Comparison of the Retinal Microvascular Density Between Open Angle Glaucoma and Nonarteritic Anterior Ischemic Optic Neuropathy

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Submitted: April 9, 2017
Accepted: May 22, 2017

Citation: Liu C-H, Wu W-C, Sun M-H, Kao L-Y, Lee Y-S, Chen HS-L. Comparison of the retinal microvascular density between open angle glaucoma and nonarteritic anterior ischemic optic neuropathy. *Invest Ophthalmol Vis Sci*. 2017;58:3350–3356. DOI: 10.1167/iovs.17-22021

Purpose. To compare optical coherence tomography angiography (OCT-A) retinal vasculature measurements between nonarteritic anterior ischemic optic neuropathy (NAION) and open angle glaucoma (OAG) with altitudinal hemifield visual field defects.

Methods. This retrospective cross-sectional study included 10 NAION eyes and 16 OAG eyes, both demonstrating hemifield visual field defects, and 27 normal eyes serving as controls. The peripapillary and macular OCT-A scans were acquired. The retinal vessel density data were compared among NAION, glaucomatous, as well as control eyes.

Results. There was statistically significant difference in peripapillary whole image vessel density (wiVD), circumpapillary vessel density (cpVD), macular wiVD, and perifoveal vessel density (pfVD) between the three groups ($P < 0.05$ for all). In comparison between OAG and NAION groups, the NAION group demonstrated marked decrease in average cpVD ($P = 0.008$) and in most sectors of cpVD except the inferior one, while the OAG group demonstrated significant decreased macular wiVD and pfVD ($P = 0.03$ and 0.003, respectively). Multivariate analysis indicated that average thickness of retinal nerve fiber layer was the only predictor for peripapillary wiVD and cpVD ($P = 0.005$ for both). By contrast, thickness of ganglion cell complex was the only predictor for macular wiVD ($P = 0.007$).

Conclusions. OCT-A detected significant difference in peripapillary and macular retinal vessel densities between OAG and NAION eyes. These differences might provide comparative insight into the pathophysiology of these two diseases.

Keywords: glaucoma, ischemic optic neuropathy, optical coherence tomography angiography

Primary open angle glaucoma (OAG) and nonarteritic anterior ischemic optic neuropathy (NAION) are the two most common causes of irreversible optic neuropathy in adults. OAG is a chronic progressive optic neuropathy associated with thinning of the neuroretinal rim, enlargement of the optic cup, loss of the retinal nerve fiber layer (RNFL), together with a particular pattern of visual field (VF) loss. By contrast, NAION occurs as a result of infarction of retrolaminar portion of the optic nerve and is characterized by acute painless visual loss along with altitudinal VF defect and optic disc swelling initially.[1] The neuroretinal rim usually becomes pale after the resolution of optic disc swelling in NAION, while it remains pinkish in OAG. Other clues such as history of acute attack and small cup-to-disc ratio in the contralateral eye can also be useful in discerning glaucomatous from ischemic optic neuropathy. However, ischemic optic neuropathy may be confused with glaucoma when the patient is seen in a nonacute phase because it might present with enlargement of optic cup as well.[2]

Optical coherence tomography (OCT) is a noninvasive imaging technique using near-infrared light to create cross-sectional images of the retina and optic nerve. Both the thickness of peripapillary RNFL and macular ganglion cell complex (GCC) will decrease in OAG, and even precede detectable VF loss.[3] In NAION, RNFL and GCC thickness are also decreased following attack of the disease.[4,5] Recently, OCT angiography (OCT-A) has been designed to measure vascularization in the retina and choroid. Using the split-spectrum amplitude-decorrelation angiography (SSADA) algorithm, OCT-A can localize blood vessels in each vascular layer of interest by detecting blood flow by decorrelating the motion of red blood cells from the static tissues without the need for contrast injection.[6] The morphologic retinal layer features in healthy eyes have previously been described by Savastano et al.[7] An accumulation of recent studies[8–13] have also evaluated the peripapillary microvasculature by OCT-A in various glaucomatous and nonglaucomatous optic neuropathies due to ischemia, inflammation, compression, and in optic disc atrophy.

Although both glaucoma and NAION cause decrease in retinal vessel density, the pattern and extent of damage to microvasculature might be different in these two disease entities. The purpose of this study was to compare the differences in peripapillary and parafoveal retinal microvasculature by using OCT-A between NAION and OAG eyes.

Materials and Methods

Participants

This retrospective cross-sectional study was conducted between April 2016 and January 2017. Patients with NAION, OAG, and healthy control (HC) group were recruited from our ophthalmology clinic at Chang Gung Memorial Hospital (Taoyuan, Taiwan). The research protocols were approved by the institutional review board and adhered to the tenets of the Declaration of Helsinki.

All of the patients underwent a comprehensive ophthalmic evaluation, including best-corrected visual acuity (BCVA) and refraction assessments, slit-lamp biomicroscopy, intraocular pressure (IOP) measurement, central corneal thickness (CCT) measurement, optic nerve head (ONH) evaluation and fundus examination, digital color fundus photography (Digital Non-Mydriatic Retinal Camera; Canon, Tokyo, Japan), standard automated perimetry, spectral-domain OCT (SD-OCT) (Avanti; Optovue, Inc., Fremont, CA, USA), and OCT-A (AngioVue; Optovue, Inc.). Systemic blood pressure (BP) was measured by sphygmomanometry in an upright sitting position after a 10-minute rest period. Mean arterial pressure (MAP) was calculated as MAP = 1/3 systolic BP + 2/3 diastolic BP.

Inclusion Criteria

Inclusion criteria for patients with NAION were as follows: (1) history of a sudden onset of painless vision loss; (2) a VF defect confined to only one hemifield consistent with NAION; (3) optic disc edema at onset that was confirmed by at least one neuro-ophthalmology expert; (4) no evidence of other ocular diseases such as glaucoma, arteritic anterior ischemic optic neuropathy, optic neuritis, or coexisting retinal pathologies that may cause the visual symptoms; and (5) resolution of the initial optic disc and retinal edema at least 3 months after acute optic disc swelling.[14]

Inclusion criteria for patients with OAG were as follows: (1) typical glaucomatous optic disc appearance (localized or diffuse neuroretinal rim thinning of the ONH, a cup-to-disc ratio greater than 0.7 or asymmetry greater than 0.2, or RNFL defects corresponding to the glaucomatous VF defects); and (2) a glaucomatous VF, using Hodapp-Parrish-Anderson criteria[15] for diagnosis and staging, with mean deviation (MD) ranging from −6.0 dB to −12.0 dB, confined to only one hemifield and reproducible in two consecutive tests.

HC eyes were defined as follows: (1) BCVA better than 20/20; (2) IOP less than 21 mm Hg; (3) normal-appearing ONH and RNFL; (4) symmetric ONH between the right and left eyes; (5) no evidence of retinal pathology or optic neuropathy; (6) normal VF; and (7) no history of intraocular surgery.

Exclusion Criteria

Exclusion criteria were as follows: (1) age younger than 20 years or older than 80 years; (2) refractive error greater than +3.0 diopters (D) or less than −6.0 D; (3) previous intraocular surgery; (4) any disease other than NAION or OAG that may cause a VF defect or optic disc abnormalities; and (5) inability to perform reliably on automated VF testing or poor cooperation in OCT imaging studies.

Standard Automated Perimetry

All participants underwent VF assessment using 30-2 pattern Swedish interactive threshold algorithm on the Humphrey Field Analyzer (Carl Zeiss Meditec, Jena, Germany) within 3 months of imaging. Only reliable tests (≤20% fixation loss, ≤33% false negative, and ≤33% false positive) were included.

SD-OCT and OCT-A Data Acquisition and Processing

Avanti SD-OCT system enables simultaneous assessment of the ocular structure and microvasculature. Details regarding the use of this system have been described by Jia et al.[6] and Liu et al.[10] The ONH protocol was used to obtain rim area measurements and peripapillary RNFL thickness measurements in a 10-pixel-wide band along a 3.45-mm-diameter circle centered on the disc. The macular GCC protocol was used to obtain GCC thickness averaged over a 7-mm-diameter circular area centered on the fovea consisting of the macular nerve fiber layer, ganglion cell layer, and inner plexiform layer.

The OCT-A images were acquired within the peripapillary (4.5 × 4.5 mm) and macular (6 × 6 mm) areas (Fig. 1). Vessel density was calculated as the percentage area occupied by flowing blood vessels in the selected region and was measured with the installed flow density mapping software AngioAnalytics. We used the radial peripapillary capillary images, which included signals from the internal limiting membrane (ILM) to the posterior boundary of the RNFL in the peripapillary area, and the superficial images, which included signals from the ILM to the posterior boundary of the inner plexiform layer in the macular area. Measurements of the peripapillary region were obtained in two areas: peripapillary wiVD was calculated over the entire 4.5 × 4.5-mm scan field, and cpVD was estimated in a 750-μm-wide elliptical annulus extending outward from the optic disc boundary. Measurements of the macular area were also obtained in two areas: macular wiVD was calculated over the entire 6.0 × 6.0-mm scan field, and pfVD was defined as an annulus with an outer diameter of 3 mm and an inner diameter of 1 mm centered at the fovea. The quality of all OCT-A images was assessed. Poor-quality images with a signal strength index less than 45, registered image sets with residual motion artifacts visible as discontinuous irregular vessel patterns or disc boundaries, and images with a local weak signal on the en face angiogram were excluded from the analysis.

Statistical Analysis

Data were expressed as mean ± standard deviation for continuous variables and as a percentage for categorical variables. The baseline characteristics and differences in the clinical features between the NAION, OAG, and HC group were compared for statistical significance by using the Kruskal-Wallis test for continuous variables, and χ^2 test for categorical data. The post hoc analysis was performed with the Mann-Whitney U test. To determine the relationship between vessel density and variables, multivariate analysis and linear regression modeling were calculated. All statistical analyses were performed by using SPSS software, version 19.0 (SPSS, Inc., Chicago, IL, USA). A P value less than 0.05 was considered statistically significant.

Results

Fifty-five eyes, consisting of 12 eyes with NAION, 16 eyes with OAG, and 27 eyes from HC subjects, met the inclusion criteria of this study. Among the eyes with NAION, two were excluded owing to insufficient quality of their OCT-A images. As a result, 10 eyes with NAION, 16 eyes with OAG, and 27 eyes from HC subjects were included for final data analysis. The demographics and clinical characteristics of the study participants are

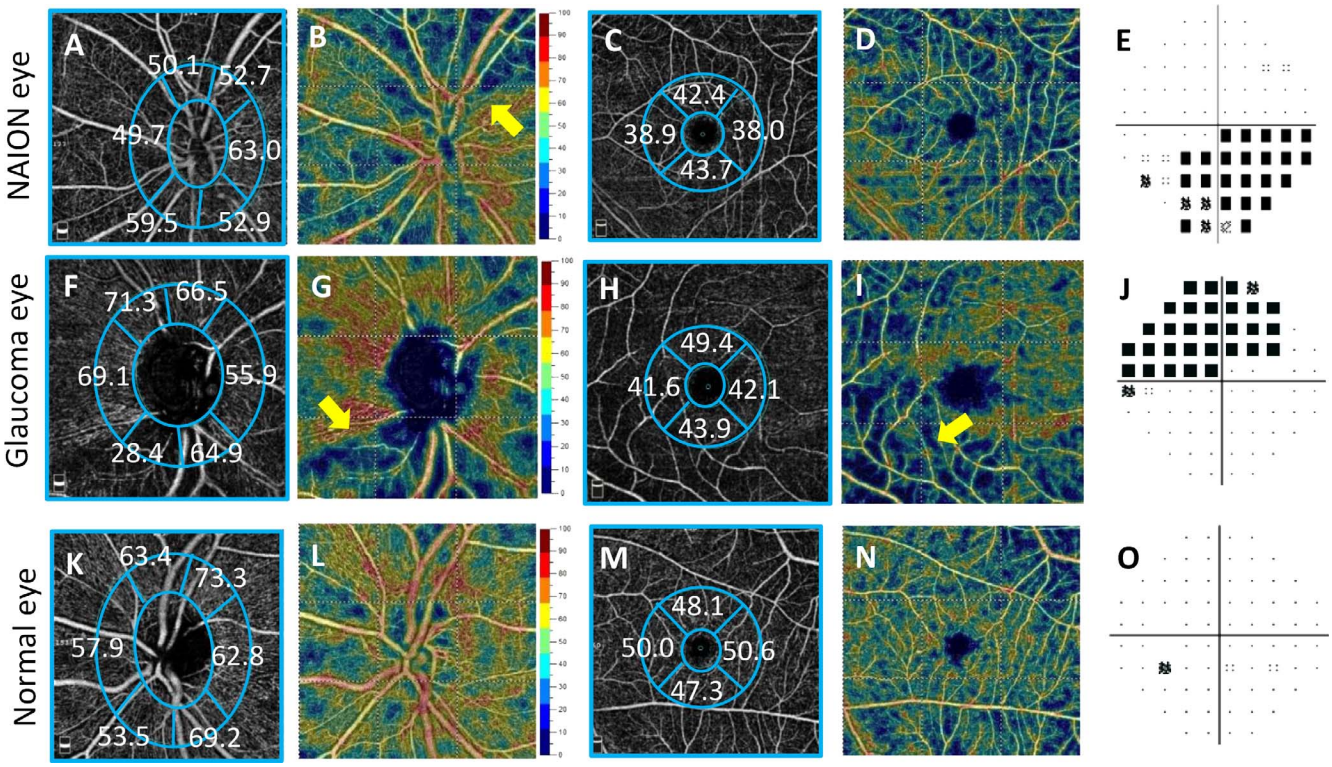

Figure 1. Comparison of peripapillary retinal and macular angiograms. En face optical coherence tomography angiograms (OCT-A) and vessel density (VD) (%) (**A**, **F**, **K**), with color-coded map (**B**, **G**, **L**) in the peripapillary area; OCT-A and VD (**C**, **H**, **M**), with color-coded map (**D**, **I**, **N**) in the macular area; total deviation of the visual field (**E**, **J**, **O**). The microvascular network of the peripapillary and macular area was attenuated (*arrow*) in the NAION eye (**A**–**E**) and OAG eye (**F**–**J**) compared with that in normal eye (**K**–**O**).

listed in Table 1. The mean interval between the onset of disease and measurement in NAION group was 9.9 months. There were no between-group differences in age, sex distribution, IOP, CCT, and the prevalence of diabetes and hypertension. The MD in VF was comparable between NAION group and OAG group ($P = 0.28$). The MAP was higher in NAION and OAG groups than in HC group ($P < 0.001$). OAG eyes were more myopic than NAION eyes and HC eyes ($P = 0.02$).

Peripapillary RNFL thickness and macular GCC thickness are shown in Table 2. The peripapillary RNFL and macular GCC thicknesses were significantly thinner in NAION and OAG groups than in HC group (all $P < 0.05$). Comparing the NAION eyes with OAG eyes, there was no significant difference in peripapillary RNFL and macular GCC between these two groups for most sectors except for the inferotemporal sector of RNFL ($P = 0.01$).

The peripapillary and macular retinal vessel densities in the three groups are displayed in Table 3. There were statistically significant differences between group means for peripapillary wiVD, average cpVD, macular wiVD, and average pfVD ($P < 0.05$ for all). Post hoc pairwise comparisons between groups indicated that peripapillary vessel densities were significantly more reduced on measurement of average cpVD ($P = 0.008$) and whole sectors of cpVD except for the inferior one in the NAION group compared to the OAG group. By contrast, the

Table 1. Demographic and Clinical Data of Patients With NAION, OAG, and the Controls

	NAION, $n = 10$	OAG, $n = 16$	Controls, $n = 27$	P Value
Age, y	59.90 ± 10.70	53.75 ± 10.21	55.74 ± 14.51	0.46
Male, No (%)	4 (40)	9 (56.3)	14 (51.9)	0.72
BCVA, logMAR	0.44 ± 0.40	0.32 ± 0.34	0.05 ± 0.11	<0.001*
Refractive error, diopters	0.00 ± 2.54	−2.89 ± 2.30	−1.46 ± 2.35	0.02*
CCT, μm	562.20 ± 24.94	536.93 ± 34.04	551.14 ± 27.99	0.20
Rim area, mm^2	1.61 ± 0.68	0.70 ± 0.27	1.31 ± 0.32	<0.001*
C/D ratio	0.30 ± 0.24	0.67 ± 0.15	0.41 ± 0.14	<0.001*
Visual field MD, dB	−12.78 ± 6.34	−9.69 ± 3.56	0.58 ± 0.44	<0.001*
Visual field PSD, dB	10.16 ± 4.03	13.73 ± 3.09	1.37 ± 0.27	<0.001*
IOP, mm Hg	13.05 ± 1.88	13.96 ± 2.68	14.24 ± 2.60	0.29
MAP	108.00 ± 9.67	99.62 ± 8.36	89.00 ± 8.04	<0.001*
Self-reported history of diabetes, No (%)	2 (20)	1 (6.3)	2 (7.4)	0.44
Self-reported history of hypertension, No (%)	4 (40)	4 (25.0)	2 (7.4)	0.60

Data are means ± standard deviations. C/D, cup-to-disc; PSD, pattern standard deviation.
* Statistical significance tested with the Kruskal-Wallis test for continuous variables, and χ^2 test for categorical variables among all three groups.

Table 2. Measurements of Peripapillary RNFL and Macular GCC Thickness of the Patients With NAION, OAG, and the Controls

	NAION, $n = 10$	OAG, $n = 16$	Controls, $n = 27$	*P* Value	*P*1 Value	*P*2 Value	*P*3 Value
Peripapillary RNFL thickness, μm							
Average RNFL	75.20 ± 12.59	77.78 ± 10.89	99.37 ± 6.85	<0.001*	0.59	<0.001*	<0.001*
Superior RNFL	87.90 ± 31.77	99.52 ± 24.76	120.46 ± 9.69	0.005*	0.26	0.01*	0.005*
Superotemporal RNFL	98.20 ± 34.73	104.06 ± 34.96	136.11 ± 11.33	0.003*	0.70	0.007*	0.005*
Superonasal RNFL	77.60 ± 30.28	94.97 ± 19.72	104.81 ± 9.67	0.01*	0.08	0.009*	0.07
Nasal RNFL	58.90 ± 13.41	67.50 ± 6.65	73.17 ± 8.07	0.005*	0.14	0.006*	0.02*
Inferior RNFL	102.20 ± 25.54	82.53 ± 18.07	124.74 ± 12.75	<0.001*	0.05	0.02*	<0.001*
Inferotemporal RNFL	114.60 ± 31.53	80.28 ± 26.92	140.93 ± 15.17	<0.001*	0.01*	0.01*	<0.001*
Inferonasal RNFL	89.80 ± 22.64	84.78 ± 17.48	108.56 ± 14.89	0.001*	0.66	0.02*	<0.001*
Temporal RNFL	60.65 ± 13.39	60.80 ± 16.30	78.81 ± 9.19	<0.001*	0.70	<0.001*	<0.001*
Sup-Inf difference†	33.60 ± 20.98	30.77 ± 19.39	8.57 ± 9.07	<0.001*	0.55	<0.001*	<0.001*
Macular GCC thickness, μm							
Average GCC	107.00 ± 6.55	105.00 ± 13.60	117.00 ± 9.71	0.005*	0.35	0.005*	0.01*
Superior GCC	101.20 ± 6.83	107.40 ± 14.04	117.00 ± 12.16	0.002*	0.32	<0.001*	0.05
Inferior GCC	112.80 ± 9.78	102.60 ± 16.89	117.18 ± 8.26	0.04*	0.17	0.19	0.02*
Sup-Inf difference†	13.60 ± 8.13	11.80 ± 10.33	4.27 ± 5.00	0.001*	0.44	<0.001*	0.02*

Data are means ± standard deviations. *P*, comparison of all groups based on Kruskal-Wallis test. *P*1, comparison of AION and OAG based on Mann-Whitney *U* test. *P*2, comparison of NAION and normal eyes based on Mann-Whitney *U* test. *P*3, comparison of OAG and normal eyes based on Mann-Whitney *U* test.

* Statistically significant.

† Sup-Inf difference was the absolute difference of measurements between superior and inferior sectors.

macular wiVD and average pfVD were significantly more reduced in the OAG group than the NAION group ($P = 0.03$ and 0.003, respectively). The mean difference in cpVD between superior and inferior quadrants was significantly greater in NAION and OAG groups than HC group ($P < 0.001$), but was not different between NAION and OAG group, while the mean difference in pfVD between superior and inferior quadrants did not reach statistical significance among the three groups ($P = 0.53$).

Table 4 shows the Pearson correlations between the clinical and ophthalmic features and OCT-A vessel density in all eyes. The association with MD was stronger with cpVD and peripapillary wiVD ($r = 0.761$ and 0.727, respectively), and weaker with macular wiVD ($r = 0.388$), while the pfVD did not show significant correlation with MD. Peripapillary RNFL thickness, macular GCC thickness, and MAP were found to be significantly associated with peripapillary wiVD, cpVD, and macular wiVD, while rim area was only associated with

Table 3. Measurements of Retinal Vessel Densities of the Patients With NAION, OAG, and the Controls

	NAION, $n = 10$	OAG, $n = 16$	Controls, $n = 27$	*P* Value	*P*1 Value	*P*2 Value	*P*3 Value
Peripapillary vessel density, %							
Peripapillary wiVD	43.07 ± 5.20	44.73 ± 4.74	53.04 ± 2.89	<0.001*	0.46	<0.001*	<0.001*
Average cpVD	47.58 ± 6.64	55.05 ± 5.20	61.41 ± 2.87	<0.001*	0.008*	<0.001*	<0.001*
Superior cpVD	43.21 ± 5.91	55.37 ± 8.09	62.01 ± 4.08	<0.001*	0.002*	<0.001*	0.009*
Superotemporal cpVD	45.33 ± 8.59	54.47 ± 11.85	64.78 ± 4.58	<0.001*	0.04*	<0.001*	0.006*
Superonasal cpVD	41.08 ± 6.95	56.27 ± 6.12	59.23 ± 5.14	<0.001*	<0.001*	<0.001*	0.09
Nasal cpVD	44.27 ± 7.58	54.95 ± 5.97	57.62 ± 4.92	<0.001*	0.002*	<0.001*	0.18
Inferior cpVD	53.60 ± 8.59	50.53 ± 7.22	64.76 ± 3.36	<0.001*	0.16	<0.001*	<0.001*
Inferotemporal cpVD	54.61 ± 9.95	46.39 ± 12.54	67.29 ± 4.01	<0.001*	0.05	<0.001*	<0.001*
Inferonasal cpVD	52.59 ± 8.96	54.66 ± 8.05	62.23 ± 4.79	<0.001*	0.64	0.001*	0.002*
Temporal cpVD	50.16 ± 9.69	58.92 ± 11.75	62.42 ± 3.98	0.002*	0.01*	<0.001*	0.62
Sup-Inf difference†	10.93 ± 6.45	11.09 ± 7.43	3.87 ± 2.63	0.001*	0.96	0.003*	0.002*
Macular vessel density, %							
Macular wiVD	40.70 ± 2.04	38.46 ± 2.46	43.11 ± 2.80	<0.001*	0.03*	0.01	<0.001*
Average pfVD	45.15 ± 3.21	40.74 ± 2.29	43.16 ± 2.96	0.007*	0.003*	0.10	0.031*
Superior pfVD	44.74 ± 3.93	40.94 ± 4.48	43.75 ± 4.52	0.19	0.11	0.60	0.11
Nasal pfVD	45.38 ± 3.81	40.81 ± 3.95	42.67 ± 3.88	0.08	0.02*	0.10	0.42
Inferior pfVD	45.30 ± 3.19	41.51 ± 2.79	43.13 ± 3.56	0.05	0.01*	0.16	0.19
Temporal pfVD	45.20 ± 4.35	39.71 ± 2.06	43.06 ± 4.13	0.004*	0.008*	0.06	0.008*
Sup-Inf difference†	3.12 ± 2.30	3.90 ± 1.68	3.40 ± 2.27	0.53	0.20	0.75	0.45

Data are means ± standard deviations. *P*, comparison of all groups based on Kruskal-Wallis test. *P*1, comparison of NAION and OAG based on Mann-Whitney *U* test. *P*2, comparison of NAION and normal eyes based on Mann-Whitney *U* test. *P*3, comparison of OAG and normal eyes based on Mann-Whitney *U* test.

* Statistically significant.

† Sup-Inf difference was the absolute difference of measurements between superior and inferior sectors.

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Table 4. Pearson Correlation Coefficient Matrix for Peripapillary and Macular Vessel Density, Structural Variables, and Visual Field in All Subjects

	Peripapillary wiVD		cpVD		Macular wiVD		pfVD	
Parameters	*r*	*P* Value	*r*	*P* Value	*r*	*P* Value	*r*	*P* Value
MD	0.727	<0.001*	0.761	<0.001*	0.388	0.01*	0.126	0.43
PSD	−0.756	<0.001*	−0.676	<0.001*	−0.563	<0.001*	−0.181	0.26
RNFL thickness, mm	0.815	<0.001*	0.791	<0.001*	0.467	0.002*	−0.102	0.52
GCC	0.760	<0.001*	0.750	<0.001*	0.651	<0.001*	0.015	0.93
Rim area, mm^2	0.314	0.02*	0.049	0.73	0.190	0.229	0.130	0.41
Age	−0.131	0.35	−0.129	0.36	−0.064	0.69	−0.092	0.56
IOP, mm Hg	0.185	0.19	0.186	0.19	−0.020	0.90	−0.071	0.66
MAP, mm Hg	−0.355	0.02*	−0.447	0.003*	−0.376	0.03*	−0.194	0.26
CCT	−0.071	0.65	−0.163	0.29	−0.005	0.98	0.229	0.19

* Statistically significant.

peripapillary wiVD. In the multiple linear regression analysis where peripapillary wiVD and cpVD were considered the dependent variables, only peripapillary RNFL thickness was a significant predictor ($P = 0.005$ for both). Other factors including age, CCT, IOP, MAP, rim area, and average macular GCC thickness were not significant explanatory variables in the multivariate models. For pfVD, only macular GCC thickness was a significant predictor ($P = 0.007$) (Table 5).

Plots of peripapillary vessel density with average peripapillary RNFL thickness and macular wiVD with average macular GCC thickness are presented in Figure 2. A linear regression model demonstrated a significant correlation between average peripapillary RNFL thickness and peripapillary wiVD and cpVD ($R^2 = 0.664$ and 0.625, respectively) and between average macular GCC thickness and macular wiVD ($R^2 = 0.424$).

Discussion

In the present study, we found there was greater decrease in the peripapillary vessel density in the NAION group than the OAG group, while there was even greater decrease in the macular vessel density in the OAG group than the NAION group. To the best of our knowledge, this is the first study to demonstrate the difference in the retinal vessel density between NAION and OAG.

The retinal blood vessels serve for nutrition of the retinal ganglion cells (RGCs) and their axons. Several studies have shown changes in these vessels after glaucomatous and nonglaucomatous optic neuropathy. By using laser Doppler flowmetry and laser speckle flowgraphy, emerging studies[16–19] have demonstrated reduced blood flow dynamics in the optic nerve head and peripapillary area in glaucoma. With the recently developed OCT-A, decreased peripapillary retinal perfusion has been shown in glaucoma and correlates with VF damage.[10,20] Decrease in peripapillary retinal perfusion has also been reported in NAION eyes by using Doppler OCT.[21] Our previous study[8] also has found there is decrease in peripapillary retinal vasculature, by using OCT-A, in patients with optic atrophy after NAION.

The reasons for decrease in peripapillary retinal vasculature in glaucoma are thought to be either an effect of an ischemic basis for glaucoma damage, or an effect of autoregulation whereby neural loss reduces metabolic load and leads to decrease in blood flow. Since the presence of inner retinal hypoperfusion reportedly coincides with the RNFL defect, Lee et al.[22] suggest the decreased retinal microvasculature indicates the closure or degeneration of capillaries due to RNFL loss rather than primary reduction of retinal perfusion, in which the area of vascular insufficiency should follow the territory of the retinal arterial branches as in cases of branched retinal arterial occlusion. In eyes with NAION, since the primary location of ischemia is in the retrolaminar portion of the optic nerve head, which is supplied by the short posterior ciliary arteries,[1] the decreased peripapillary retinal vasculature in chronic phase is thought to be the result of secondary changes of tissue loss and diminished metabolic demands.[8,23] This hypothesis is supported by the close correlation between thinning of RNFL and changes of peripapillary retinal vasculature.

Though attenuation of peripapillary retinal vasculature was found in both NAION and glaucoma, the distribution and severity was different to some extent as revealed by the present study. The decrease in peripapillary VD was more prominent in eyes with NAION than eyes with OAG even with similar change in peripapillary RNFL thickness and MD in VF.

Table 5. Association Between Retinal Vessel Density and Structural, Demographic, and Ocular Variables: Multiple Regression Analysis

	Peripapillary wiVD			cpVD			Macular wiVD			pfVD		
	Coefficient	95% CI	*P* Value	Coefficient	95% CI	*P* Value	Coefficient	95% CI	*P* Value	Coefficient	95% CI	*P* Value
RNFL	0.549	0.073∼0.383	0.005*	0.586	0.072∼0.380	0.005*	0.029	−0.114∼0.128	0.91	0.106	−0.156∼0.204	0.78
GCC	0.166	−0.090∼0.231	0.38	0.289	−0.045∼0.273	0.16	0.736	0.052∼0.294	0.007*	0.124	−0.152∼0.208	0.75
Age	−0.190	−0.176∼0.005	0.06	−0.187	−0.169∼0.011	0.09	−0.233	−0.159∼0.015	0.10	−0.158	−0.177∼0.082	0.45
CCT	−0.150	−0.079∼0.020	0.23	−0.178	−0.082∼0.016	0.18	−0.112	−0.054∼0.026	0.48	0.017	−0.058∼0.062	0.94
Rim area	0.205	−0.274∼4.461	0.08	−0.134	−3.620∼1.078	0.28	0.026	−1.556∼1.848	0.86	0.115	−1.914∼3.140	0.62
IOP	0.157	−0.187∼0.891	0.19	0.146	−0.231∼0.839	0.26	0.123	−0.277∼0.629	0.43	0.136	−0.485∼0.860	0.57
MAP	−0.091	−0.194∼0.080	0.41	−0.077	−0.180∼0.092	0.51	−0.056	−0.121∼0.084	0.71	0.001	−0.152∼0.152	1.0

* Statistically significant. CI, confidence interval.

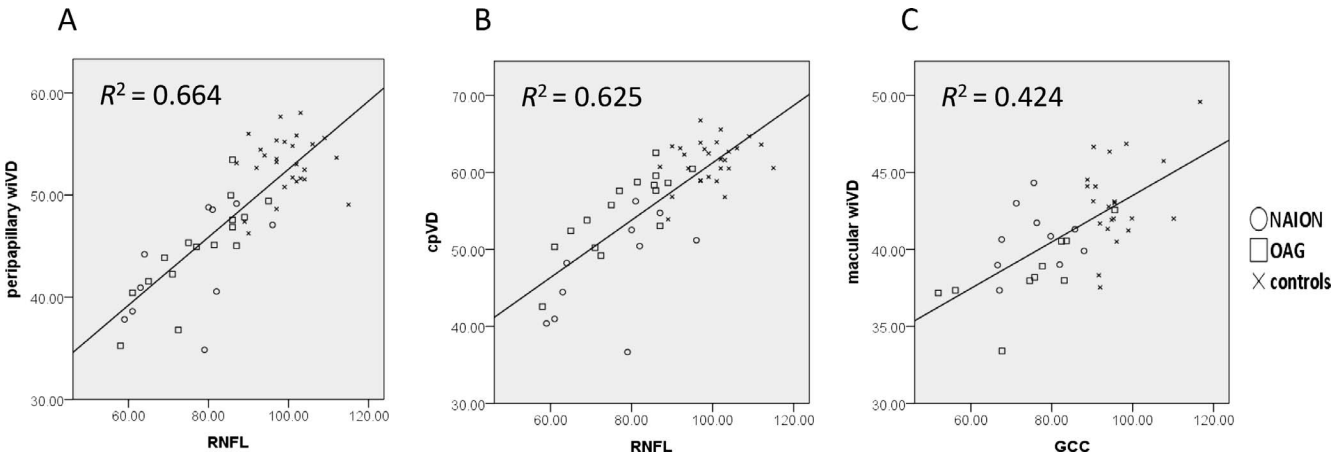

FIGURE 2. Scatter plots illustrating the linear associations between peripapillary RNFL thickness, macular GCC thickness, peripapillary wiVD, cpVD, and macular wiVD in NAION, OAG, and controls. R^2: adjusted R^2 from the linear regression model.

This finding may reflect the different pathogenesis and impact of vascular ischemia on these two diseases. RGC death is the final common pathway in glaucoma and most optic neuropathies. Porciatti and Ventura[24] have suggested that, under exposure to a stressful environment, RGCs undergo a stage of reversible dysfunction and will finally die when autoregulatory mechanisms fail to sustain normal RGC function. The period of RGC reversible dysfunction may be relatively longer in glaucoma than in NAION. Since our study recruited patients with moderate-stage instead of end-stage glaucoma, the RGCs may still be in the stage of reversible dysfunction, and therefore, the attenuation of peripapillary retinal vasculature in most sectors was less severe in glaucomatous eyes than in NAION eyes. For the inferior sector, the cpVD was similarly involved in both glaucomatous and NAION eyes because this region was affected earlier in glaucoma.[25,26]

In addition, we found marked attenuation of macular retinal vasculature in the OAG group. There is growing evidence that macular damage is very common in early glaucoma.[26,27] The macula contains more than 30% of the RGC, of which the axons, bodies, and dendrites make up the RNFL, ganglion cell layer, and inner plexiform layer, respectively. A mouse model of chronic ocular hypertension shows that the ganglion cells die initially from their synapses and cell bodies, while the eventual axonal death detected as RNFL thinning on OCT measurement may occur many months later.[28] However, there is also a study that argues against these sequential changes of nerve damage, suggesting instead that the initial site of damage in glaucoma begins at the axons and progresses toward the cell body.[29] No matter which theory is right, clinical application of OCT has shown that glaucomatous damage of the macula in early stage is common. The detectable change of macular RGC on OCT measurement precedes the change of its corresponding RNFL loss, and the outside macular RGC loss even precedes macular RGC loss in glaucoma.[25] The macular wiVD composed of superficial retinal vascular plexus[7] was found to be highly associated with macular GCC thickness in the present study. Yarmohammadi et al.[30] have also reported that the involvement of macular vessel density in glaucoma could be a relatively early event, even in the perimetrically intact hemiretina. Therefore, marked decrease in macular retinal vasculature was found in the OAG group in the present study, and the macular wiVD demonstrated stronger discriminating power than pfVD because the former covers wider peripheral changes.

By contrast, the attenuation of macular retinal vasculatures in NAION eyes was relatively insignificant. This result was unexpected because the macular GCC thinning in NAION eyes was as prominent as in OAG eyes. One possible explanation for this result is that chronic NAION only affects the inner retinal layer in the macular area, while the middle and outer retinal layers are still unchanged,[31] which could maintain autoregulation of macular blood flow in its normal status. But this still does not explain why the macular blood flow was more decreased in OAG eyes than NAION eyes, since both diseases affect the inner retina only. Moreover, given that the visual loss after NAION correlates with severity of the damage to the papillomacular bundle,[32] the less severe visual loss of NAION eyes in our study may be associated with less damage to the papillomacular bundles, and relative preservation of the macular retinal vasculatures. Taken together, the attenuation of macular retinal vasculature was more severe in OAG than NAION eyes as revealed in the current study.

There were several limitations in our study. The sample size was relatively small. However, a prospective power calculation suggested the total sample size of more than 21 eyes was sufficient to test the hypothesis at a significance level of 0.05 and power of 0.8. Besides, the severity of disease stage was restricted to a specific range, so the OAG and NAION groups could be comparable. Patients with advanced diseases or poor acuity were also excluded in the present study to obtain images with adequate quality. However, it might limit the external validity of the current study. In addition, both high-tension and normal-tension glaucomatous eyes were recruited in the OAG group in the present study. Vascular dysfunction has been proposed as a contributing factor in the development of glaucoma, especially in normal-tension glaucoma,[33] and other confounding factors including ocular hypotensive eye drops, medications, and other systemic vascular conditions might also affect retinal vasculature and its relationship between structural and functional measurements. Further research is required to determine the effects of these variables. In addition, the present study only measured the retinal vasculature because the current OCT-A modality has limitations in analysis of deeper layers. Further investigations using swept-source OCT or enhanced-depth imaging SD-OCT may help to evaluate the deeper vessels of the optic nerve head and choroid.

In summary, this study demonstrated the difference in peripapillary and macular retinal vessel densities between OAG and NAION eyes. OCT-A may help to elucidate the structure–perfusion relationships and offer a better understanding of the pathophysiology of these two diseases.

Acknowledgments

The authors alone are responsible for the content and writing of the paper.

Disclosure: **C.-H. Liu**, None; **W.-C. Wu**, None; **M.-H. Sun**, None; **L.-Y. Kao**, None; **Y.-S. Lee**, None; **H.S.-L. Chen**, None

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