Changes in Peripapillary Microvasculature and Retinal Thickness in the Fellow Eyes of Patients With Unilateral Retinal Vein Occlusion: An OCTA Study

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Purpose. To evaluate changes in peripapillary microvascular parameters in the fellow eyes of patients with unilateral retinal vein occlusion (RVO) using optical coherence tomography angiography (OCTA) and to determine the relationships between peripapillary microvasculature and retinal nerve fiber layer (RNFL) and ganglion cell-inner plexiform layer (GC-IPL) thickness.

Methods. Eighty-three patients with unilateral RVO (50 patients with branch RVO and 33 with central RVO) and 83 normal controls were enrolled. OCTA (Cirrus HD-OCT 5000 with AngioPlex) 6 × 6-mm scans centered on the optic disc were acquired. Peripapillary vessel density (VD) and perfusion density (PD) were automatically calculated.

Results. The average RNFL and GC-IPL thicknesses in the fellow eyes of RVO patients were significantly thinner than in normal controls (93.5 vs. 96.6 μm, $P = 0.013$ and 81.3 vs. 84.1 μm, $P = 0.003$, respectively). In the fellow eyes of patients with unilateral RVO, the peripapillary VD of the inner ring, outer ring, and full area (17.47, 18.50, and 17.89, respectively) were significantly lower than those of controls (17.87, 18.87, and 18.27, respectively). The peripapillary PD of the inner ring, outer ring, and full area (0.456, 0.467, and 0.456, respectively) were also significantly lower than those of controls (0.468, 0.476, and 0.466, respectively). RNFL and GC-IPL thicknesses were correlated with both peripapillary VD and PD.

Conclusions. OCTA revealed that peripapillary microvascular parameters in the fellow eyes of patients with unilateral RVO were decreased, and GC-IPL and RNFL thinning were also observed. The RNFL and GC-IPL thicknesses were positively correlated with both peripapillary VD and PD.

Keywords: retinal nerve fiber layer, ganglion cell-inner plexiform layer, retinal vein occlusion, peripapillary OCTA, vessel density, perfusion density, fellow eye

Retinal vein occlusion (RVO) is the second most common retinal vascular disease following diabetic retinopathy and is a frequent cause of significant visual loss and associated morbidity,[1–3] which increases with age, and reported a prevalence of approximately 0.7%–1.6%.[4,5] Various systemic diseases, such as hypertension (HTN), diabetes, arteriosclerosis, and hyperlipidemia are considered to be risk factors for the development of RVO.[6–11] Many studies have found an association between RVO and glaucoma and increased intraocular pressure (IOP).[4,12–15] In 1913, Verhoeff[16] first postulated that elevated IOP collapses and compresses the wall of the retinal vein, causing intimal proliferation in the vein. An ocular HTN study reported that a larger horizontal cup-to-disc ratio was associated with the development of RVO.[13]

Recently, optical coherence tomography angiography (OCTA) has been used as a new and noninvasive imaging modality that allows microvascular visualization of the retina and choroid in various layers, as well as quantitative measurement of perfusion, including in the optic nerve head and peripapillary and macular areas. In recent reports, a decrease in peripapillary microvascular perfusion using OCTA was associated with glaucoma.[17–19]

Kim et al.[20] reported that retinal nerve fiber layer (RNFL) thickness decreased in the fellow eyes of unilateral RVO patients, and that RVO and glaucoma may share systemic risk factors, reflecting a common pathogenic mechanism, such as systemic HTN, diabetes mellitus, and arteriosclerosis. There are several studies on changes in foveal microvascular perfusion in the fellow eyes of RVO patients with OCTA.[21,22] However, to our knowledge, no such study has investigated peripapillary microvascular alterations in the fellow eyes of patients with unilateral RVO. In this study, we hypothesized that decreased RNFL thickness in fellow eyes of RVO might be associated with peripapillary microvasculature changes. Therefore, we evaluated changes in peripapillary microvascular parameters in the fellow eyes of patients with unilateral RVO using OCTA.

Methods

Study Design

We reviewed the medical records of unilateral RVO patients referred to the Retina Clinic of Chungnam National University

Hospital from April 2017 to August 2018. The study protocol was approved by the Institutional Review Board of Chungnam National University Hospital. The study adhered to the tenets of the Declaration of Helsinki.

Participants

Retinal specialists (YJJ and JYK) diagnosed unilateral RVO using dilated fundus examination, fundus photography (FP), and fluorescein angiography (FA). FP and FA were used to check changes of blood vessels in the fellow eyes of RVO, and patients with vascular abnormalities were excluded. The healthy fellow eyes of unilateral RVO patients were enrolled in this study. The subjects who visited our clinic for a routine eye examination or health-screening checkup were enrolled as controls. Age-matched subjects were enrolled as normal controls without ocular disease, as confirmed by history and ophthalmic examinations. We randomly selected one of the two eyes in the normal control group. The exclusion criteria in the fellow eyes and controls were as follows: (1) a history of retinal or optic nerve diseases or glaucoma; (2) a best-corrected visual acuity (BCVA) <20/25; (3) high myopia (spherical equivalent [SE] >6 diopters, axial length [AL] ≥26.0 mm); and (4) significant media opacity. All patients underwent measurement of their BCVA using a Snellen chart, IOP, SE, AL, slit-lamp biomicroscopy, dilated fundus examination, spectral-domain OCT (SD-OCT), and OCTA.

Optical Coherence Tomography

SD-OCT imaging was performed (Cirrus HD-OCT; Carl Zeiss Meditec, Dublin, CA, USA) by an experienced examiner. A macular cube 512 × 128 combination scan mode was used for central macular thickness (CMT) and ganglion cell-inner plexiform layer (GC-IPL) thickness measurements. The ganglion cell analysis algorithm automatically measured GC-IPL thickness by identifying the outer boundaries of the RNFL and inner plexiform layer (IPL) of the macula using three-dimensional information obtained from the macular cube. We analyzed the CMT and average macular GC-IPL thickness. An optic disc cube 200 × 200 scan mode was used for RNFL measurements. The RNFL thickness parameters evaluated were average thickness and the thicknesses of four-quadrant sectors (superior, nasal, inferior, and temporal). For inclusion, OCT images required a signal strength ≥7 and the absence of artifacts, poor centration, or segmentation errors. Two scans were performed for each participant by an experienced examiner, and we selected the best scan showing a signal strength ≥7.

Optical Coherence Tomography Angiography

OCTA imaging was performed using the Cirrus HD-OCT 5000 and AngioPlex device with a wavelength of 840 nm and an A-scan rate of 68,000 scans per second. The volumetric scans were processed using optical microangiography (OMAG) algorithms to identify perfused vessels. The OMAG algorithm analyzes changes in the phase and intensity information of the OCT scans to quantify motion contrast and then produces en face microvascular images of the superficial capillary plexus (SCP) (from the internal limiting membrane [ILM] to the IPL) and the deep capillary plexus (DCP) (from the inner nuclear layer [INL] to the outer plexiform layer [OPL]).

To investigate peripapillary microvasculature, OCTA was conducted using a 6 × 6-mm scan centered on the optic disc for data analysis (Fig. 1). In the 6 × 6-mm scan pattern, there were 350 A-scans in each B-scan along the horizontal dimension, and 350 B-scans were repeated twice at each location. All scans were analyzed using Cirrus OCTA software (AngioPlex, version 10.0; Carl Zeiss Meditec). Vessel density (VD; the total length of perfused vasculature per unit area in a region of measurement) and perfusion density (PD; the total area of perfused vasculature per unit area in a region of measurement) of the SCP, according to the Early Treatment of Diabetic Retinopathy Study subfields, were automatically measured by software. The diameters of the three concentric circles were 1, 3, and 6 mm, and each ring was divided into quadrants. We analyzed the peripapillary VD and PD of the quadrants of the inner and outer rings and the average of the inner ring, outer ring, and full area. Only scans of signal intensity ≥8 and without motion artifacts and segmentation errors were included in the analysis. Two scans were performed of each participant by an experienced examiner, and we selected the best scan showing a signal strength of ≥8.

Statistical Analysis

All statistical analyses were performed using software (SPSS, ver. 22.0; SPSS Inc., Chicago, IL, USA). For statistical analyses, BCVA values were transformed into the logarithm of the minimum angle of resolution (logMAR) values. Independent *t*-tests and chi-square tests were used to compare clinical factors, OCT parameters, and OCTA parameters between fellow eyes of RVO patients and healthy normal controls. Pearson's correlation was used to investigate the associations between peripapillary OCTA parameters and OCT parameters. A P value < 0.05 was considered statistically significant.

Results

Patient Characteristics

After excluding poor quality of the OCTA images (fellow eyes of RVO: eight patients, controls: five subjects), a total of 83 unilateral RVO patients (50 patients with branch RVO and 33 with central RVO) were enrolled. The mean age of the participants was 63.3 ± 10.8 years (38 males and 45 females). The normal control group included 33 males and 50 females, with a mean age of 60.6 ± 9.2 years. HTN was more prevalent in the RVO patients (41 patients, 49.4%) compared with normal controls (24 patients, 28.9%) ($P = 0.005$). There were no significant differences in mean age, sex, diabetes, laterality, BCVA, SE, IOP, and AL between the two groups (Table 1).

OCT Measurements

The CMT was 249.7 ± 22.8 μm in the fellow eyes of RVO patients and 254.3 ± 17.4 μm in normal controls, which was not statistically significant. The mean GC-IPL thickness was 81.3 ± 6.3 μm in the fellow eyes of RVO patients, which was significantly thinner than that in normal controls. (84.1 ± 5.7 μm, $P = 0.003$)

Peripapillary RNFL thicknesses in the fellow eyes of RVO patients and the normal control group are presented in Table 2. The average RNFL thickness was 93.5 ± 8.4 μm in the fellow eyes of RVO patients and was significantly thinner than that in normal controls (96.6 ± 7.5 μm, $P = 0.013$). In quadrant measurements, the RVO group showed significantly thinner RNFL thickness in the inferior and temporal quadrants ($P = 0.029$ and 0.008, respectively) (Table 2).

Peripapillary OCTA Measurements

The signal strength was 9.5 ± 0.7 in the fellow eyes of RVO patients and 9.6 ± 0.6 in normal controls, which was not statistically significant.

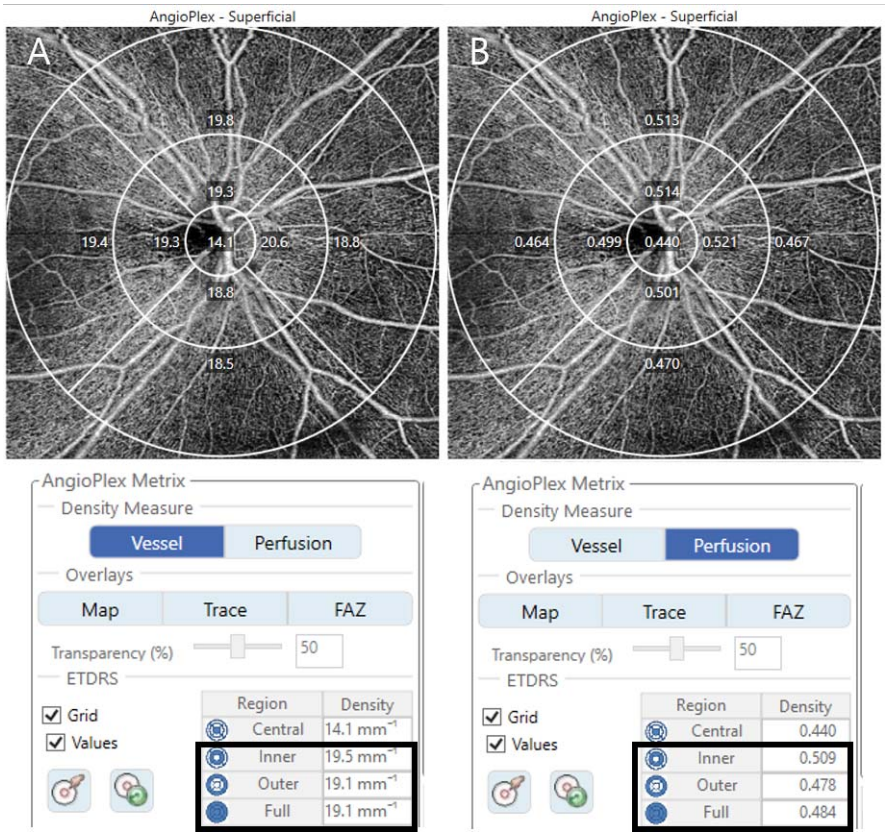

Figure 1. OCTA 6 × 6-mm scan image centered on the optic disc. The en face image of the superficial layer overlaid with the Early Treatment of Diabetic Retinopathy Study grid. The diameters of the three concentric circles are 1, 3, and 6 mm. The measurement tool (AngioPlex software) provided (**A**) peripapillary VD and (**B**) PD measurements in individual subfields. The *bold box* shows the automatic quantitative measurements for an average of the inner ring, outer ring, and full area.

The average peripapillary VDs of the inner ring, outer ring, and full area were 17.47 ± 1.45, 18.50 ± 1.14, and 17.89 ± 1.02 in the fellow eyes of RVO patients, and 17.87 ± 1.11, 18.87 ± 0.71, and 18.27 ± 0.66 in the normal controls, respectively. Those were significantly lower than in normal controls (all $P < 0.05$) (Table 3).

The average peripapillary PDs of the inner ring, outer ring, and full area were 0.456 ± 0.040, 0.467 ± 0.030, and 0.456 ± 0.026 in the fellow eyes of RVO patients and 0.468 ± 0.028, 0.476 ± 0.017, and 0.466 ± 0.016 in the normal controls, respectively. Those were significantly lower than in normal controls (all $P < 0.05$) (Table 4).

The inner inferior quadrant, outer inferior quadrant, and outer temporal quadrant were significantly decreased in peripapillary VD and PD compared with normal controls.

Table 1. Demographics and Clinical Features of the RVO and Control Groups

Characteristic	RVO	Control	*P* Value
Number of eyes	83	83	
Sex, male/female	38/45	33/50	0.265†
Hypertension, *n* (%)	41 (49.4%)	24 (28.9%)	0.005†
Diabetes, *n* (%)	9 (10.8%)	5 (6.0%)	0.264†
Age, years	63.3 ± 10.8	60.6 ± 9.2	0.086‡
Laterality, OD/OS	34/49	44/39	0.081†
BCVA, logMAR*	0.00 ± 0.07	−0.02 ± 0.07	0.121‡
SE, diopters*	−0.15 ± 2.19	−0.34 ± 1.30	0.508‡
IOP, mm Hg*	14.8 ± 3.1	14.5 ± 2.8	0.561‡
AL, mm*	23.7 ± 1.0	23.7 ± 0.9	0.703‡

Values are presented as mean ± SD unless otherwise indicated.
* Values are for the fellow eyes in the RVO group.
† By chi-square test.
‡ By independent *t*-test.

Correlation Analysis Between Peripapillary OCTA and OCT Parameters

Correlation analysis showed that the average peripapillary VD of the inner ring, outer ring, and full area was significantly positively correlated with GC-IPL and RNFL thicknesses (Fig. 2). The average peripapillary PD of the inner ring, outer ring,

Table 2. Comparison of the CMT, Average GC-IPL Thickness, and RNFL Thickness in the Fellow Eyes of RVO and Control Groups

OCT Parameters	RVO Fellow Eye	Control	*P* Value*
CMT, μm	249.7 ± 22.8	254.3 ± 17.4	0.147
Average GC-IPL thickness, μm	81.3 ± 6.3	84.1 ± 5.7	0.003
RNFL thickness, μm			
Average	93.5 ± 8.4	96.6 ± 7.5	0.013
Superior	117.9 ± 14.1	120.8 ± 19.3	0.274
Nasal	70.6 ± 11.7	72.4 ± 11.0	0.298
Inferior	119.5 ± 15.2	124.3 ± 13.2	0.029
Temporal	66.1 ± 9.8	70.2 ± 9.6	0.008

Values are presented as mean ± SD.
* By independent *t*-test.

Table 3. Comparison of Superficial Peripapillary VD in the Fellow Eyes of RVO and Control Groups

VD	RVO Fellow Eye	Control	*P* Value*
Full area	17.89 ± 1.02	18.27 ± 0.66	0.005
Inner ring			
Average	17.47 ± 1.45	17.87 ± 1.11	0.048
Superior	17.70 ± 1.37	18.04 ± 1.19	0.092
Nasal	18.02 ± 1.82	18.44 ± 1.39	0.098
Inferior	18.13 ± 1.24	18.55 ± 1.46	0.047
Temporal	16.01 ± 2.79	16.49 ± 2.16	0.219
Outer ring			
Average	18.50 ± 1.14	18.87 ± 0.71	0.013
Superior	18.97 ± 1.11	19.12 ± 0.69	0.291
Nasal	17.05 ± 1.97	17.37 ± 1.42	0.230
Inferior	18.78 ± 1.11	19.11 ± 1.02	0.049
Temporal	19.21 ± 1.64	19.85 ± 1.03	0.003

Values are presented as mean ± SD.
* By independent *t*-test.

Table 4. Comparison of Superficial Peripapillary PD in the Fellow Eyes of RVO and Control Groups

PD	RVO Fellow Eye	Control	*P* Value*
Full area	0.456 ± 0.026	0.466 ± 0.016	0.003
Inner ring			
Average	0.456 ± 0.040	0.468 ± 0.028	0.031
Superior	0.473 ± 0.042	0.483 ± 0.035	0.094
Nasal	0.478 ± 0.052	0.490 ± 0.028	0.068
Inferior	0.485 ± 0.035	0.498 ± 0.029	0.011
Temporal	0.389 ± 0.072	0.400 ± 0.058	0.267
Outer ring			
Average	0.467 ± 0.030	0.476 ± 0.017	0.013
Superior	0.488 ± 0.030	0.496 ± 0.019	0.068
Nasal	0.432 ± 0.555	0.441 ± 0.039	0.194
Inferior	0.479 ± 0.029	0.486 ± 0.020	0.048
Temporal	0.467 ± 0.043	0.481 ± 0.024	0.011

Values are presented as mean ± SD.
* By independent *t*-test.

and full area was also significantly positively correlated with GC-IPL and RNFL thicknesses (Fig. 3). The RNFL thickness showed the highest correlation between peripapillary VD and PD in the full area ($r = 0.378$, $P < 0.001$; $r = 0.335$, $P = 0.002$, respectively). The GC-IPL thickness also showed the highest correlation between peripapillary VD and PD in the full area ($r = 0.382$, $P < 0.001$; $r = 0.343$, $P = 0.001$, respectively). There was a strong positive correlation between RNFL thickness and GC-IPL thickness ($r = 0.577$, $P < 0.001$). However, CMT was not correlated with average peripapillary VD and PD.

Discussion

The results of OCTA[21,22] and adaptive optics scanning light ophthalmoscope FA[23] in the fellow eyes of patients with unilateral RVO reported a wider foveal avascular zone and lower microvascular density in the macula. Even before an occlusive event, such vascular compromises can cause structural[20] and functional[24] abnormalities in the fellow eye. Although the fellow eye may appear normal on funduscopic examination, it is affected by microvascular perfusion. This suggests that RVO development may not have originated solely from localized ocular damage, but rather that, at least in some patients, systemic changes may have affected the retinal vascular system simultaneously in both eyes, leading to RVO in one eye.

The GC-IPL thickness in the fellow eyes of RVO was significantly thinner than in normal controls. We previously reported a reduction of the GC-IPL thickness in affected eyes with branch RVO.[25] To our knowledge, this is the first study to investigate GC-IPL thickness in fellow eyes with RVO. The

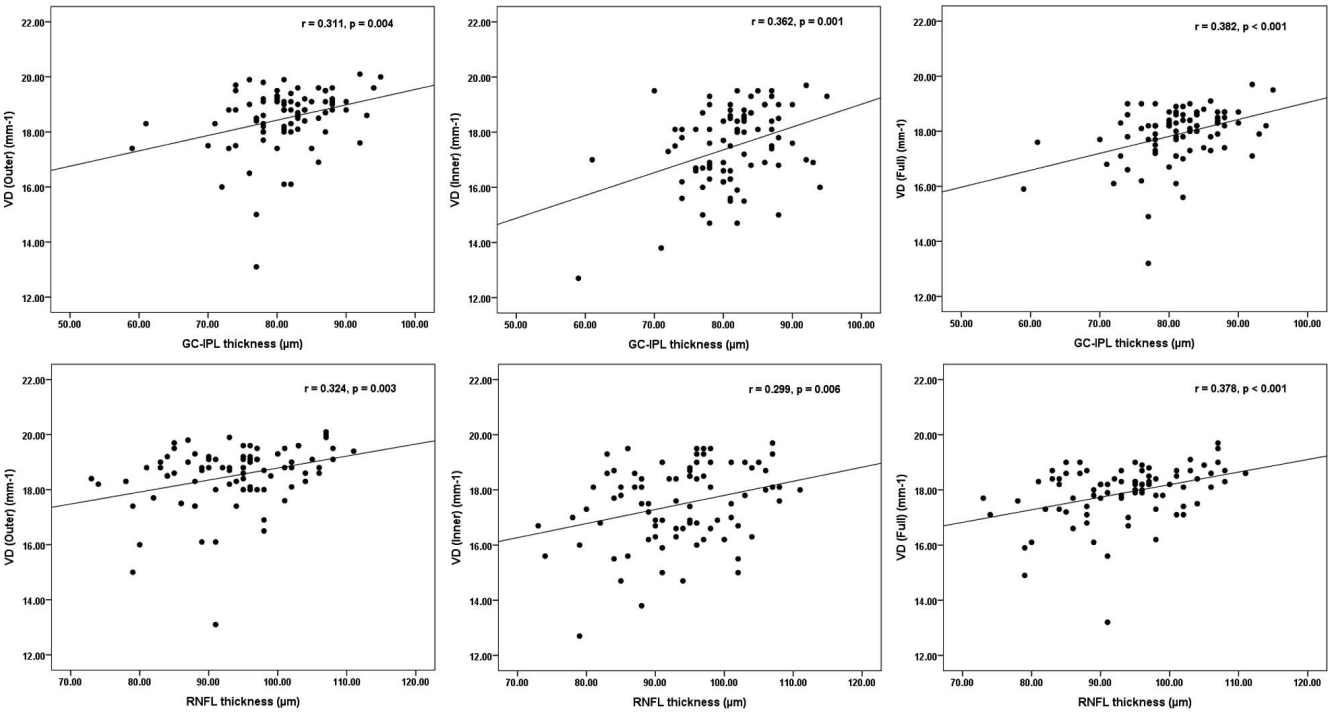

Figure 2. Scatter plots of GC-IPL thickness, RNFL thickness, and VD. Average peripapillary VD of the inner ring, outer ring, and full area were significantly positively correlated with GC-IPL and RNFL thicknesses. Correlation coefficients (*r*) and *P* values are shown.

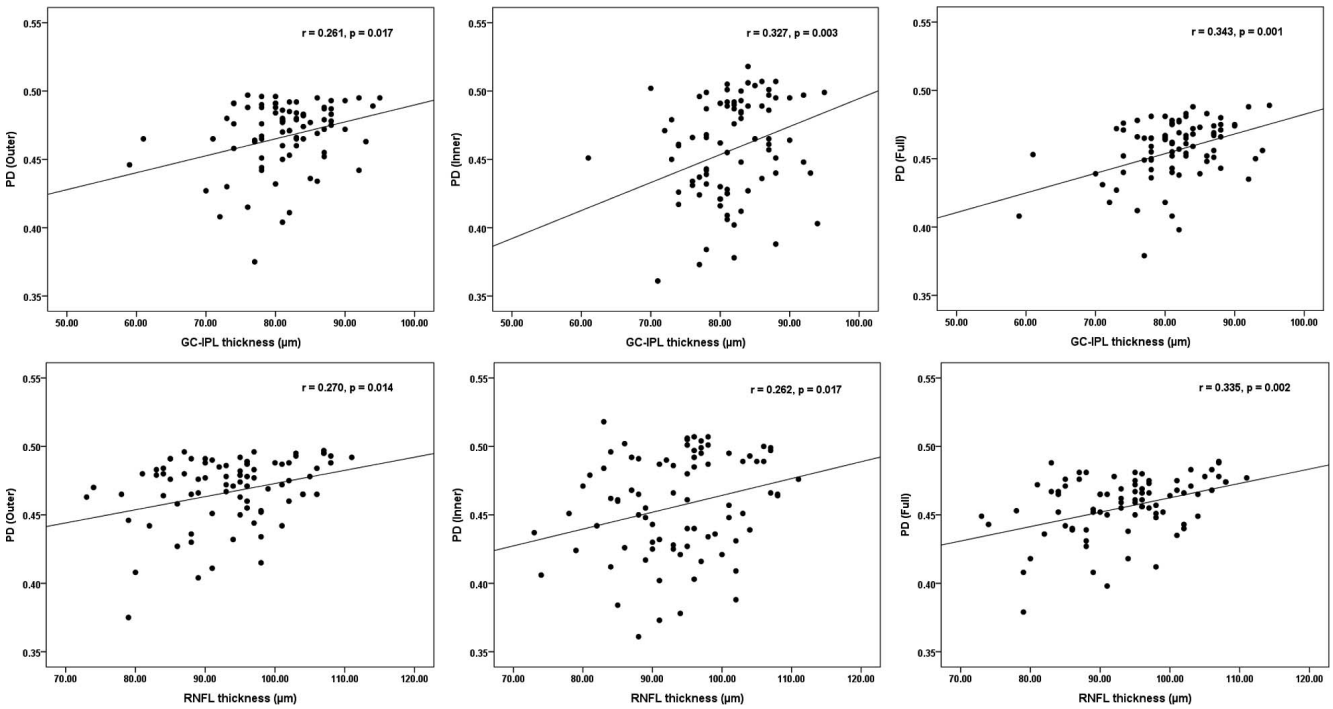

FIGURE 3. Scatter plots of GC-IPL thickness, RNFL thickness, and PD. Average peripapillary PD of the inner ring, outer ring, and full area were significantly positively correlated with GC-IPL and RNFL thicknesses. Correlation coefficients (*r*) and *P* values are shown.

inner retinal layers, and especially the retinal ganglion cells (RGCs), are particularly sensitive to hypoxia. Mild systemic hypoxia alters the flash electroretinogram b-wave and oscillatory potential, but not the a-wave.[26] In animal models, the inner layer is reduced, but the outer retina is preserved in the retinal ischemia.[27] Foveal microvascular compromise in the fellow eyes can affect GC-IPL thickness because it mainly affects the inner retina.

In our study, RNFL layer thinning in the fellow eyes of RVO was significant in the average, inferior, and temporal quadrants. This finding is consistent with those of a previous study[20] that suggested that RVO may have a common mechanism with glaucoma because it is similar to the frequent site of RNFL thinning in glaucoma. Systemic risk factors affecting the vascular pathophysiology, such as HTN, diabetes, and atherosclerosis, have been suggested as possible mechanisms of damage in both glaucoma and RVO. The decreased ocular blood flow[28] and increased retinal venous pressure[29] in the fellow eyes of RVO patients compared with normal controls may be related to the pathogenesis of RVO and glaucoma. However, glaucoma and RVO are multifactorial diseases, and it is difficult to completely understand the vascular dysregulation related to the pathogenesis.

Recently, microvascular perfusion of the optic disc was measured using OCTA to identify optic nerve head (ONH) vascular dysfunction in glaucoma patients.[30,31] OCTA parameters in the peripapillary area were significantly lower in glaucoma patients.[17–19] Recently, Moghimi et al.[32] reported that the VD of macular and ONH using OCTA is associated with the rate of RNFL loss and should be considered when assessing the risk for glaucoma progression. Blood flow of the ONH is supplied by the posterior ciliary artery and central retinal artery, which also supply the superficial RNFL layer of the ONH. Blood flow to the RNFL is supplied by the microcirculation from the retinal radial peripapillary capillaries (RPCs). RPCs are difficult to observe with conventional FA. OCTA is advantageous for evaluating ONH perfusion. Because of its high axial resolution, it enables visualization of the RPC and can quantify the microvascular perfusion. Also, OCTA is less affected by the absorbance and reflectance of disc tissue compared to laser Doppler flowmetry.[33]

There are no established methods for determining the appropriate region for peripapillary microvascular perfusion. Because the RPCs spread as far as 7.6 mm from the temporal edge of the optic disc using OCTA,[34] a larger measurement area was better for evaluating changes in the RPCs.[18] Thus, we measured 6×6-mm scans centered on the optic disc, which is the largest area that the machine can measure. We measured the peripapillary VD and PD of the SCP automatically using the machine, which includes both RPCs and the large retinal vessels around the disc; thus, it was a mixture of both disc and retinal circulation and not a pure measurement of a single vascular bed. However, the measurement described may be more meaningful, as it can understand both the optic nerve and the retinal blood flow supply in retinal diseases.

In this study, we reported the first use of OCTA to quantify peripapillary microvascular parameters in the fellow eyes of RVO patients. We found that the fellow eyes had lower peripapillary VD and PD compared with those of controls. The average of the inner and outer ring and full areas were significantly decreased. When analyzed by quadrant, the inner inferior quadrant, outer inferior quadrant, and outer temporal quadrant were significantly decreased in a manner similar to the reduction in the RNFL. The large retinal vessel becomes narrower from the inner to the outer ring. Because small vessels are vulnerable to ischemia, the average of the outer ring may be affected more than that of the inner ring. In the outer ring, the nasal area may be less affected than the temporal area due to the large vessels.

Lower microvascular parameters using OCTA are found in RVO and glaucoma patients. There are some reasons for these observations. First, it may be affected by vascular dysfunction. Second, it may be a secondary change due to ganglion cell damage. However, it is unclear in the current study whether

RVO and glaucoma patients had a common cause or effect. Further prospective longitudinal studies are needed to clarify this relationship.

We investigated the associations of peripapillary OCTA parameters and OCT parameters. The GC-IPL thickness and peripapillary RNFL thickness were correlated with both peripapillary VD and PD. This suggests that reduced GC-IPL and RNFL thicknesses may be related to peripapillary retinal microcirculation. There was a strong positive correlation between RNFL thickness and GC-IPL thickness ($r = 0.577$, $P < 0.001$). The RNFL contains axons of the RGCs that travel from RGC bodies to the optic disc, and the GC-IPL consists of nuclei and dendrites of the RGCs. Because glaucoma primarily affects RGCs and their axons, GC-IPL and RNFL thinning are associated with glaucomatous structural damage.

This study was limited in that we did not analyze the DCP and choriocapillaris. However, projection and shadow artifacts caused by the superficial retinal vessels can result in inaccurate DCP and choriocapillaris.[35] Further study is needed using instruments that can resolve these artifacts. Second, OCTA measurements can be affected by intravitreal Avastin injections.[36] RVO patients with macular edema underwent intravitreal Avastin injections. Although the intravitreal injection was done into the RVO eyes, not into the fellow eyes of RVO, only patients with at least 3 months since the last injection were included to minimize the intravitreal injection effect. However, it might affect the results. Third, there may be diurnal variation in the OCTA measurements,[37] but since our study did not measure OCTA parameters at the same time, this should be taken into account in interpreting the results. Finally, the measurements of peripapillary microvascular parameters in this study were performed automatically by the software. The OCTA algorithm, in its current form, includes large vessels along with capillaries in its estimation of VD. If novel software is developed, it may be possible to quantify perfusion status separately for the large vessel and RPC. Nevertheless, a strength of our study was that it was the first study, to our knowledge, to evaluate changes in peripapillary microvascular parameters and the associations of peripapillary OCTA and OCT parameters in the fellow eyes of patients with unilateral RVO using OCTA.

In conclusion, OCTA revealed changes in peripapillary microvascular parameters in the fellow eyes of patients with unilateral RVO. The peripapillary VD and PD were decreased compared with those of the controls. GC-IPL and RNFL thinning were also observed. The RNFL and GC-IPL thicknesses were positively correlated with both peripapillary VD and PD. Prospective longitudinal studies should be performed to investigate the cause and effect relationship between RNFL and GC-IPL thinning and the reduction in peripapillary VD in RVO and glaucoma patients.

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