* 50:797–804
- Palombi K, Renard E, Levy P et al (2006) Non-arteritic anterior ischaemic optic neuropathy is nearly systematically associated with obstructive sleep apnoea. *Br J Ophthalmol* 90:879–882
- Chou KT, Huang CC, Tsai DC et al (2012) Sleep apnea and risk of retinal vein occlusion: a nationwide population-based study of Taiwanese. *Am J Ophthalmol* 154:200–205
- Mason RH, West SD, Kiire CA et al (2012) High prevalence of sleep disordered breathing in patients with diabetic macular edema. *Retina* 32(9):1791–1798
- Shi Y, Liu P, Guan J, Lu Y, Su K (2015) Association between glaucoma and obstructive sleep apnea syndrome: a meta-analysis and systematic review. *PLoS One* 10(2):e0115625
- Wu X, Liu H (2015) Obstructive sleep apnea/hypopnea syndrome increases glaucoma risk: evidence from a meta-analysis. *Int J Clin Exp Med* 8(1):297–303
- Liu S, Lin Y, Liu X (2016) Meta-analysis of association of obstructive sleep apnea with glaucoma. *J Glaucoma* 25(1):1–7
- Zhao XJ, Yang CC, Zhang JC, Zheng H, Liu PP, Li Q (2016) Obstructive sleep apnea and retinal nerve fiber layer thickness: a meta-analysis. *J Glaucoma* 25(4):e413–e418
- Cioffi GA, Van Buskirk EM (2008) Microvasculature of the anterior optic nerve. *Surv Ophthalmol* 43:308–312
- Yu J, Xiao K, Huang J, Sun X, Jiang C (2017) Reduced retinal vessel density in obstructive sleep apnea syndrome patients: an optical coherence tomography angiography study. *Invest Ophthalmol Vis Sci* 58(9):3506–3512
- Berry RB, Budhiraja R, Gottlieb DJ et al (2012) 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* 8(5):597–619
- Gordon MO, Kass MA (1999) The ocular hypertension treatment study: design and baseline description of the participants. *Arch Ophthalmol* 117(5):573–583
- Jia Y, Tan O, Tokayer J et al (2012) Split-spectrum amplitude-decorrelation angiography with optical coherence tomography. *Opt Express* 20(4):4710–4725
- Marin JM, Carrizo SJ, Vicente E, Agusti AG (2005) Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *Lancet* 365:1046–1053
- Khayati H, Pepin JL, Geiser MH et al (2011) Choroidal blood flow regulation after posture change or isometric exercise in men with obstructive sleep apnea syndrome. *Invest Ophthalmol Vis Sci* 52(13):9489–9496
- Kara S, Ozcimen M, Bekci TT et al (2014) Evaluation of choroidal thickness in patients with obstructive sleep apnea/hypopnea syndrome. *Arq Bras Oftalmol* 77(5):280–284
- Karakucuk S, Goktas S, Aksu M et al (2008) Ocular blood flow in patients with obstructive sleep apnea syndrome (OSAS). *Graefes Arch Clin Exp Ophthalmol* 246(1):129–134
- Tsang CS, Chong SL, Ho CK, Li MF (2006) Moderate to severe obstructive sleep apnoea patients is associated with a higher incidence of visual field defect. *Eye (Lond)* 20(1):38–42
- Lin CC, Hu CC, Ho JD, Chiu HW, Lin HC (2013) Obstructive sleep apnea and increased risk of glaucoma: a population-based matched-cohort study. *Ophthalmology* 120:1559–1564
- O'Brien C, Butt Z, Ludlam C, Detkova P (1997) Activation of the coagulation cascade in untreated primary open-angle glaucoma. *Ophthalmology* 104:725–730
- Priou P, Gagnadoux F, Tesse A et al (2010) Endothelial dysfunction and circulating microparticles from patients with obstructive sleep apnea. *Am J Pathol* 177:974–983
- Sugiyama T, Moriya S, Oku H, Azuma I (1995) Association of endothelin-1 with normal-tension glaucoma: clinical and fundamental studies. *Surv Ophthalmol* 39(Suppl.):49–56
- Tothova L, Hodosy J, Mucska I, Celec P (2014) Salivary markers of oxidative stress in patients with obstructive sleep apnea treated with continuous positive airway pressure. *Sleep Breath* 18(3):563–570
- Barceló A, Elorza MA, Barbé F, Santos C, Mayorals LR, Agusti AG (2001) Angiotensin converting enzyme in patients with sleep apnoea syndrome: plasma activity and gene polymorphisms. *Eur Respir J* 17(4):728–732
- Li DQ, Golding J, Choudhry N (2016) Swept-Source Optical Coherence Tomography Angiography and Vascular Perfusion Map Findings in Obstructive Sleep Apnea. *Ophthalmic Surg Lasers Imaging Retina* 47(9):880–884