# Reduced Retinal Vessel Density in Obstructive Sleep Apnea Syndrome Patients: An Optical Coherence Tomography Angiography Study

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JY and KX contributed equally to the work presented here and therefore should be regarded as equivalent authors.

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DESIGN. Prospective, cross-sectional study.

**M**ETHODS. Sixty-nine consecutive subjects who underwent polysomnography were enrolled. Patients were divided into three groups according to the severity of OSAS, which was defined using the apnea-hypopnea index (AHI) as normal-to-mild (AHI <15), moderate ( $\geq$ 15 to <30), or severe ( $\geq$ 30). The vessel densities, and macular and retinal nerve fiber layer thicknesses were compared among the three groups. The correlations between clinical variables (age, heart rate, body mass index, ocular perfusion pressure, spherical equivalence, IOP, inner retinal thickness, and AHI) and vessel densities were also determined.

**R**ESULTS. The full and inner parafoveal retinal thickness and the retinal nerve fiber layer thickness were similar in all three groups. The retinal vessel density decreased with greater severity of OSAS. The decrease in vessel density differed between the peripapillary and parafoveal areas. The moderate group had a significantly lower vessel density than the normal-to-mild group in the peripapillary area (P < 0.05), but similar vessel density as the normal-to-mild group in the parafoveal area (P > 0.05). The vessel densities in the parafoveal and peripapillary areas were significantly and negatively correlated with AHI (both P < 0.05); the relative reduction in vessel density was greater in the peripapillary area than in the parafoveal area.

CONCLUSIONS. In OSAS patients, the vessel densities in the peripapillary and parafoveal areas decreased with greater disease severity, and the decrease was more prominent in the peripapillary area.

Keywords: obstructive sleep apnea syndrome, optical coherence tomography angiography, vessel density

bstructive sleep apnea-hypopnea syndrome (OSAS) is the most common type of sleep-disordered breathing.<sup>1</sup> OSAS has been identified as a possible risk factor for systemic disorders, such as hypertension, coronary artery disease, and renal disease.<sup>2-4</sup> In ophthalmologic settings, OSAS is associated with glaucoma, nonarteritic ischemic optic neuropathy, central serous chorioretinopathy, and other ocular disorders.<sup>5-11</sup> In addition, a recent study suggested that, compared with healthy subjects, OSAS patients have a thinner retinal nerve fiber layer (RNFL).<sup>12</sup> Although the underlying mechanism is unclear, vascular factors were speculated to play an important pathologic role. It was reported that the choroid was significantly thinner in severe OSAS patients than in patients with mild OSAS.<sup>13,14</sup> However, the choroidal vascular system supplies the outer part of the retina, whereas the retinal vascular system supplies the inner part, including the RNFL.

Copyright 2017 The Authors iovs.arvojournals.org | ISSN: 1552-5783 Therefore, we performed this study to examine the retinal vasculature in patients with OSAS and to determine the correlation between retinal vascularity and the severity of OSAS.

## METHODS

# Subjects

Consecutive patients who underwent polysomnography at the Eye and ENT Hospital of Fudan University between January and July 2015 were enrolled in this study. All subjects underwent comprehensive ophthalmologic examinations, which included best-corrected visual acuity (BCVA), slit-lamp biomicroscopy, refraction measurement using auto refraction, calculation of the spherical equivalence (SE) based on the spherical diopter plus

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one-half of the cylindrical dioptric power, dilated fundus examination, and measurement of IOP using a noncontact tonometer. The subjects' heart rate and blood pressure were also recorded. The mean arterial pressure was calculated as the diastolic blood pressure plus one-third of the difference between the diastolic blood pressure and the systolic blood pressure. The ocular perfusion pressure (OPP) was determined by subtracting the IOP from two-thirds of the mean arterial pressure. The subjects' medical and family histories were also collected.

Subjects were included if they met the following criteria: BCVA  $\geq 16/20$ , SE between +1 and -6 diopters, and IOP  $\leq 21$ mm Hg. Subjects with any of the following were excluded: history of ocular surgery or trauma; BCVA < 16/20; IOP > 21mm Hg; family history of glaucoma in a first-degree relative; signs of myopic degeneration or a pathologic form of myopia; other ophthalmic diseases; or the presence of diabetes mellitus, hypertension, migraine, or any systemic disease other than OSAS. The study was approved by the Institutional Review Board of the Eye and ENT Hospital of Fudan University, and conformed to the tenets of the Declaration of Helsinki. All subjects signed informed consent forms.

#### Polysomnography

Patients underwent polysomnography performed over a minimum of 6 hours in a quiet, private room in our hospital. The apnea-hypopnea index (AHI; times/h) was calculated and used as an indicator of the severity of OSAS. An apneic event was defined as cessation of airflow for  $\geq 10$  seconds with an effort to breathe. A hypoapneic event was defined as a minimal 30% reduction in the thoracoabdominal movements or airflow compared with baseline that lasted for  $\geq 10$  seconds together with oxygen desaturation of  $\geq 4\%$ . The severity of OSAS was graded into three groups based on AHI, as follows: normal-tomild, AHI <15; moderate, AHI  $\geq 15$  to <30; and severe, AHI  $\geq 30$ .<sup>15</sup> The lowest percutaneous oxygen saturation (SpO<sub>2</sub>) and the mean SpO<sub>2</sub> during sleep were measured using a transcutaneous finger pulse oximeter.

#### **Optical Coherence Tomography Angiography**

Both eyes were imaged at the same visit. Optical coherence tomography (OCT) angiography was performed using a spectral domain system (RTVue-XR Avanti; Optovue, Fremont, CA, USA). This system has an A-scan rate of 70 kHz with a light source centered at a wavelength of 840 nm and a bandwidth of 45 nm.<sup>16-19</sup> Optic disc ( $4.5 \times 4.5$  mm) and macular ( $6 \times 6$  mm) OCT angiography scans were acquired. Then, en face retinal angiograms were created by projecting the flow signal internal to the retinal pigment epithelium. All procedures were performed using RTVue-XR Avanti software. The vessel densities in the peripapillary and parafoveal areas were assessed as follows. The peripapillary area was defined as a 700-µm-wide elliptical annulus extending outward from the optic disc boundary. The parafoveal area was defined as an annulus with an outer diameter of 3 mm and an inner diameter of 1 mm centered on the fovea. The peripapillary and parafoveal vessel densities were defined as the percentage area occupied by vessels in the corresponding segmented areas.20

The RNFL and macular thicknesses were measured at the same time using the same OCT system. The RNFL thickness was measured along a circular profile with a diameter of 3.45 mm that was centered on the disc, and was corrected for ocular magnification (using the axial length), as previously reported.<sup>21</sup> Macular thicknesses were obtained using the retinal map protocol. The parafoveal area was defined using

TABLE 1. Characteristics of Subjects According to the Severity of OSAS

	Normal-to-	Moderate	Severe	D
	Mild OSAS	OSAS	OSAS	P
Age, y	$43 \pm 11$	$46 \pm 10$	38 ± 10	0.089
BMI, kg/m <sup>2</sup>	$25.05 \pm 3$	$25.8\pm2.7$	$27 \pm 3.1$	0.075
HR, beats per min	$78 \pm 8$	81 ± 9	$84 \pm 9$	0.074
IOP, mm Hg	$14 \pm 2$	$14 \pm 3$	$14 \pm 3$	0.514
OPP, mm Hg	$46 \pm 8$	$48 \pm 5$	$46 \pm 4$	0.551
SE, diopters	$-0.9 \pm 1.4$	$-0.6 \pm 1.7$	$-0.8\pm1.2$	0.798
AL, mm	$23.9 \pm 0.95$	$23.9 \pm 1.0$	$23.9 \pm 0.96$	0.997
VA	$1.1 \pm 0.2$	$1.2\pm0.2$	$1.1\pm0.2$	0.842
AHI, times/h	$7.3 \pm 1$	$21.7\pm1$	$62.3 \pm 4$	$0.000^{*}$
Lowest SpO <sub>2</sub> , %	$89 \pm 4$	$81 \pm 10$	$70 \pm 12$	$0.000^{*}$
Mean SpO <sub>2</sub> , %	$97 \pm 1$	96 ± 2	$92 \pm 4$	$0.000^{*}$

Values are expressed as the mean  $\pm$  SD.

AL, axial length; BMI, body mass index; HR, heart rate; VA, visual acuity.

\* P < 0.05 was considered statistically significant.

the definition programed in the OCT angiogram system. The full retinal thickness was measured from the internal limiting membrane to the middle of the RPE, inner retinal thickness from the internal limiting membrane to the outer boundary of the inner plexiform layer. The full and inner retinal thicknesses of the parafoveal areas were automatically determined using the system's software and were defined as the mean thicknesses of each area.

#### **Statistical Analysis**

For each patient, the right eye was included in the data analyses. Statistical analyses were performed using SPSS software version 20.0 (SPSS, Inc., Chicago, IL, USA). Continuous variables are presented as the mean  $\pm$  SD. One-way analysis of variance was used to compare variables among the three groups, followed by the least significant difference test for multiple comparisons. A general linear model was used to compare the vessel densities among the three groups. The model was corrected for the possible correlation between the parafoveal and peripapillary densities. Correlations between AHI and vessel densities were analyzed using Pearson correlation coefficients, and were adjusted for other factors (age, heart rate, body mass index, OPP, SE, IOP, and inner retinal thickness) in multiple regression analysis. *P* < 0.05 was considered statistically significant.

## **R**ESULTS

Overall, 69 OSAS patients were included in the final analysis, including 56 males. Their mean age was  $43 \pm 11$  years (range, 23-66 years). Their demographic and clinical characteristics are summarized in Table 1. These patients were then divided according to their severity of OSAS: 23 subjects had normal-to-mild OSAS, 19 subjects had moderate OSAS, and 27 subjects had severe OSAS. The three groups were similar in terms of their age, heart rate, body mass index, SE, axial length, visual acuity, IOP, and OPP (all P > 0.05; Table 1). In addition, the full and inner parafoveal retinal thicknesses, and the RNFL thickness were similar in all three groups (all P > 0.05; Table 2).

The vessel densities in the peripapillary and parafoveal areas decreased with increasing severity of OSAS (P < 0.05; Table 2), but there were slight differences in the decreases of vessel densities in the peripapillary and parafoveal areas. The severe OSAS group had significantly lower vessel densities in

 
 TABLE 2. Retinal Thicknesses and Vessel Densities According to the Severity of OSAS

	Normal-to- Mild OSAS	Moderate OSAS	Severe OSAS	Р
Fovea thickness um	241 + 20	246 + 16	247 + 24	0.572
Parafoveal thickness, µm	$316 \pm 14$	$316 \pm 12$	$320 \pm 14$	0.398
Inner parafoveal thickness, µm	124 ± 6	$121 \pm 8$	124 ± 7	0.194
RNFL thickness, µm	$106 \pm 10$	$101 \pm 15$	$107 \pm 8$	0.219
Parafoveal vessel density, %	58.2 ± 2.1	58.7 ± 2.2	56.4 ± 1.8	0.002*
Peripapillary vessel density, %	66 ± 2	63 ± 3	63 ± 3	0.004*

Values are expressed as the mean  $\pm$  SD.

\* P < 0.05 was considered statistically significant.

the peripapillary and parafoveal areas than the normal-to-mild OSAS group (P < 0.05; Table 2; Fig. 1). In contrast, compared with the normal-to-mild group, the moderate group had a significantly lower vessel density in the peripapillary area (P < 0.05; Table 2; Fig. 1) but a similar vessel density in the parafoveal area (P > 0.05; Table 2; Fig. 1). Figure 2 shows representative OCT angiography images of mild, moderate, and severe OSAS patients.

The vessel densities in the parafoveal and peripapillary areas (both P < 0.05), but not the retinal thicknesses (i.e., full and inner parafoveal retinal thicknesses, and RNFL thickness; all P > 0.05), were significantly and negatively correlated with AHI. The correlations between vessel density and AHI remained significant (both P < 0.05) after adjustment for age, heart rate, body mass index, OPP, SE, IOP, and inner retinal thickness (Table 3). The relative reduction in vessel density with AHI was greater in the peripapillary area than in the macular area. Each 10-unit decrease in AHI was associated with a 0.43% decrease in the mean parafoveal vessel density.

The vessel density in the parafoveal area was also positively correlated with the lowest nocturnal peripheral oxygen saturation (SpO<sub>2</sub>) (P < 0.05; Fig. 3), but not the mean SpO<sub>2</sub> (P > 0.05). However, this correlation was not significant (P > 0.05) after adjustment for age, heart rate, body mass index,

OPP, SE, IOP, and inner retinal thickness. Meanwhile, the vessel density in the peripapillary area was positively correlated with the lowest SpO<sub>2</sub> (r = 0.405) and the mean SpO<sub>2</sub> (r = 0.380) (both P < 0.05; Fig. 3). These correlations remained significant even after adjustment for age, heart rate, body mass index, OPP, SE, IOP, and inner retinal thickness (both P < 0.05; Tables 4, 5). The retinal thicknesses (i.e., full and inner parafoveal retinal thicknesses, and RNFL thickness) were not significantly correlated with the lowest or mean SpO<sub>2</sub> (all P > 0.05).

## DISCUSSION

In this study, we compared the retinal vasculature between patients with different stages of OSAS. The analysis revealed that the retinal vessel densities in the parafoveal and peripapillary areas decreased with greater severity of OSAS. In addition, retinal vessel density was significantly correlated with AHI and SpO2, and the relative decrease in vessel density seemed to be more prominent in the peripapillary area.

OCT angiography was recently reported to be an effective, reliable, and noninvasive tool for monitoring retinal vessels.<sup>17</sup> Theoretically, the reduction in vessel density could be due to either a loss of retinal capillaries or vasoconstriction. We used OCT angiography to study the retinal vessels in OSAS patients in our study. We found that the vessel densities in the peripapillary and parafoveal areas decreased with increasing severity of OSAS. Furthermore, the retinal vessel densities were significantly correlated with AHI. These findings are consistent with those of prior studies showing that the impairments of the brain vascular system were correlated with the severity of OSAS.<sup>22,23</sup> Nasr et al.<sup>22</sup> reported that impaired cerebral autoregulation is correlated with the severity of OSAS, and Baril et al.<sup>23</sup> reported that reduced regional cerebral blood flow is associated with more frequent hypopnea, snoring, hypoxemia, and sleepiness.

OSAS is characterized by intermittent upper airway obstruction during sleep with concurrent hypoxia and hypercapnic acidosis, and is an important risk factor for vascular diseases. Coloma et al.<sup>24</sup> previously reported a reduction in mean cerebral blood flow velocity in OSAS patients compared with control subjects, and that the mean flow velocity was positively correlated with the mean nocturnal O<sub>2</sub> saturation (r = .232, P = 0.043). We also found



**FIGURE 1.** Box plots of vessel density in the parafoveal (*right*) and peripapillary (*left*) areas. P < 0.05 was considered statistically significant. *Circles* indicate outliers (lower margin 5%), upper margin 5%).



FIGURE 2. Representative OCT angiography images showing the vessel density in typical patients with mild (A), moderate (B), or severe (C) OSAS.

a positive correlation between vessel density and SpO<sub>2</sub>. It was proposed that, in OSAS, intermittent hypoxemia in combination with rapid fluctuations in blood flow and variations in blood pressure can lead to oxidative stress, inflammation, endothelial dysfunction, and atherosclerosis.<sup>25-27</sup> Endothelial dysfunction and atherosclerosis can directly reduce the diameter of blood vessels, and affect vasoreactivity, which might result in hypoperfusion, even during wakefulness.<sup>26,28</sup> Therefore, severe hypoxemia might result in prominent impairments of the retinal vascular system.

Although the retinal vessel density was decreased in OSAS, the RNFL and macular thicknesses were similar in all three groups. These findings suggest that, in OSAS, vascular changes might occur before changes in RNFL thickness. It was reported that OSAS patients are at increased risk of open-angle glaucoma<sup>29-31</sup> and have a thinner RNFL.<sup>15,31</sup> Mechanical and vascular theories have been proposed to explain these changes.<sup>29,32</sup> Our results seem to support the vascular theory.<sup>29</sup> Although Shiba et al.<sup>15</sup> reported that the RNFL thickness was correlated with the severity of OSAS, we did not find a correlation between RNFL thickness and OSAS severity in our study. The reason for these different results are not fully clear, but all our patients were initially diagnosed with OSAS, and were relatively younger than those in the study by Shiba et al.<sup>15</sup> (mean age: 43 vs. 61 years). Therefore, patients included in our study possibly had a shorter duration of OSAS. This might explain the difference, and might also support the hypothesis that the retinal vessel density decreases before the reduction in RNFL thickness in OSAS. Accordingly, monitoring the retinal vasculature by OCT angiography could be helpful

 TABLE 3.
 Multiple Linear Regression Analysis of AHI and Other Factors

 Associated With Retinal Vessel Density

	Peripar Vessel D	oillary Density	Paraf Vessel 1	òvea Density
	β	Р	β	Р
AHI, times/h	-0.038	0.004*	-0.025	0.023*
Age, y	0.0252	0.448	0.052	0.066
HR, beats per min	-0.017	0.664	0.005	0.882
OPP, mm Hg	0.047	0.395	0.038	0.409
SE, diopters	-0.199	0.409	-0.041	0.838
IOP, mm Hg	0.059	0.642	0.203	0.067
BMI, kg/m <sup>2</sup>	-0.065	0.596	0.007	0.945
Inner retinal	0.070	0.016*	-0.004	0.918
thickness, µm				

Multiple linear regression analysis was performed with adjustment for the indicated variables.

\* P < 0.05 was considered statistically significant.

for detecting early retinal changes, and might enable early interventions. This concept might also apply to other ocular disorders, such as open-angle glaucoma, in which vascular factors play important pathologic roles.

Interestingly, although the vessel densities in the parafoveal and peripapillary areas were negatively correlated with AHI, the extent of the decrease seemed to be greater in the peripapillary area because each 10-unit decrease in AHI was associated with a 0.43% decrease in vessel density in the parafoveal area and 0.63% in the peripapillary area. Additionally, the moderate group had lower vessel density in the peripapillary area compared with the normal-to-mild group, but vessel density in the parafoveal area was similar in both groups. These findings suggest that the vascular impairment in moderate OSAS is more prominent in the peripapillary area. Lin et al.<sup>8</sup> previously reported that the RNFL was significantly thinner in patients with severe OSAS than in patients with mild OSAS, but the macular thickness was similar in both groups. This may also support our findings. Although it is unclear why the vascular impairment differs between the peripapillary and macular area, it might be explained as follows. The vessels in the peripapillary area originate from two systems, the central retinal artery and the short posterior ciliary arteries, whereas the vessels in the macula originate from the central retinal artery.<sup>33</sup> It was reported that, in glaucoma, the posterior ciliary arteries are most susceptible to the deleterious effects of high IOP, whereas the central retinal artery is more resistant to these effects.<sup>34</sup> In addition, Hosking et al.<sup>35</sup> found an abnormal



FIGURE 3. Correlations between nocturnal peripheral oxygen saturation and retinal vessel density in the parafoveal and peripapillary areas.

TABLE 4. Multiple Linear Regression Analysis of Lowest  $SpO_2$  and Other Factors Associated with Retinal Vessel Density at the Peripapillary Area

	Peripapillary Vessel Density	
	β	Р
Lowest SpO <sub>2</sub> , %	0.077	0.007*
Age, y	0.023	0.487
HR, beats/min	-0.026	0.462
OPP, mm Hg	0.053	0.344
SE, diopters	-0.236	0.331
IOP, mm Hg	0.033	0.792
BMI, kg/m <sup>2</sup>	-0.094	0.438
RNFL, µm	0.068	0.020*

Multiple linear regression analysis was performed with adjustment for the indicated variables.

\* P < 0.05 was considered statistically significant.

response to hypercapnia in the short posterior ciliary arteries, but not in the central retinal artery, in glaucoma. These findings suggest that the ciliary vascular system might experience more severe damage than the retinal vascular system in glaucoma, supporting our finding that the reduction in vessel density was more pronounced in the peripapillary area. However, the macular area contains only capillaries or small vessels, whereas the peripapillary area contains the four principal intraretinal arteries and veins. Kornfield and Newman<sup>36</sup> found differences in the flicker-evoked responses between the first- or second-order arterioles and capillaries. Therefore, the different origins and sizes of the vessels between the parafoveal and peripapillary areas might contribute to the prominent reduction in vessel density in OSAS patients.

Our study was limited by the number of subjects and its cross-sectional design. As OCT angiography was unable to distinguish the reduction of vascular diameter from the loss/ occlusion of the vessels, the pathologic change behind the reduction of vessel density found this time still needs to be further explored. As OCT angiography was unable to distinguish between the reduction in vascular diameter and loss/ occlusion of the vessels, the pathological reason for the reduction in vessel density found in the present study requires further investigation. The patients enrolled in our study did not have any ocular disorders. But, because they were newly diagnosed with OSAS and because OSAS is a chronic disease, future studies with a longer follow-up might provide more insight into the clinical relevance of our current findings.

**TABLE 5.** Multiple Linear Regression Analysis of Mean  $SpO_2$  and OtherFactors Associated With Retinal Vessel Density at the Peripapillary Area

	Peripapillary Vessel Density	
	β	Р
Mean SpO <sub>2</sub> , %	0.279	0.010*
Age, y	0.033	0.323
HR, beats/min	-0.034	0.344
OPP, mm Hg	0.061	0.279
SE, diopters	-0.230	0.346
IOP, mm Hg	0.054	0.677
BMI, kg/m <sup>2</sup>	-0.063	0.616
RNFL, µm	0.067	0.022*

Multiple linear regression analysis was performed with adjustment for the indicated variables.

\* P < 0.05 was considered statistically significant.

Future studies with a larger number of subjects and follow-up assessments might further improve our knowledge of the ocular effects of OSAS and the correlation between retinal vessel changes and other findings, such as retinal dysfunction, in OSAS patients.

In conclusion, we found that the vessel densities in the peripapillary and parafoveal areas decreased with greater severity of OSAS, and the decrease in vessel density was more prominent in the peripapillary area.

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