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Normal tension glaucoma in obstructive sleep apnea syndrome

A structural and functional study

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Abstract

This study characterized and evaluated normal tension glaucoma (NTG) in obstructive sleep apnea syndrome (OSAS).

In this retrospective, cross-sectional study, all participants were examined with polysomnography (PSG). Functional parameters of standard automated perimetry (SAP) were recorded. Structural parameters in optical coherence tomography angiography (OCTA) included peripapillary superficial vessel density (VD RPC), peripapillary whole-layer (VD NH), and superficial and deep macular area VD. Participants were categorized into perimetric and nonperimetric groups by SAP result. Low reliability of SAP and signal strength index <50 in OCTA were excluded.

Severity of OSAS was graded by apnea-hypopnea index (AHI) in PSG. Those with moderate/severe OSAS (AHI ≥ 15, n = 39) had longer neck circumference and shorter ocular axial length than mild OSAS (AHI < 15, n = 14). Furthermore, there was significantly higher AHI and larger neck circumference in the NTG perimetric group (n = 27) than in the control group (n = 26; $p < 0.001$ and $p = 0.047$, respectively). Superficial and deep-layer peripapillary and macular area VD significantly decreased in the perimetric group. Overall, structural and functional parameters show that VF PSD was negatively correlated with VD NH and VD RPC ($p = 0.007$, $p = 0.015$); and VF MD was positively correlated with VD NH ($p = 0.029$), but not significantly to VD RPC ($p = 0.106$).

OSAS is a risk factor of NTG. With aid of OCTA, whole-layer retinal capillary dropout supports that the vascular dysregulation of OSAS leads to NTG.

Abbreviations: AASM = American Association of Sleep Medicine, AHI = apnea-hypopnea index, BCVA = best-corrected visual acuity, BMI = body mass index, CPAP = continuous positive airway pressure, GCC = ganglion cell complex, GHT = glaucoma hemifield test, ILM = internal limiting membrane, IOP = intraocular pressure, IPL = inner plexiform layer, MD = mean deviation, MDVD = macular deep vessel density, NH = nerve head (peripapillary whole-layer), NTG = normal tension glaucoma, OCT = optical coherence tomography, OCTA = optical coherence tomography angiography, ODI = oxygen desaturation index, OSAS = obstructive sleep apnea syndrome, PACG = primary angle-closure glaucoma, POAG = primary open angle glaucoma, PSD = pattern standard deviation, PSG = polysomnography, RNFL = retinal nerve fiber layer, RPC = radial peripapillary capillary (peripapillary superficial), RPE = retinal pigment epithelium, SAP = standard automated perimetry, SSADA = split-spectrum amplitude-decorrelation angiography, VD = vessel density, VF = visual field.

Keywords: normal tension glaucoma, obstructive sleep apnea syndrome, optical coherence tomography angiography

1. Introduction

To the best of our knowledge, obstructive sleep apnea syndrome (OSAS) is an entity with prevalence 2% to 5% in middle-aged adults, and it may be undetected for patients without definite diagnoses. OSAS patients usually snore loudly and have excessive daytime sleep and insomnia; there are several risk factors for OSAS, including male sex, obesity, thick neck, and upper respiratory tract abnormality, according to the literature.[1] OSAS is characterized with intermittent apnea and upper airway collapse during sleep. Recurrent airway interference triggers hypoxia, hypercapnia, and intrathoracic pressure changes that consequently affect autonomic, hemodynamic, humoral, and neuroendocrine regulation.[2] The clinical standards for OSAS diagnosis are overnight polysomnography (PSG) and American Association of Sleep Medicine (AASM) criteria using the apnea–hypopnea index (AHI). The severity of OSAS is graded as mild ($AHI < 15$), moderate ($15 \leq AHI < 30$), or severe ($AHI \geq 30$). Hypoxemia will cause cardiovascular morbidity and mortality such as by stroke, hypertension, and heart failure.[3] Ocular manifestations of OSAS include floppy eyelids; retinal vascular tortuosity and congestion; papilledema; non-arteritic ischemic optic neuropathy; and normal tension glaucoma (NTG) have been illustrated.[4–9]

Editor: Stela Vujosevic.

This study was supported by the Chang Gung Memorial Hospital under Grant CMRPG2G0262. The funding organization had no role in the design or conduct of this research.

The authors have no conflicts of interest to disclose.

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How to cite this article: Chuang LH, Koh YY, Chen HS, Lo YL, Yu CC, Yeung L, Lai CC. Normal tension glaucoma in obstructive sleep apnea syndrome-a structural and functional study. Medicine 2020;99:13(e19468).

Received: 2 August 2019 / Received in final form: 11 December 2019 / Accepted: 4 February 2020

http://dx.doi.org/10.1097/MD.0000000000019468

Glaucoma is a wide-spectrum disease with progressive vision deterioration, and is one of the leading causes of blindness in the world.[10] The mechanism of hypertensive glaucoma is complex; the conventional theory is that the aqueous auto-regulation dysfunction leads to increase of intraocular pressure (IOP). In contrast, for NTG with normal IOP, there is a theory of mechanism that abnormal ocular blood flow induces optic nerve dysfunction; the autonomic nerve system and circadian rhythms may play a role in glaucoma.

Although a mainstay of NTG treatment is lowering IOP to preserve the function of the optic nerve, half of cases still result in disease progression under IOP control after long-term follow-up.[11] The pathomechanism is still unknown for glaucomatous optic nerve change with irreversible vision loss. At present, monitoring and managing glaucoma is a crucial and challenging issue.[12]

In 2000, Onen et al used a questionnaire and published a retrospective study without performing PSG, showing that a high incidence of POAG was found in sleep-disorder breathing. Recent studies using PSG for evaluation of OSAS severity have shown that there is a higher prevalence (around 20%), with most having NTG with retinal nerve fiber layer (RNFL) defects, among OSAS cases. Patt et al first illustrated defective endothelial function in OSAS microcirculation with subcutaneous vascular tissue.[13] Lin et al have demonstrated through optical coherence tomography (OCT) that RNFL decreases in OSAS among Asian populations.[14] More advanced, Yu et al have demonstrated that in an optical coherence tomography angiography (OCTA) study of OSAS, the vessel density (VD) decreases in parafoveal and peripapillary areas, and is further correlated with the severity of OSAS.[15] Beyond illustrating structural changes measured with OCTA, whether the impact of vascular dysfunction on ocular microcirculation of the optic nerve and macular area is related to vision dysfunction awaits clarification.

Both NTG and OSAS are chronic progressive neurovascular diseases that may be confounded with vision deterioration during long-term care by physicians. Therefore, in our study, it is first essential to identify and evaluate the correlation of ocular microcirculation with OCTA and visual function through visual field examination of NTG in OSAS.

2. Materials and methods

This is a retrospective, cross-sectional, hospital-based observational study. In total, there were 53 OSAS cases enrolled in our study. According to the Helsinki Declaration of 1975 (1983 revision), this study via chart review was performed and was approved by the Institutional Review Board of Chang Gung Memorial Hospital, Keelung, Taiwan. Demographic data, including the severity of OSAS, duration of OSAS, and other systemic diseases, was documented. By examination with overnight PSG, the severity of OSAS was graded according to the AHI and defined as the total number of apnea and hypopnea incidents occurring per hour of sleep. Although OSAS was graded as normal to mild (AHI <15), moderate (AHI $=15$ to <30), or severe (AHI ≥ 30),[16] in our study, we used categories of mild (AHI <15) and moderate/severe (AHI ≥ 15) to analyze the ocular manifestation in OSAS. In addition to AHI, oxygen desaturation was measured with a subcutaneous finder pulse oximeter and scored as oxygen desaturation index (ODI) as acquired from the PSG test. All participants first were diagnosed with OSAS and then had the ocular examination accordingly within 6 months.

In general, ocular examination was the best-corrected visual acuity (BCVA); slit-lamp biomicroscope; gonioscopy; IOP measured with applanation tonometer; axial length checked with biometry (IOLMaster; Carl Zeiss, Jena, Germany); and indirect ophthalmoscopy for the fundus. Related ocular findings and ocular surgery history were also documented. For structural evaluation of the optic nerve and macular area, the OCTA imaging system (AngioVue; Optovue, Inc, Fremont, CA) was used to measure blood flow, and split-spectrum amplitude-decorrelation angiography (SSADA) was performed. The imaging system uses an 840-nm superluminescent diode and has an A-scan rate of 70,000 scans per second. Parameters were recorded in detail, based on version A2016.2. 0.35. The default settings for the en face retinal image were superficial vascular layer: 3 μm below internal limiting membrane (ILM) to 15 μm below inner plexiform layer (IPL); and deep vascular layer: 15 μm below IPL to 70 μm below IPL. The macular area scanned was 3.00×3.00 mm.

There were two settings for en face disc imaging. The "Nerve head" mode was used to calculate the peripapillary VD of capillaries, from top of image to retinal pigment epithelium (RPE), and the "RPC" mode was used to calculate the VD, from ILM to posterior boundary of retinal nerve fiber layer (RNFL). The optic disc image was analyzed, with an area 4.5 mm in diameter.[17–19] In addition, the summary of parameters of OCTA, including RNFL analysis, ONH analysis, and ganglion cell complex (GCC) analysis, were recorded and analyzed.

NTG was defined as normal IOP (IOP lower than 21 mm Hg) with open angle and glaucomatous optic neuropathy. Regarding objective quantification of the visual function for OSAS, standard automated perimetry (SAP) (Humphrey Field Analyzer II; Carl Zeiss Meditec, Dublin, CA) was collected. For categorization of all OSAS participants, the perimetric group was defined with NTG as the study group. Enrolled cases with glaucomatous VF damage were reported as glaucoma hemifield test (GHT) outside normal limits, or PSD was significant at $P<5\%$. And with a cluster of three or more adjacent points in typical glaucomatous locations, all of which were depressed on the pattern deviation plot at a $P<5\%$ level, and one of which was depressed at a $P<1\%$ level in at least two consecutive plots. Participants with GHT within normal limits were classified as the control group. In this study, we recorded both mean deviation (MD) and pattern standard deviation (PSD) of SAP for analysis of the severity of visual field defect.

Exclusion criteria were ocular hypertensive history, including primary open angle glaucoma (POAG) and primary angle-closure glaucoma (PACG); non-arteritic anterior ischemic optic neuropathy; arteritic anterior ischemic optic neuropathy; optic neuritis; diabetic retinopathy; hypertensive retinopathy; or other maculopathy. Low reliability of VF exam (≥33% fixation losses, ≥10% false-positives, and ≥10% false-negatives) and signal strength index <50 of OCTA were excluded in this study.

For comparison of demographic data between groups, we analyzed via the chi-square test. To compare the continuous variables of OCTA and VF data between groups, the independent sample *t* test was used. In addition, we analyzed the relationship between paired data for SAP and OCTA using Pearson's correlation coefficient. *P* values of $<.05$ were considered statistically significant. Statistical analyses were performed using SPSS software, version 20.0 (SPSS, Inc, Chicago, IL).

Table 1

Demographic data of patients with OSAS.

	Severity of OSAS		
	AHI < 15 (n = 14)	AHI ≥ 15 (n = 39)	*P*
Age, mean ± SD*	48.21 ± 16.93	54.10 ± 11.56	.16
Sex, n (%)†			.43
Male	10 (71.4%)	33 (84.6%)	
Female	4 (28.6%)	6 (15.4%)	
AHI, mean ± SD*	9.83 ± 2.89	48.93 ± 17.19	**<.001**
ODI, mean ± SD*	7.49 ± 4.39	44.35 ± 19.50	**<.001**
Duration of OSAS, mean ± SD*	2.79 ± 4.25	2.87 ± 3.13	.94
Neck circumference, mean ± SD*	37.61 ± 3.43	39.87 ± 3.62	**.047**
BMI, mean ± SD*	25.71 ± 3.35	27.56 ± 3.94	.12
Diabetes mellitus, n (%)†	0	8 (20.5%)	.09
Hypertension, n (%)†	4 (28.6%)	19 (48.7%)	.19

AHI = apnea–hypopnea index, BMI = body mass index, ODI = oxygen desaturation index, OSAS = obstructive sleep apnea syndrome.

* Comparing the values between two groups via independent sample *t* test.

† Comparing the values between two groups via Chi-square test.

Table 2

Ocular characteristics of OSAS.

	Severity of OSAS		
	AHI < 15 (n = 14)	AHI ≥ 15 (n = 39)	*P*
logMAR VA, mean ± SD*	0.18 ± 0.21	0.21 ± 0.32	.76
IOP, mean ± SD*	15.67 ± 3.14	15.32 ± 2.50	.68
CCT, mean ± SD*	538.71 ± 53.66	529.49 ± 93.39	.723
AL, mean ± SD*	25.08 ± 1.74	20.97 ± 10.05	**.012**
VF MD, mean ± SD*	−0.79 ± 1.80	−2.79 ± 2.94	**.02**
VF PSD, mean ± SD*	1.55 ± 1.72	4.14 ± 2.59	**.001**
VD NH, mean ± SD*	57.61 ± 3.36	54.58 ± 4.16	**.02**
VD RPC, mean ± SD*	60.11 ± 4.04	57.05 ± 5.48	.06
RNFL, mean ± SD*	96.64 ± 10.64	88.72 ± 13.58	.05
MVD Sup, mean ± SD*	50.28 ± 4.69	49.52 ± 4.09	.57
MVD Deep, mean ± SD*	57.14 ± 1.81	55.53 ± 4.29	.06
GCC, mean ± SD*	96.28 ± 6.34	88.13 ± 11.89	**.003**

AL = axial length, CCT = central corneal thickness, GCC = ganglion cell complex, IOP = intraocular pressure, MVD = macular vessel density, RNFL = retinal nerve fiber layers, VD NH = vessel density of optic nerve head, VD RPC = vessel density of radial peripapillary capillary network, VF MD = visual field mean deviation, VF PSD = visual field pattern standard deviation.

* Comparing the values between two groups via independent sample *t* test.

3. Results

In our retrospective study, there were a total of 53 cases enrolled; all had PSG performed in the same sleep center. At first, to identify the impact of severity of OSAS, we compare the groups with mild (AHI < 15) (n = 14) and moderate/severe OSAS (AHI ≥ 15) (N = 39) in ocular microcirculation and visual function accordingly. The demographic data for mild and moderate/severe OSAS is listed in Table 1. Via the PSG test, AHI and ODI were significantly higher in the moderate/severe group than in the mild group (Table 1). Age, gender, body mass index (BMI), and duration of OSAS diagnosis history were not significantly different between the mild and moderate/severe groups. Neck circumference was larger in the moderate/severe OSAS (39.87 ± 3.62 cm) group, illustrating that thicker necks were found in comparison to the mild OSAS group (37.61 ± 3.43 cm) ($P = .047$). Among ocular characteristics, ocular axial length with moderate/severe OSAS was significantly shorter than that with mild OSAS (20.97 ± 10.05 mm vs 25.08 ± 1.74 mm, $P = .02$). The other ocular characteristics, such as IOP or central corneal thickness, made no difference.

In comparison of ocular microcirculation characteristics with aid of OCTA between mild and moderate/severe OSAS, the peripapillary superficial VD (RPC) was 60.11% vs 57.05%, and whole VD (NH) was 57.61% vs 54.58% ($P = .06$, $P = .02$, respectively) (Table 2). Peripapillary whole-layer microcirculation, in terms of VD NH, was significantly lower with moderate/severe OSAS. In comparison to mild OSAS, RNFL thickness decreased in moderate/severe OSAS, though it was not significant. Macular area VD of the superficial and deep layers with the whole image decreased, though this was not significant ($P = .38$, $P = .12$). However, the GCC thickness demonstrated significant decreases in moderate/severe cases (Table 2).

For comparison of visual function, we recorded the visual field and conducted analysis. With moderate/severe OSAS, MD was −2.79 ± 2.94, lower than with mild OSAS (−0.79 ± 1.80), and PSD was 4.14 ± 2.59, higher than with mild OSAS (1.55 ± 1.72) ($P = .02$, $P = .001$, respectively). Visual function was significantly worse in moderate/severe than in mild OSAS, according to the SAP result (Table 2).

As the next part of our study, we classified the participants based on SAP results. There were 27 cases in the perimetric group as NTG with glaucomatous change, and 26 nonperimetric cases as the control. Comparing the demographic data of the two groups, age, gender, BMI, and OSAS duration were similar (Table 3). BMI was higher in the perimetric group, though this was not significant. A novel finding is that neck circumference was greater in the perimetric group, and that this was significant (38.40 cm vs 40.11 cm, $P = .047$). According to the PSG data, the AHI of the perimetric group was significantly higher than the control group (31.554 vs 45.389, $P < .001$, *t* test). In the perimetric group, there were 15 moderate and 10 severe OSAS cases, therefore, high prevalence of OSAS who had AHI ≥ 15 of was noted (92.6%) and there were 8 cases (29.6%) with continuous positive airway pressure (CPAP). The data demonstrated more severe OSAS in the perimetric group. Parallel with AHI, the severity of oxygen desaturation during sleep also revealed severe hypoxia, with higher ODI in the perimetric group (39.93 vs 29.09, $P < .001$, *t* test). In comparison of visual function, the SAP was significantly different between the two groups: visual field MD (−0.7 ± 1.75 vs −3.77 ± 2.84, $P < .001$)

Table 3

Demographic data of perimetric and nonperimetric group of OSAS.

	Perimetric (n = 27)	Nonperimetric (n = 26)	*P*
Age, mean ± SD*	54.19 ± 10.98	50.85 ± 15.34	.16
Sex, n (%)†			.50
Male	23 (85.2%)	20 (76.9%)	
Female	4 (14.8%)	6 (23.1%)	
AHI, mean ± SD*	45.39 ± 18.34	31.55 ± 25.15	**<.001**
ODI, mean ± SD*	39.93 ± 20.45	29.09 ± 25.51	**<.001**
Duration of OSAS, mean ± SD*	2.70 ± 3.31	3.00 ± 3.58	.94
Neck circumference, mean ± SD*	40.11 ± 3.79	38.40 ± 3.42	**.047**
BMI, mean ± SD*	27.91 ± 4.06	26.20 ± 3.49	.12
Diabetes mellitus, n (%)†	7 (25.9%)	1 (3.8%)	.05
Hypertension, n (%)†	14 (51.9%)	9 (34.6%)	.21

AHI = apnea–hypopnea index, BMI = body mass index, ODI = oxygen desaturation index, OSAS = obstructive sleep apnea syndrome.

* Comparing the values between two groups via independent sample *t* test.

† Comparing the values between two groups via Chi-square test.

Table 4

Comparison of ocular characteristics of perimetric and nonperimetric groups.

	Perimetric (n = 27)	Nonperimetric (n = 26)	*P*
logMAR VA, mean ± SD*	0.26 ± 0.37	0.14 ± 0.17	.12
IOP, mean ± SD*	15.36 ± 2.89	15.47 ± 2.45	.87
CCT, mean ± SD*	529.07 ± 111.54	534.88 ± 42.81	.81
AL, mean ± SD*	20.99 ± 10.32	23.16 ± 6.98	.37
VF MD, mean ± SD*	−3.77 ± 2.84	−0.70 ± 1.75	**<.001**
VF PSD, mean ± SD*	4.85 ± 2.72	2.01 ± 1.58	**<.001**
VD NH, mean ± SD*	53.67 ± 4.40	57.16 ± 3.06	**.002**
VD RPC, mean ± SD*	56.06 ± 5.94	59.72 ± 3.76	**.01**
RNFL, mean ± SD*	84.67 ± 13.51	97.19 ± 9.60	**<.001**
MVD Superficial, mean ± SD*	48.41 ± 4.19	51.08 ± 3.89	**.02**
MVD Deep, mean ± SD*	54.55 ± 4.69	57.42 ± 1.89	**.006**
GCC, mean ± SD*	85.43 ± 13.22	95.32 ± 5.41	**.001**

AL = axial length, CCT = central corneal thickness, GCC = ganglion cell complex, IOP = intraocular pressure, MVD = macular vessel density, RNFL = retinal nerve fiber layers, VD NH = vessel density of optic nerve head, VD RPC = vessel density of radial peripapillary capillary network, VF MD = visual field mean deviation, VF PSD = visual field pattern standard deviation.

* Comparing the values between two groups via independent sample *t* test.

and visual field PSD (2.01 ± 1.58 vs 4.85 ± 2.72, $P < .001$) (Table 4).

Furthermore, the structural changes from ocular microcirculation for both peripapillary and macular area were analyzed with the aid of OCTA. There were parameters measuring different layers regarding peripapillary VD of the capillaries: "Nerve Head," scanning the whole retinal layer, and "RPC,", scanning the superficial retinal layer in OCTA, were analyzed (Table 4). In the perimetric group, these two parameters for superficial-layer (VD RPC) (56.06 vs 59.72%, $P = .01$) and whole retinal layer (VD NH) (53.67 vs 57.16%, $P = .002$) illustrated peripapillary capillary dropout more severe than in the control group. Peripapillary RNFL thickness and GCC thickness also demonstrated significant thinning in the perimetric group ($P < .001$, $P = .001$, respectively).

In addition to the peripapillary area as the OCTA setting, the superficial and deep-layer VD in the macular area showed more significant capillary dropout in the perimetric group ($P = .02$) than in the control group ($P = .006$). To summarize, for both the peripapillary and macular area, the capillary dropout was significantly diminished in deep and superficial retinal layer measurement with OCTA, in both groups. Our study also

Table 5

Pearson's coefficient correlation of ocular microcirculation and visual function in OSAS.

Variables	Mean		Age	VA	IOP	NC	OSASD	BMI	AHI	ODI	VF MD	VF PSD	VD NH	VD RPC	MSVD	MDVD	RNFL	GCC
Age	52.55 ± 13.275	*r*	1															
		P	0															
VA (logMAR)	0.202 ± 0.291	*r*	0.12	1														
		P	.38	0														
IOP	15.413 ± 2.659	*r*	**−0.36**†	−0.13	1													
		P	**.01**	.34	0													
NC	39.274 ± 3.682	*r*	−0.20	−0.11	**0.34***	1												
		P	.14	.42	**.01**	0												
OSASD	2.85 ± 3.416	*r*	**0.31***	−0.07	−0.07	0.04	1											
		P	**.02**	.62	.62	.78	0											
BMI	27.068 ± 3.852	*r*	−0.24	−0.01	0.25	**0.68**†	−0.01	1										
		P	.08	.94	.07	**<.001**	.93	0										
AHI	38.602 ± 22.825	*r*	0.22	−0.15	−0.11	0.26	0.11	0.221	1									
		P	.12	.30	.45	.06	.46	.11	0									
ODI	34.613 ± 23.491	*r*	**0.28***	−0.11	−0.07	0.25	0.06	0.24	**0.91**†	1								
		P	**.04**	.43	.64	.07	.68	.08	**<.001**	0								
VF MD	-2.2606 ± 2.812	*r*	−0.09	**−0.42**†	0.17	−0.08	0.11	−0.20	−0.07	−0.07	1							
		P	.50	**.002**	.22	.57	.44	.16	.63	.62	0							
VF PSD	3.4581 ± 2.639	*r*	0.02	**0.40**†	−0.07	0.13	−0.11	0.20	0.25	0.21	**−0.83**†	1						
		P	.89	**.003**	.62	.34	.42	.15	.07	.13	**<.001**	0						
VD NH	55.3815 ± 4.155	*r*	0.03	**−0.40**†	0.10	−0.23	0.13	−0.15	−0.006	0.03	**0.30***	−0.36†	1					
		P	.81	**.003**	.48	.10	.34	.28	.97	.86	**.03**	.01	0					
VD RPC	57.858 ± 5.281	*r*	−0.01	−0.01	**−0.45**†	0.06	−0.14	−0.03	−0.05	−0.05	0.22	−0.33*	**0.86**†	1				
		P	.94	.94	**.001**	.65	.31	.85	.73	.71	.11	.02	**<.001**	0				
MSVD	49.722 ± 4.224	*r*	−0.03	−0.16	0.002	−0.21	−0.23	−0.25	−0.21	−0.25	0.13	−0.25	0.17	0.13	1			
		P	.83	.24	.99	.14	.10	.07	.13	.07	.36	.08	.24	.37	0			
MDVD	55.956 ± 3.848	*r*	−0.18	−0.26	0.18	−0.13	−0.21	−0.07	−0.14	−0.19	0.18	−0.27	**0.39**†	**0.36**†	**0.67**†	1		
		P	.20	.06	.20	.37	.13	.62	.32	.19	.19	.05	**.004**	**.007**	**<.001**	0		
RNFL	90.81 ± 11.245	*r*	0.08	−0.23	−0.02	−0.14	0.16	−0.12	−0.002	0.06	**0.36**†	−0.38†	**0.45**†	**0.40**†	0.10	0.06	1	
		P	.56	.10	.91	.32	.26	.40	.99	.65	**.008**	.006	**.001**	**.003**	.46	.69	0	
GCC	90.282 ± 11.245	*r*	0.12	−0.19	−0.14	−0.21	0.16	−0.19	−0.12	−0.11	**0.40**†	−0.51†	**0.40**†	**0.38**†	0.25	0.03	**0.80**†	1
		P	.39	.18	.33	.13	.25	.17	.38	.43	**.003**	<.001	**.003**	**.005**	.07	.83	**<.001**	0

AHI = apnea–hypopnea index, BMI = body mass index, GCC = ganglion cell complex, IOP = intraocular pressure, ODI = oxygen desaturation index, MDVD = macular deep vessel density, MSVD = macular superficial vessel density, NC = neck circumference, OSASD = duration of obstructive sleep apnea syndrome, RNFL = retinal nerve fiber layers, VA = visual acuity, VD NH = vessel density of optic nerve head, VD RPC = vessel density of radial peripapillary capillary network, VFMD = visual field mean deviation, VF PSD = visual field pattern standard deviation.

* Correlation is significant at the .05 level (2-tailed).

† Correlation is significant at the .01 level (2-tailed).

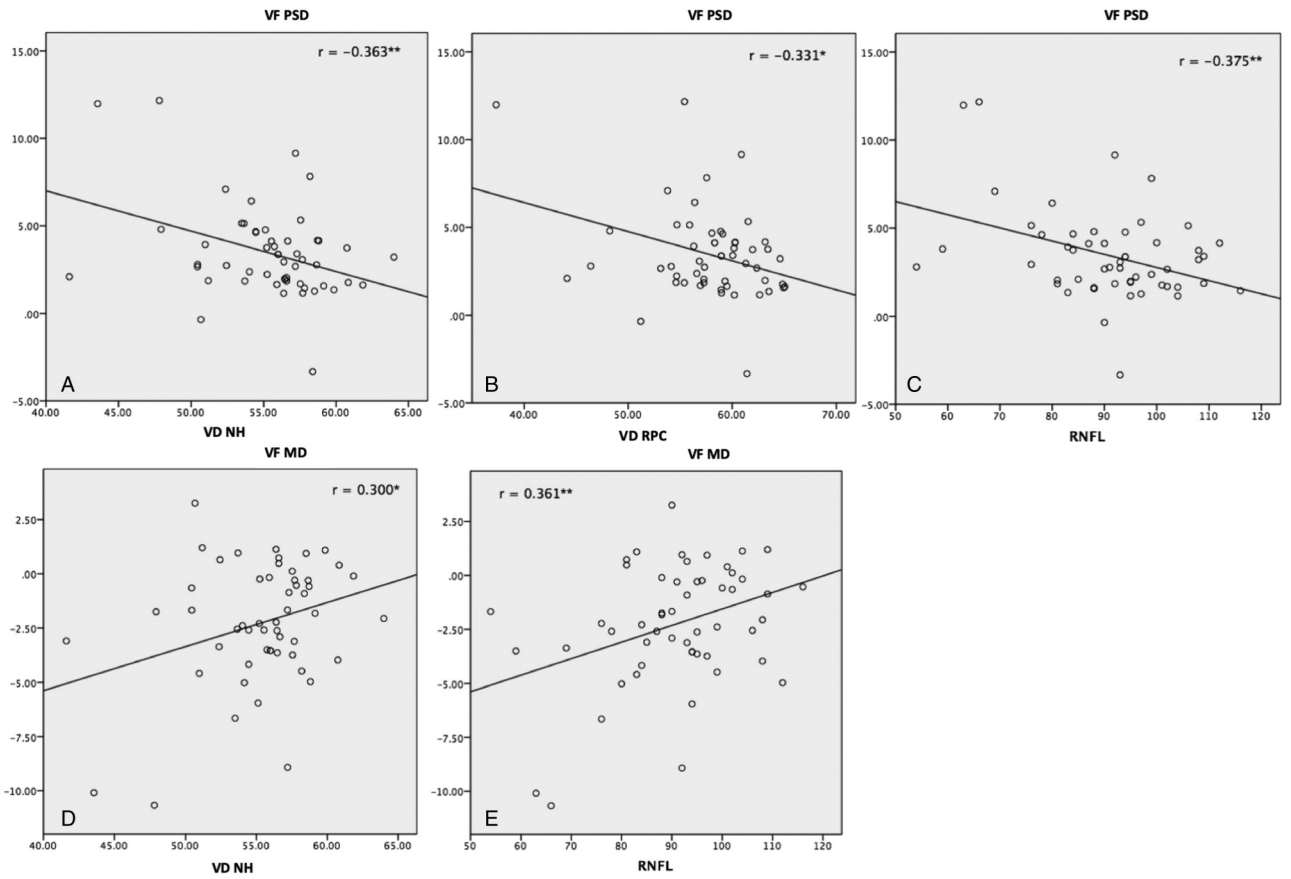

Figure 1. Correlation between visual field defect and peripapillary vessel density in OSAS. (A–C) show visual field pattern standard deviation (VF PSD) vs vessel density of optic nerve head (VD NH), vessel density of radial peripapillary capillary network (VD RPC) and retinal nerve fiber layers (RNFL); (C and D) show visual field mean deviation (VF MD) vs VDNH and RNFL. *Correlation is significant at the .05 level (2-tailed). **Correlation is significant at the .01 level (2-tailed).

demonstrated the parallel results of RNFL and GCC thinning of NTG in OSAS.

For the entire group of participants evaluated with PSG, we would like to further elucidate the relationship between demographic data related to severity of OSAS and visual function and parameters of ocular microcirculation assessed through OCTA measurements. After analysis with Pearson correlation for this paired data, AHI and ODI via PSG did not correlate to VD RPC, VD NH nor VF MD, VF PSD.

As structural optic nerves change based on OCTA measurement, the correlation to visual function based on VF in OSAS was analyzed as well (Table 5). Among the OSAS with normal IOP, VF PSD negatively correlated with VD NH ($r=-0.36$, $P=.007$) and VDRPC ($r=-0.33$, $P=.02$). VF MD was positively correlated with VD NH ($r=0.30$, $P=.03$), but not correlated with VD RPC ($r=0.22$, $P=.11$). Therefore, VD NH had significant correlation with both VF PSD and VF MD. Additionally, VF MD and VF PSD were also correlated with RNFL, as shown in the scatter plot (Fig. 1). As for correlation between peripapillary VD and macular area VD, VDRPC and VDNH also positively correlated with deep MVD ($r=0.36$, $P=.007$; $r=0.39$, $P=.004$) and GCC ($r=0.38$, $P=.005$; $r=0.40$, $P=.003$), but not significant in superficial MVD ($P=0.37$, $P=.17$) (Fig. 2).

4. Discussion

After overnight PSG exam, OSAS can be diagnosed with certainty. For OSAS patients, endothelial dysfunction of systemic circulation may lead to cardiovascular disease.[13] NTG is one of the ocular manifestation of OSAS which causes visual deterioration.[6–8] Although obesity is one of the characteristics of OSAS, the other predisposing factors of associated ocular manifestation and guidelines for OSAS to evaluate ocular structural and functional changes need to be established.

We first categorized mild (AHI < 15) and moderate/severe OSAS (AHI ≥ 15) groups, to identify demographic data and ocular manifestation. Similar to prior studies relating to predisposing factors for OSAS, neck circumference with moderate/severe OSAS was significantly larger than that with mild OSAS (Table 1). A novel finding is that the ocular axial length was significantly shorter in moderate/severe OSAS (Table 2).

Despite there being no consensus for ocular microcirculation diminished with conventional methods of categorizing OSAS severity by AHI as mild (AHI < 15), moderate (AHI = 15 to <30), and severe (AHI ≥ 30),[15,18] we have newly illustrated that moderate/severe OSAS with AHI ≥ 15 has ocular structural and functional changes significantly worse than with mild OSAS at AHI < 15. For structural changes evaluated via OCTA parameters, the significant decrease of the peripapillary disc VD of the

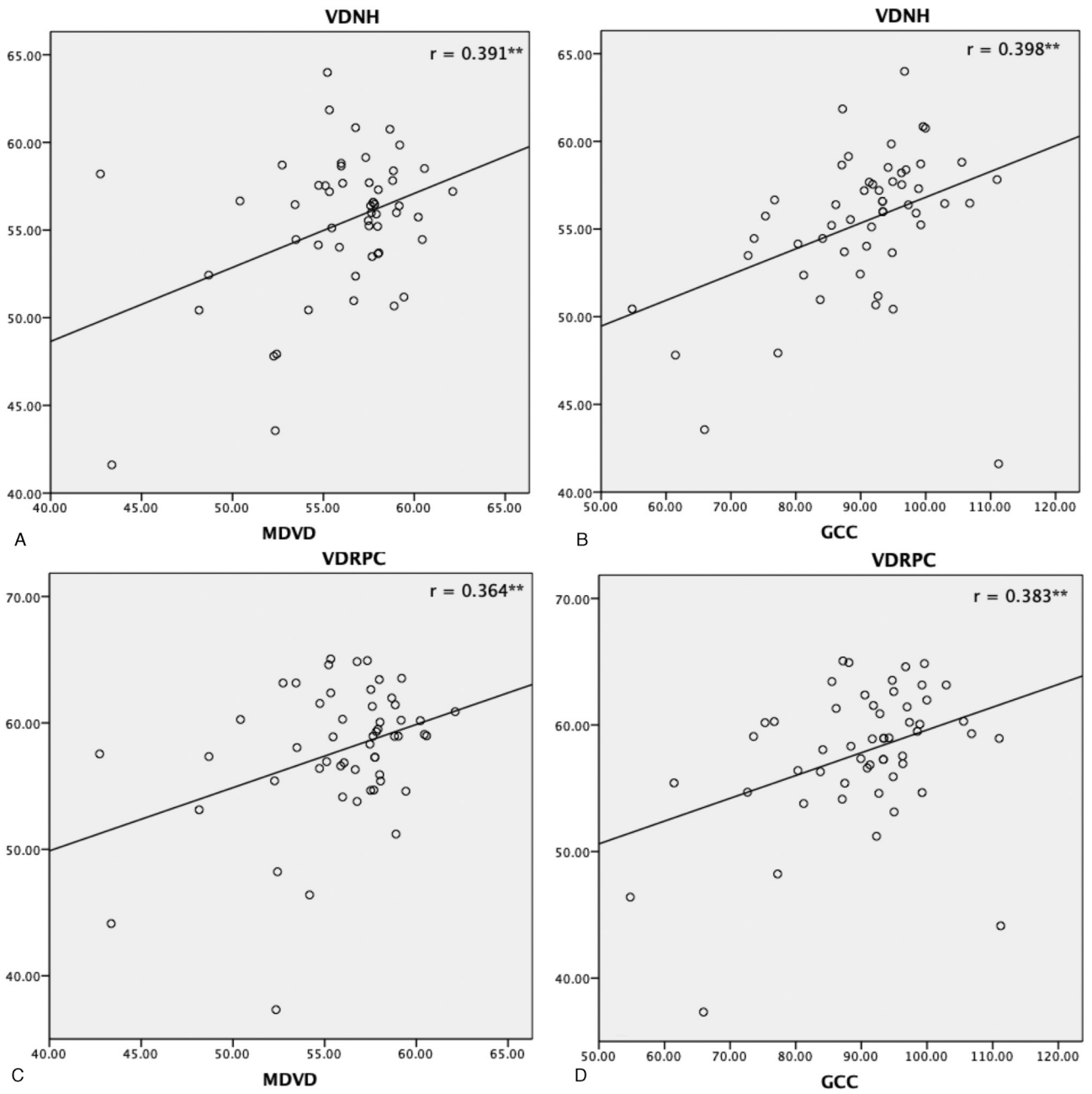

Figure 2. Correlation between peripapillary vessel density and deep-layer macular vessel density in OSAS. (A and B) show (VD NH) vs macular deep vessel density (MDVD) and ganglion cell complex (GCC); (C and D) show vessel density of radial peripapillary capillary network (VD RPC) vs MDVD and GCC. *Correlation is significant at the .05 level (2-tailed). **Correlation is significant at the .01 level (2-tailed).

whole-layer (VD NH) instead of superficial-layer (VD RPC) demonstrates that whole retinal layer capillary dropout is related to severity of OSAS. Moreover, visual function change in SAP recorded via MD and PSD was demonstrated to be significantly worse in moderate/severe OSAS (AHI $\geq$ 15). However, for the VD of the macular area, there was no difference with this method of categorization for OSAS (Table 2). The difference in microcirculation for the peripapillary and macular areas might imply a greater impact of hypoxia to the peripapillary capillaries supplied from the posterior ciliary artery than to capillaries in the macular area supplied from the central retinal artery. This result also supports the hypothesis of vasculopathy of OSAS leading to NTG. Hence, categorizing OSAS severity via AHI 15 may help to suggest further pre-ophthalmic examination as a guideline for OSAS long-term care.

Secondarily, for all OSAS with normal IOP, we classified participants as perimetric and nonperimetric groups, according to glaucomatous change by SAP. There was no significant difference in systemic disease, DM, hypertension, BMI, or duration of OSAS between groups. Although there was similar BMI, neck circumference was significantly greater in the perimetric group, and it is a risk factor for screening glaucoma

in OSAS. Furthermore, both AHI and ODI's relation to severity of OSAS was significantly different, illustrating that among the perimetric group, OSAS was more severe than in the control (Table 3). Recently, Yamada et al have demonstrated that in open angle glaucoma patients with OSAS, there is increased oxidative stress, with higher Diacron-reactive oxygen metabolites and biological antioxidant potential, and steeper MD slope than with non-OSAS.[20]

As we know, NTG is related to an unknown mechanism, and glaucomatous optic neuropathy may still progress during treatment. One possible theory for pathogenesis of NTG is perfusion deficit and vascular dysregulation.[21,22] Although there has been no study of tissue biopsies of retinal vessels proving the change in OSAS, Patt et al have illustrated reversible endothelial dysfunction in the systemic microcirculation of OSAS.[13] Our data also supports the idea that OSAS severity relates to hypoxia, and that vascular change may play a role in the mechanism of NTG as an ocular manifestation.

Furthermore, Lin et al have found that the incidence of OSA is also higher in Asian populations, and that RNFL changes have been concluded. There is at present no consensus on the structural and functional correlation of NTG with OSAS, or ways to monitor the changes; appropriate intervention needs further evaluation. There has been no large-scale study, but simultaneous structural and functional evaluation in our study support that the idea that NTG with diminished ocular microcirculation is found in OSAS. In our study, NTG in OSAS was identified with a glaucoma definition, and ocular microcirculation was achieved with aid of OCTA (AngioVue) during the study period. As an important parameter regarding optic disc area microcirculation, the radial peripapillary capillary (RPC) layer is the most superficial layer of capillaries, and the source of nutrition to retinal ganglion cells.[23] Currently, most studies have elucidated superficial VD decrease through AngioVue OCTA measurement in primary open angle glaucoma.[24–26] Akagi et al have further demonstrated that ocular microvascular reduction is associated with region-specific VF defects in glaucomatous eyes.[24] However, deeper capillary networks have been illustrated to be structurally normal in glaucoma by using Speckle variance OCTA.[27] In contrast to this, in our analysis for NTG in OSAS, participants' measured changes in both superficial and whole-layer capillary dropout of the peripapillary area and macular area were significantly decreased in the perimetric group (Table 4). This echoes our previous finding that peripapillary whole-layer vascular density VD NH (default set from top of image to RPE) significantly decreases in moderate/severe OSAS; and the results for whole-layer change in the perimetric group illustrate that whole-layer endothelial dysfunction causing vasculopathy plays a role in glaucomatous optic nerve change in OSAS. This is the first study using AngioVue OCTA to demonstrate decreased peripapillary and macular VD in NTG with OSAS.

In addition, we evaluated the relationships between PSG data, OCTA parameters, and visual field defects for the entire participant group. AHI and ODI, related to severity of OSAS by PSG, did not correlate to BMI, neck circumference, VD RPC, VD NH, or VF, in our study (Table 5). Although the study by Yu[15] illustrated that AHI is negatively correlated with peripapillary VD, clinically we found that AHI and ODI may vary with body weight changes, nasolaryngeal surgery, or CPAP use. With normal IOP status, Shin et al demonstrated that in NTG, although both superficial and deep-layer VD decrease, worse VF MD and RNFL thickness is significantly correlated with superficial VD, as measured in a 6×6 mm region disc scan by AngioPlex (Carl ZeissMeditec).[28] For OSAS, we found whole-layer capillary VD to be correlated with visual field defects, presented via both MD and PSD, yet superficial VD only correlated with VF PSD (Table 5). Additionally, as we mentioned above, comparing mild and moderate/severe OSAS and VD NH showed significant differences; therefore, whole-layer capillary VD measurement may identify the impact rather than superficial-layer capillary VD in OSAS. In addition, the other ocular structural parameters of peripapillary and macular area, including RNFL thickness and GCC thickness, also correlated with peripapillary VD RPC and VD NH (Figs. 1 and 2). This correlation implies that the vasculopathy of OSAS might lead to collateral damage to the superficial to deep ocular microcirculation in the macular area.

There are some limits to our study, including a small sample size, cross-sectionality, and a retrospective nature. Similar to other studies with OCTA, the flow projection artifacts for deep-layer vascular density should be considered in image processing. More exploration of longitudinal studies for the influence of ocular microcirculation after managing OSAS, with or without glaucoma, is necessary for chronic disease. Although the exact mechanism of vascular impact on the optic nerve is unknown, compared to conventional OCT, OCTA can offer more information related to ocular microcirculation for OSAS at different severities. In addition to PSG with oxygen desaturation measurement, simultaneous OCTA helps to evaluate the severity of OSAS in vivo, and to predict visual function through the peripapillary VD.

In conclusion, we have identified that thick neck and high AHI are predisposing factors for NTG within OSAS. Whole-layer vascular change with capillary dropout was found in these cases. The correlation of OCTA parameters with visual field defects shows that OCTA is an option with OSAS to monitor morphological and functional changes in ocular microcirculation.

Acknowledgments

We thank Tay-Wey Lee of the Medical Research Center, Chang Gung Memorial Hospital, Keelung for their statistical assistance.

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References

[1] Stradling JR, Davies RJ. Sleep. 1: obstructive sleep apnoea/hypopnoea syndrome: definitions, epidemiology, and natural history. Thorax 2004;59:73–8.
[2] Mannarino MR, Di Filippo F, Pirro M. Obstructive sleep apnea syndrome. Eur J Intern Med 2012;23:586–93.
[3] Yaggi HK, Concato J, Kernan WN, et al. Obstructive sleep apnea as a risk factor for stroke and death. N Engl J Med 2005;353:2034–41.

[4] Onen SH, Mouriaux F, Berramdane L, et al. High prevalence of sleep-disordered breathing in patients with primary open-angle glaucoma. Acta Ophthalmol Scand 2000;78:638–41.
[5] Muniesa M, Sanchez-de-la-Torre M, Huerva V, et al. Floppy eyelid syndrome as an indicator of the presence of glaucoma in patients with obstructive sleep apnea. J Glaucoma 2014;23:e81–5.
[6] Lin PW, Friedman M, Lin HC, et al. Normal tension glaucoma in patients with obstructive sleep apnea/hypopnea syndrome. J Glaucoma 2011;20:553–8.
[7] Hashim SP, Al Mansouri FA, Farouk M, et al. Prevalence of glaucoma in patients with moderate to severe obstructive sleep apnea: ocular morbidity and outcomes in a 3 year follow-up study. Eye (Lond) 2014; 28:1304–9.
[8] Lin CC, Hu CC, Ho JD, et al. Obstructive sleep apnea and increased risk of glaucoma: a population-based matched-cohort study. Ophthalmology 2013;120:1559–64.
[9] Gherghel D, Hosking SL, Orgul S. Autonomic nervous system, circadian rhythms, and primary open-angle glaucoma. Surv Ophthalmol 2004;49: 491–508.
[10] Bourne RR, Stevens GA, White RA, et al. Causes of vision loss worldwide, 1990–2010: a systematic analysis. Lancet Glob Health 2013;1:e339–49.
[11] Komori S, Ishida K, Yamamoto T. Results of long-term monitoring of normal-tension glaucoma patients receiving medical therapy: results of an 18-year follow-up. Graefes Arch Clin Exp Ophthalmol 2014;252: 1963–70.
[12] de Moraes CG, Liebmann JM, Medeiros FA, et al. Management of advanced glaucoma: characterization and monitoring. Surv Ophthalmol 2016;61:597–615.
[13] Patt BT, Jarjoura D, Haddad DN, et al. Endothelial dysfunction in the microcirculation of patients with obstructive sleep apnea. Am J Respir Crit Care Med 2010;182:1540–5.
[14] Lin PW, Friedman M, Lin HC, et al. Decreased retinal nerve fiber layer thickness in patients with obstructive sleep apnea/hypopnea syndrome. Graefes Arch Clin Exp Ophthalmol 2011;249:585–93.
[15] Yu J, Xiao K, Huang J, et al. Reduced retinal vessel density in obstructive sleep apnea syndrome patients: an optical coherence tomography angiography study. Invest Ophthalmol Vis Sci 2017;58:3506–12.
[16] 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.
[17] Chen HS, Liu CH, Wu WC, et al. Optical coherence tomography angiography of the superficial microvasculature in the macular and peripapillary areas in glaucomatous and healthy eyes. Invest Ophthalmol Vis Sci 2017;58:3637–45.
[18] Moyal L, Blumen-Ohana E, Blumen M, et al. Parafoveal and optic disc vessel density in patients with obstructive sleep apnea syndrome: an optical coherence tomography angiography study. Graefes Arch Clin Exp Ophthalmol 2018;256:1235–43.
[19] Xu H, Zhai R, Zong Y, et al. Comparison of retinal microvascular changes in eyes with high-tension glaucoma or normal-tension glaucoma: a quantitative optic coherence tomography angiographic study. Graefes Arch Clin Exp Ophthalmol 2018;256:1179–86.
[20] Yamada E, Himori N, Kunikata H, et al. The relationship between increased oxidative stress and visual field defect progression in glaucoma patients with sleep apnoea syndrome. Acta Ophthalmol. 2018;96(4): e479-e484.
[21] Buckley C, Hadoke PW, Henry E, et al. Systemic vascular endothelial cell dysfunction in normal pressure glaucoma. Br J Ophthalmol 2002; 86:227–32.
[22] Killer HE, Pircher A. Normal tension glaucoma: review of current understanding and mechanisms of the pathogenesis. Eye (Lond) 2018; 32:924–30.
[23] Yu DY, Cringle SJ, Balaratnasingam C, et al. Retinal ganglion cells: energetics, compartmentation, axonal transport, cytoskeletons and vulnerability. Prog Retin Eye Res 2013;36:217–46.
[24] Akagi T, Iida Y, Nakanishi H, et al. Microvascular density in glaucomatous eyes with hemifield visual field defects: an optical coherence tomography angiography study. Am J Ophthalmol 2016; 168:237–49.
[25] Liu L, Jia Y, Takusagawa HL, et al. Optical coherence tomography angiography of the peripapillary retina in glaucoma. JAMA Ophthalmol 2015;133:1045–52.
[26] Yarmohammadi A, Zangwill LM, Diniz-Filho A, et al. Optical coherence tomography angiography vessel density in healthy, glaucoma suspect, and glaucoma eyes. Invest Ophthalmol Vis Sci 2016;57:OCT451–9.
[27] Mammo Z, Heisler M, Balaratnasingam C, et al. Quantitative optical coherence tomography angiography of radial peripapillary capillaries in glaucoma, glaucoma suspect, and normal eyes. Am J Ophthalmol 2016;170:41–9.
[28] Shin JW, Sung KR, Lee JY, et al. Optical coherence tomography angiography vessel density mapping at various retinal layers in healthy and normal tension glaucoma eyes. Graefes Arch Clin Exp Ophthalmol 2017;255:1193–202.