

Parapapillary Choroidal Microvasculature Dropout in Branched Retinal Vein Occlusion and Glaucoma

Jiwon Baek,^{1,2} Hae-Young Lopilly Park,^{1,3} Seong Ah Kim,^{1,3} Kyung Euy Hong,^{1,3} Soo Ji Jeon,^{1,2} Da Young Shin,^{1,4} Younhea Jung,^{1,5} and Chan Kee Park^{1,3}

¹Department of Ophthalmology, College of Medicine, The Catholic University of Korea, Seoul, South Korea

²Bucheon St. Mary's Hospital, Gyeonggi-do, South Korea

³Seoul St. Mary's Hospital, Seoul, South Korea

⁴Eunpyeong St. Mary's Hospital, Seoul, South Korea

⁵Yeouido St. Mary's Hospital, Seoul, South Korea

Correspondence: Hae-Young Lopilly Park, Department of Ophthalmology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea, 505 Banpo-dong, Seocho-ku, Seoul 137-701, Korea; lopilly@catholic.ac.kr

Received: December 28, 2021

Accepted: March 9, 2022

Published: March 29, 2022

Citation: Baek J, Park HYL, Kim SA, et al. Parapapillary choroidal microvasculature dropout in branched retinal vein occlusion and glaucoma. *Invest Ophthalmol Vis Sci.* 2022;63(3):27.

<https://doi.org/10.1167/iovs.63.3.27>

PURPOSE. To investigate parapapillary choroidal microvasculature dropout (MvD) in branch retinal vein occlusion (BRVO) patients and compare them with open-angle glaucoma (OAG) patients using optical coherence tomography angiography (OCT-A).

METHODS. In total, 85 eyes of BRVO patients and 85 eyes of OAG patients, matched by age, spherical equivalent, and baseline mean deviation (MD) of the visual field (VF), were assessed. MvD was defined as complete loss of microvasculature within the choroidal layer on OCT-A. Linear regression analysis was used to obtain the slope of the MD change of the VF.

RESULTS. The presence of MvD on OCT-A was significantly more frequent in OAG eyes (63.1%) compared to BRVO eyes (31.8%). BRVO eyes with MvD showed worse baseline MD of the VF than BRVO eyes without MvD (-10.19 ± 8.50 and -7.77 ± 6.46 dB, respectively; $P = 0.045$). The presence of MvD was the only factor significantly associated with MD change of the VF in OAG eyes. Lower baseline average RNFL thickness, greater MvD angle, and lower macular superficial vessel density were significantly associated with MD change of the VF in BRVO eyes.

CONCLUSIONS. OCT-A of the parapapillary area showed choroidal microvasculature impairment in both BRVO and OAG patients. However, the frequency was higher in glaucoma patients with similar degrees of VF damage, which suggests that the glaucomatous process contributes to MvD development. The effect of MvD on VF change was different between BRVO and OAG, suggesting that the underlying pathogenesis may also be different.

Keywords: glaucoma, branch retinal vein occlusion, microvasculature dropout

Glaucoma is a progressive optic neuropathy that involves loss of the retinal ganglion cells (RGCs). Recent optical coherence tomography angiography (OCT-A) studies have identified microvasculature dropout (MvD) in the parapapillary choroid of glaucoma patients.¹⁻³ These findings have demonstrated a topographic correlation with the location of retinal nerve fiber layer (RNFL) defects, visual field (VF) defects, and changes in the lamina cribrosa (LC).³⁻⁵ As elevated intraocular pressure (IOP) is an important causative factor of glaucoma, and LC changes are a key finding in glaucomatous optic nerve heads (ONHs), the development of MvD may be related to the mechanical processes involved in glaucoma. However, MvD has also been observed in nonglaucomatous, healthy eyes with systemic vascular dysregulation.⁶ In glaucoma patients with MvD, disease tends to progress faster and is associated with features like disc hemorrhage, cold extremities, migraines, low ocular perfusion pressure, and nocturnal blood pressure dips.⁷⁻⁹ Therefore vascular insufficiency and instability are also thought to contribute to MvD. Recently, MvD has also

been reported in patients with compressive optic neuropathy.¹⁰ This indicates that MvD may also develop as a result of RGC loss. However, it remains unclear whether MvD is a mechanical process within the ONH that precedes glaucoma or is a secondary change thereof. Because OCT-A has shown good repeatability and reproducibility in the measurements, now we could use OCT-A imaging to reveal the pathogenesis of MvD.¹¹

Branch retina vein occlusion (BRVO) is a representative condition of vascular insufficiency followed by loss of RNFL and VF defect at the affected site.¹² Given the evidence of differences in LC structures and peripapillary vessel densities between BRVO and NTG, the RNFL loss in BRVO is caused by the occlusion of branches of the retinal vessels, not by changes at the level of LC.¹³ To determine whether a mechanical process within the ONH is required for the development of parapapillary choroidal MvD, we compared the presence and features of MvD between patients with glaucoma and BRVO. We hypothesized that if choroidal MvD results from vascular compromise and not from ONH



changes, it would be seen in BRVO. The purpose of this study was to characterize and compare the parapapillary microvasculature focusing on MvD between BRVO and open-angle glaucoma (OAG) patients.

METHODS

Subjects

BRVO patients were prospectively enrolled between January 2017 and September 2019 at Seoul St. Mary's Hospital. This study followed the Declaration of Helsinki and guidelines for experimental investigation in human subjects laid down by the Institutional Review Board of Seoul St. Mary's Hospital (KC18RESI0852). Written informed consent was obtained from consecutive patients who met the eligibility criteria.

BRVO was diagnosed on the basis of ophthalmoscopic slit lamp fundus examination and color fundus photographs. BRVO was defined as retinal vein occlusions localized to a retinal sector of obstructed venules, characterized by scattered superficial and deep retinal hemorrhages, venous dilation, intraretinal microvascular abnormalities, and occluded and sheathed retinal venules. BRVO eyes with central macular thickness 300 μm or less were included to avoid interference of macular edema on measurement of VF and OCT-A analysis. Patients with IOP of more than 21 mm Hg, or family history of glaucoma were excluded.

The medical records of OAG patients were obtained from the database of the Catholic Medical Center Glaucoma Progression Study (CMC-GPS). OAG patients in the CMC-GPS database were matched 1:1 by age, spherical equivalent, and baseline mean deviation (MD) of the VF with the BRVO group. OAG was diagnosed by two glaucoma specialists (H.Y.P. and C.K.P.) using the following criteria: open angle on gonioscopic examination, glaucomatous optic disc appearance (e.g., diffuse or localized rim thinning, notch in the rim, or a vertical cup-to-disc ratio > 0.6 , or higher than that of the other eye by more than 0.2), and glaucomatous VF loss (a cluster of three points with a probability of $< 5\%$ on the pattern deviation map in ≥ 1 hemifield, including ≥ 1 point with a probability of $< 1\%$; or a cluster of two points with a probability of $< 1\%$ on two qualifying VFs).

Patients followed up for at least 2 years, with at least four VF examinations, were selected for the study. Patients also had to meet the following criteria to be included: best-corrected visual acuity (BCVA) $\geq 20/40$, spherical refraction within ± 6.0 diopters (D), cylinder correction within ± 3.0 D, and MD > -12.00 dB. The exclusion criteria were as follows: glaucoma patients who developed BRVO during follow-up; a history of other retinal disease (such as diabetic or hypertensive retinopathy); a history of eye trauma or surgery (with the exception of uncomplicated cataract surgery); optic nerve diseases other than glaucoma; and a history of systemic or neurological diseases that might affect the VF. If both eyes were eligible for the study, only the right eye was included.

All participants underwent a complete ophthalmological examination including medical history, measurement of BCVA, refraction assessment, slit-lamp biomicroscopy, gonioscopy, Goldmann applanation tonometry, measurement of central corneal thickness using ultrasound pachymetry (Tomey Corp., Nagoya, Japan), measurement of axial length using ocular biometry (IOL Master; Carl Zeiss Meditec, Jena, Germany), dilated stereoscopic optic disc examination, red-free fundus photography (Canon, Tokyo,

Japan), OCT (Cirrus OCT; Carl Zeiss Meditec), Humphrey VF examination using the Swedish interactive threshold Standard 24-2 algorithm (Carl Zeiss Meditec), and OCT-A (DRI OCT Triton; Topcon Corp., Tokyo, Japan). The included patients were followed up every one to three months with color disc and fundus photography. VF and OCT examinations were performed at six-month intervals.

OCT-A Examination

A commercial, swept-source OCT-A device (DRI OCT Triton; Topcon) was used for imaging the macular and parapapillary regions. The central wavelength was 1,050 nm, the acquisition speed was 100,000 A-scans/s, and the axial and transverse resolutions were 7 and 20 μm , respectively. Cubes measuring 4.5×4.5 mm were scanned with 320 clusters of four repeated B-scans centered on the optic disc and the macula in each cube.

The deep-layer parapapillary microvasculature in the relevant region was evaluated using *en face* images generated by automated layer segmentation of signals from the retinal pigment epithelium, which extended to the outer scleral border. MvD was defined as focal, sectoral capillary dropout within the visible microvascular network. MvD was identified based on a dropout width $>$ twofold that of the visible juxtapapillary microvessels (Fig. 1A). Two independent observers (H.Y.P. and S.A.K.) blinded to the clinical data identified MvD. Disagreements were resolved by a third observer (C.K.P.). Only clear images (quality scores > 30 and no motion blurring) were analyzed.

The circumferential extent of MvD was measured using ImageJ software (<http://rsb.info.nih.gov/ij/index.html>). Two lines were drawn from the disc center to the points where the MvD border met the disc margin (Fig. 1B). The angle between these two lines was the angular extent of MvD. All angles were measured by two independent observers (H.Y.P. and S.A.K.) blinded to the clinical data. The angles were measured twice by each observer, and the mean of the four values was used for the analysis.

The automatically segmented retinal vascular plexus consists of superficial and deep layers. Vessel density (VD) of the superficial layer represented the macular VD in this study and was calculated automatically by the built-in

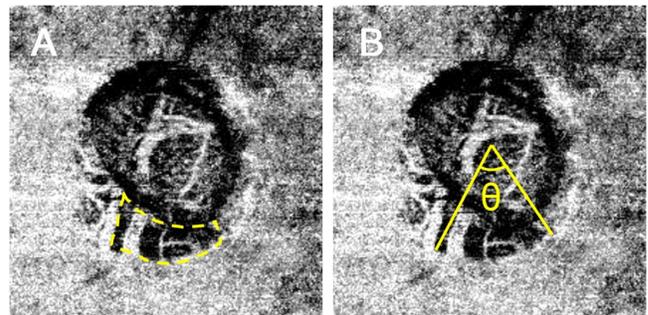


FIGURE 1. Detection of MvD and measurement of its extent. (A and B) Choroidal layer on the *en face* OCT-A images. Focal sectoral capillary dropout with no visible microvascular network adjoining the disc margin on *en face* images of the choroid was considered to indicate MvD (A, yellow dashed lines). From the disc center, two lines were drawn to the points at which the MvD border met the disc margin (B, yellow solid lines), and the angle between these two lines was taken as the extent of MvD (θ).

software of the DRI OCT Triton, ImageNet software (ImageNet 6, ver. 1.19.11030; Topcon), which removed the deep retinal and choriocapillary layers through an algorithm. According to the default setting of the device, the superficial vascular plexus extends from 2.6 μm below the internal limiting membrane to 15.6 μm below the junction of the inner plexiform layer and inner nuclear layer. VD measurements were obtained over five subfields with an Early Treatment Diabetic Retinopathy Study grid overlay combining the two inner rings.¹⁴

MD Change of the VF

Patients with at least four reliable VF test results (defined as < 15% false-negatives, < 15% false-positives, and < 20% fixation losses) were included in the analysis. We performed linear regression analysis to obtain the slope of the MD change of the VF.

Data Analysis

Student's *t*-test and the χ^2 test were used to compare continuous and categorical variables, respectively. Interobserver difference in MvD identifications were evaluated using κ coefficients. Interobserver difference in measuring MvD angle was calculated as the intraclass correlation coefficients (ICCs) and their confidence intervals (CIs) in 30 randomly selected images. Logistic regression analysis was used to identify factors associated with the presence of MvD, whereas linear regression analysis was used to identify factors associated with the extent of MvD. Univariate

and multivariate logistic regression analyses were used to identify factors associated with the MD change of the VF. Independent variables with *P* values < 0.10 in the univariate model were included in the multivariate model. A *P* value < 0.05 was considered to indicate statistical significance. All statistical analyses were performed using SPSS Statistics software (ver. 16.0; IBM Corp., Armonk, NY, USA).

RESULTS

In total, 85 BRVO eyes and 85 OAG eyes were included in the study, of patients matched on the basis of age, spherical equivalent, and baseline MD. Interobserver agreement in terms of MvD identification was excellent ($\kappa = 0.912$; 95% CI, 0.897–0.945; *P* < 0.001). Interobserver agreement in terms of MvD angle measurement was excellent (ICC = 0.896; 95% CI, 0.881–0.910; *P* < 0.001). The baseline characteristics are compared between the BRVO and OAG eyes in Table 1. Although the eyes were matched according to the baseline MD of the VF, there was in fact a significant difference between the BRVO and OAG eyes in terms of pattern standard deviation (6.68 ± 3.94 and 5.43 ± 3.89 , respectively; *P* = 0.039). The presence of MvD on OCT-A was significantly more frequent in OAG (63.1%) compared to BRVO (31.8%) eyes (*P* < 0.001), while the presence of β -peripapillary atrophy (β -PPA) showed no difference (*P* = 0.434). The location was predominant in the superior region in BRVO (69.4%), however, the predominant location in OAG was in the inferior region (77.6%) and this showed significant difference between groups (*P* < 0.001). In eye showing

TABLE 1. Demographics and Clinical Characteristics

Variables	BRVO Eyes (n = 85)	OAG Eyes (n = 85)	P Value
Age at diagnosis (y)	72.64 \pm 11.53	73.62 \pm 10.73	0.982*
Male	40 (47.1%)	38 (44.7%)	0.439†
History of systemic hypertension	36 (42.4%)	43 (50.6%)	0.178†
History of diabetes mellitus	22 (25.9%)	23 (27.1%)	0.500†
Spherical equivalent (D)	-1.05 \pm 2.51	-1.00 \pm 1.79	0.824*
Axial length (mm)	23.66 \pm 1.19	23.20 \pm 3.55	0.414*
Central corneal thickness (μm)	520.69 \pm 35.13	515.47 \pm 31.15	0.415*
Baseline IOP (mm Hg)	15.23 \pm 6.21	14.18 \pm 6.79	0.308*
Mean follow-up IOP (mm Hg)	14.19 \pm 3.31	14.22 \pm 3.07	0.946*
Baseline average RNFL thickness (μm)	75.59 \pm 15.21	72.58 \pm 12.53	0.161*
VF examination			
Baseline MD (dB)	-7.37 \pm 7.42	-7.15 \pm 6.95	0.751*
Baseline PSD (dB)	6.68 \pm 3.94	5.43 \pm 3.89	0.039*
Last MD (dB)	-8.67 \pm 8.27	-8.38 \pm 6.23	0.799*
Last PSD (dB)	7.37 \pm 4.05	7.45 \pm 4.22	0.901*
Presence of DH	11 (12.9%)	5 (5.9%)	0.094†
Presence of β -PPA	58 (65.9%)	60 (70.6%)	0.434†
Presence of MvD on OCT-A	27 (31.8%)	53 (63.1%)	<0.001†
MvD angle	22.55° \pm 26.35°	16.00° \pm 23.73°	0.154*
Parapapillary superficial VD	46.72% \pm 10.54%	49.93% \pm 10.26%	0.930*
Macular superficial VD			
Global	43.59% \pm 5.74%	44.16 \pm 5.56%	0.421*
Superior quadrant	45.99% \pm 5.96%	44.71 \pm 9.27%	0.070*
Temporal quadrant	42.37% \pm 5.05%	44.42 \pm 5.72%	0.059*
Inferior quadrant	42.87% \pm 8.15%	45.74 \pm 6.13%	0.237*
Nasal quadrant	43.16% \pm 4.96%	41.86 \pm 5.64%	0.451*

PSD, pattern standard deviation; DH, disc hemorrhage.

Data are mean \pm standard deviation unless otherwise indicated. Factors with statistical significance are shown in bold.

* Student's *t*-test.

† χ^2 test.

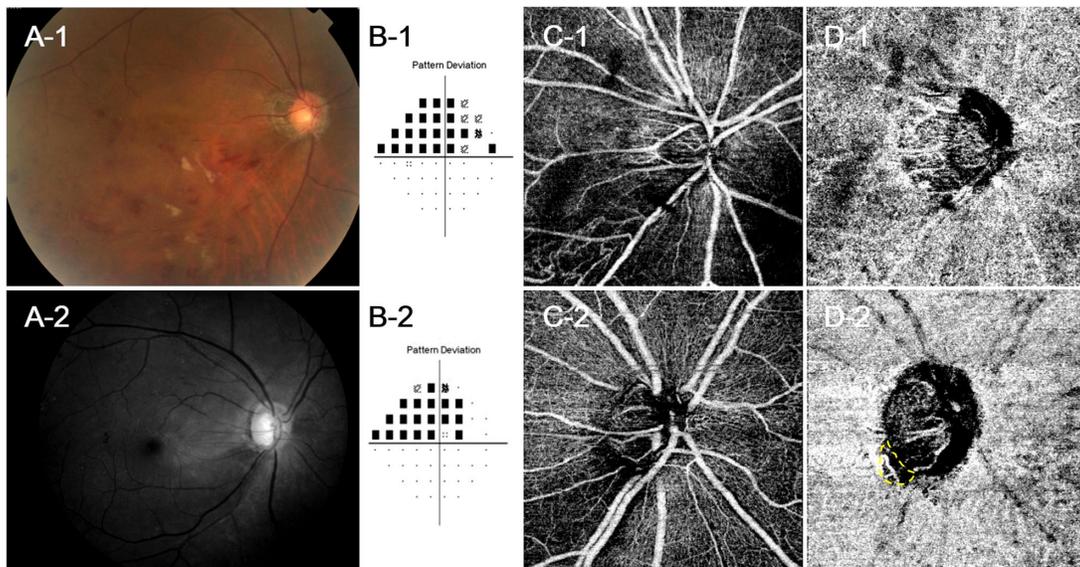


FIGURE 2. Findings in a patient with BRVO and glaucoma. (A) Fundus or red-free photographs. (B) Pattern deviation map of the VF. (C, D) En face OCT-A images obtained in the (C) inner-retinal and (D) choroidal layers. The upper image shows a BRVO patient, and the lower image shows a glaucoma patient. The BRVO patient had a cotton-wool patch and hemorrhage along the inferotemporal region of the retina (A-1). This patient had a superior VF defect (B-1). After resolution of the edema and hemorrhage, OCT-A images were obtained and showed a loss of inferotemporal superficial vessel density (C-1), without MvD, in the choroidal layer (D-1). The glaucoma patient with inferotemporal RNFL (A-2) had a similar VF defect (B-1). A loss of inferotemporal superficial vessel density (C-2) corresponding to the RNFL loss with MvD in the choroidal layer can be seen (D-2, yellow dashed line).

TABLE 2. Comparison Between Eyes With and Without Microvasculature Dropout

Variables	BRVO Eyes With MvD (n = 27)	BRVO Eyes Without MvD f (n = 58)	P Value	OAG Eyes With MvD (n = 53)	OAG Eyes Without MvD (n = 21)	P Value
Age at diagnosis (y)	72.96 ± 14.20	71.95 ± 10.18	0.716 [†]	73.94 ± 11.48	72.67 ± 9.74	0.478 [*]
Male	13 (48.1%)	27 (46.6%)	1.000 [†]	18 (35.3%)	5 (23.8%)	0.114 [†]
History of systemic hypertension	13 (48.1%)	23 (39.7%)	0.488 [†]	32 (62.7%)	11 (33.3%)	0.014[†]
History of diabetes mellitus	8 (29.6%)	14 (24.1%)	0.604 [†]	15 (29.4%)	8 (24.2%)	0.803 [†]
Best-corrected visual acuity	0.68 ± 0.32	0.63 ± 0.36	0.545 [*]	0.68 ± 0.32	0.68 ± 0.33	0.998 [*]
Spherical equivalent (D)	-1.07 ± 3.19	-1.09 ± 2.11	0.534 [*]	-1.03 ± 2.11	-1.07 ± 1.15	0.562 [*]
Axial length (mm)	23.59 ± 1.37	23.70 ± 1.11	0.769 [*]	23.29 ± 4.15	23.02 ± 0.61	0.804 [*]
Central corneal thickness (µm)	513.32 ± 22.90	524.69 ± 39.99	0.260 [*]	513.72 ± 34.53	517.35 ± 28.16	0.667 [*]
Baseline IOP (mm Hg)	15.44 ± 6.49	15.15 ± 6.14	0.850 [*]	14.04 ± 7.25	14.25 ± 6.19	0.896 [*]
Mean follow-up IOP (mm Hg)	14.77 ± 3.97	13.91 ± 3.53	0.266 [*]	14.22 ± 3.44	14.15 ± 2.51	0.927 [*]
Baseline average RNFL thickness (µm)	72.22 ± 13.19	77.15 ± 15.94	0.165 [*]	73.15 ± 11.38	71.27 ± 14.28	0.505 [*]
VF examination						
Baseline MD (dB)	-10.19 ± 8.50	-7.77 ± 6.46	0.045[*]	-5.44 ± 4.24	-5.47 ± 9.46	0.320 [*]
Baseline PSD (dB)	7.19 ± 3.86	6.45 ± 3.98	0.423 [*]	5.51 ± 3.95	4.63 ± 3.01	0.279 [*]
Last MD (dB)	-10.69 ± 8.32	-7.79 ± 8.16	0.145 [*]	-8.59 ± 5.50	-7.73 ± 7.76	0.568 [*]
Last PSD (dB)	8.70 ± 4.15	6.78 ± 3.69	0.057 [*]	7.69 ± 4.00	-6.52 ± 4.56	0.236 [*]
Presence of DH	2 (7.4%)	9 (15.5%)	0.490 [†]	5 (9.8%)	0	0.151 [†]

PSD, pattern standard deviation; DH, disc hemorrhage.

Data are mean ± standard deviation unless otherwise indicated. Factors with statistical significance are shown in bold.

^{*} Student's *t*-test.

[†] χ^2 test.

MvD, the extent of MvD was greater in BRVO compared to OAG eyes (22.55° ± 26.35° and 16.00° ± 23.73°, respectively), but the difference was not statistically significant (*P* = 0.154). As shown by the representative cases in Figure 2, a superior VF defect with corresponding inferotemporal parapapillary superficial VD loss was present on OCT-A at the location where BRVO occurred. However, BRVO eyes did

not show choroidal MvD on deep choroidal OCT-A map. In contrast, OAG eyes with a similar degree of VF damage had inferotemporal RNFL and VD loss, and a corresponding MvD on the deep choroidal OCT-A map.

BRVO and OAG eyes were classified on the basis of the presence or absence of MvD (Table 2). BRVO eyes with MvD showed worse baseline MD of the VF than BRVO eyes

TABLE 3. Factors Associated With the Presence and the Extent of Microvasculature Dropout in Eyes With Glaucoma

Variables	Presence of MvD		MvD Angle	
	Beta (95% CI)	P Value	Beta (95% CI)	P Value
Age	1.092 (0.954–1.131)	0.686	0.245 (–0.377–0.866)	0.434
Best-corrected visual acuity	0.950 (0.226–4.002)	0.945	3.939 (–22.499–30.376)	0.766
Axial length	1.008 (0.855–1.188)	0.923	–5.134 (–13.711–3.443)	0.230
Mean baseline IOP	1.003 (0.939–1.072)	0.923	–0.928 (–2.626–0.770)	0.279
Mean follow-up IOP	1.052 (0.912–1.214)	0.488	1.057 (0.918–1.217)	0.443
Baseline MD of VF	0.970 (0.954–0.993)	0.047	0.345 (–0.608–1.299)	0.472
Baseline average pRNFL thickness	0.994 (0.972–1.058)	0.795	–0.169 (–0.567–0.229)	0.400
Presence of DH	2.600 (0.856–5.974)	0.999	0.781 (0.190–3.211)	0.732
Macular superficial VD	0.824 (0.721–0.942)	0.005	0.028 (–0.920–0.977)	0.952

DH, disc hemorrhage.
Factors with statistical significance are shown in bold.

TABLE 4. Factors Associated With the Presence and the Extent of Microvasculature Dropout in Eyes With Branch Retinal Vein Occlusion

Variables	Presence of MvD		MvD Angle	
	Beta (95% CI)	P Value	Beta (95% CI)	P Value
Age	0.998 (0.959–1.039)	0.933	–0.045 (–0.653 to 0.563)	0.882
Best-corrected visual acuity	0.472 (0.107–2.079)	0.321	–5.244 (–8.663 to –2.826)	0.001
Axial length	0.769 (0.426–1.386)	0.382	0.269 (–1.709 to 2.246)	0.784
Mean baseline IOP	0.941 (0.928–1.084)	0.941	–0.320 (–2.224 to 1.583)	0.738
Mean follow-up IOP	1.057 (0.918–1.217)	0.443	0.220 (–1.696 to 2.137)	0.819
Baseline MD of VF	0.925 (0.867–0.986)	0.016	–1.497 (–2.899 to –0.095)	0.037
Baseline average pRNFL thickness	0.981 (0.952–1.012)	0.226	0.134 (–0.235 to 0.503)	0.470
Presence of DH	0.781 (0.190–3.211)	0.732	0.781 (0.190–3.211)	0.732
Macular superficial VD	0.951 (0.929–0.977)	0.047	–0.936 (–2.126 to 1.097)	0.083

DH, disc hemorrhage.
Factors with statistical significance are shown in bold.

without MvD (–10.19 ± 8.50 and –7.77 ± 6.46 dB, respectively; *P* = 0.045). Patients with OAG eyes with MvD were more likely to have a history of systemic hypertension than those with OAG eyes without MvD (62.7% and 33.3%, respectively; *P* = 0.014). MD slope did not differ between BRVO

eyes with and without MvD (*P* = 0.250), however, showed significant difference between OAG eyes with and without MvD (–2.97 ± 4.55 and 0.67 ± 13.77 dB/y, respectively; *P* = 0.012), having OAG eyes with MvD showing significantly steeper MD slope.

TABLE 5. Factors Associated With Mean Deviation of the Visual Field in Eyes With Glaucoma

Variables	Univariate		Multivariate	
	OR (95% CI)	P Value	OR (95% CI)	P Value
Age	0.994 (0.954–1.035)	0.771		
Male gender	1.941 (0.767–4.916)	0.162		
History of systemic hypertension	1.500 (0.595–3.779)	0.390		
History of diabetes mellitus	2.310 (0.709–7.525)	0.165		
Best-corrected visual acuity	0.362 (0.083–1.584)	0.177		
Axial length	1.106 (0.804–1.522)	0.534		
Central corneal thickness	1.005 (0.985–1.024)	0.639		
Spherical equivalent	1.178 (0.848–1.636)	0.330		
Mean baseline IOP	1.076 (0.935–1.246)	0.488		
Mean follow-up IOP	1.061 (0.910–1.237)	0.451		
Baseline MD of VF	0.877 (0.754–1.020)	0.088	0.862 (0.713–1.042)	0.773
Baseline PSD of VF	1.106 (0.997–1.227)	0.056	1.020 (0.890–1.170)	0.125
Baseline average pRNFL thickness	0.990 (0.979–1.042)	0.546		
Presence of DH	2.600 (1.456–9.974)	0.006	3.125 (0.923–3.974)	0.999
Presence of MvD	12.031 (2.619–25.277)	0.001	12.121 (2.425–26.597)	0.002
MvD angle	1.009 (0.987–1.030)	0.175		
Macular superficial VD	0.947 (0.864–1.039)	0.251		

PSD, pattern standard deviation; VD, vessel density.
Factors with *P* < 0.1 in univariate analysis were included in multivariate analysis. Factors with statistical significance are shown in bold.

TABLE 6. Factors Associated With Mean Deviation of the Visual Field in Eyes With Branch Retinal Vein Occlusion

Variables	Univariate		Multivariate	
	OR (95% CI)	P Value	OR (95% CI)	P Value
Age	1.015 (0.968–1.065)	0.540		
Male gender	0.861 (0.304–2.439)	0.778		
History of systemic hypertension	1.150 (0.399–3.313)	0.738		
History of diabetes mellitus	1.594 (0.515–4.931)	0.419		
Best-corrected visual acuity	0.763 (0.418–1.075)	0.516		
Axial length	0.874 (0.351–2.178)	0.772		
Central corneal thickness	1.003 (0.983–1.024)	0.770		
Spherical equivalent	1.283 (0.914–1.801)	0.149		
Mean baseline IOP	1.008 (0.925–1.099)	0.853		
Mean follow-up IOP	1.010 (0.862–1.184)	0.899		
Baseline MD of VF	0.966 (0.845–1.105)	0.127		
Baseline PSD of VF	1.072 (0.980–1.172)	0.613		
Baseline average pRNFL thickness	0.995 (0.938–1.183)	0.085	0.948 (0.919–0.995)	0.046
Presence of DH	1.475 (0.348–6.243)	0.598		
Presence of MvD	1.826 (0.541–6.160)	0.332		
MvD angle	1.023 (1.001–1.046)	0.040	1.034 (1.001–1.067)	0.041
Macular superficial VD	0.945 (0.911–0.973)	0.033	0.929 (0.890–0.951)	0.019

PSD, pattern standard deviation; DH, disc hemorrhage.

Factors with $P < 0.1$ in univariate analysis were included in multivariate analysis. Factors with statistical significance are shown in bold.

Regression analysis was performed to determine the factors associated with the presence and extent of MvD in OAG and BRVO eyes. Worse baseline MD of the VF and lower macular superficial VD were significantly associated with the presence of MvD in OAG ($P = 0.047$ and 0.016 , respectively; Table 3) and BRVO eyes ($P = 0.005$ and 0.047 , respectively; Table 4). The extent of MvD showed no associations with any other variables in OAG eyes, but, worse BCVA and worse baseline MD of the VF were significantly associated with the extent of MvD in BRVO eyes ($P = 0.001$ and 0.037 , respectively).

We performed a univariate regression analysis to investigate the effects of MvD on the MD change of VF in OAG and BRVO eyes (Table 5). Worse baseline MD of the VF (Beta: 0.819; 95% CI: 0.622–1.016; $P < 0.001$), thinner baseline average RNFL thickness (Beta: 0.377; 95% CI: 0.254–0.501; $P < 0.001$), presence of MvD (Beta: -5.651 ; 95% CI: -9.271 to 2.022 ; $P = 0.003$) were significantly associated with MD slope of the VF in OAG eyes. History of systemic hypertension (Beta: -3.858 ; 95% CI: -6.790 to 0.925 ; $P = 0.011$), worse baseline MD of the VF (Beta: 0.608; 95% CI: 0.352–0.863; $P < 0.001$), thinner baseline average RNFL thickness (Beta: 0.148; 95% CI: 0.010–0.285; $P = 0.035$), and presence of MvD (Beta: -2.729 ; 95% CI: -5.539 to 0.062 ; $P = 0.050$) were significant factors associated with MD slope of the VF in OAG eyes in multivariate analysis. In BRVO eyes, worse baseline MD of the VF (Beta: 0.218; 95% CI: 0.044–0.392; $P = 0.015$), greater MvD angle (Beta: -0.055 ; 95% CI: -0.105 to 0.005 ; $P = 0.033$), lower macular superficial VD (Beta: 0.263; 95% CI: 0.017–0.419; $P = 0.001$), and longer follow-up period (Beta: -1.613 ; 95% CI: -3.152 to -0.073 ; $P = 0.004$) were significantly associated with MD slope of the VF in the univariate analysis (Table 6). Worse baseline MD of the VF (Beta: 0.475; 95% CI: 0.227–0.724; $P = 0.001$), greater MvD angle (Beta: -0.055 ; 95% CI: -0.102 to 0.009 ; $P = 0.020$), and lower macular superficial VD (Beta: 0.325; 95% CI: 0.132–0.519; $P = 0.002$) were significantly associated with MD slope of the VF in BRVO eyes in the multivariate analysis.

DISCUSSION

In this study, we aimed to determine whether mechanical process within the ONH is crucial to the development of parapapillary choroidal MvD. BRVO manifests as an occlusion of the retinal vessel branches, resulting in RNFL and superficial VD loss, and sometimes VF damage, in the affected region. The frequency of MvD in BRVO eyes in this study was 31.8%, which suggests a relationship between vascular compromise and MvD. However, the MvD frequency in OAG was 63.1% despite matching with BRVO eyes based on age, spherical equivalent, and the baseline MD of the VF. This shows that with similar VF defect, MvD was more frequent in OAG than BRVO eyes. Therefore a glaucomatous process, which is different from vascular insufficiency in BRVO, may mainly or additionally contribute to the development of MvD.

An association between BRVO and glaucoma has been reported in many studies.^{15–24} The Ocular Hypertension Treatment Study reported that a higher cup-to-disc ratio was associated with BRVO development in patients with elevated IOP.²⁵ The prevalence of glaucoma was much higher in BRVO patients than in the general population. In case-control studies, it has also been reported that a history of glaucoma in the contralateral eye was significantly more common in BRVO patients than controls. The association between BRVO and glaucoma suggests that a common pathogenic mechanism may contribute to both diseases.²⁶ However, OAG has distinct features, such as elevated IOP and LC changes in the ONH, which are usually absent in BRVO. Therefore the glaucomatous process may contribute to MvD development.

Previous studies have demonstrated that OAG eyes with LC defects had lower parapapillary VDs.⁵ A larger β -PPA and the presence of an LC defect were associated with choroidal MvD in OAG eyes.¹ Interestingly, this study demonstrated an association between presence of systemic hypertension and MvD development in OAG eyes. Both systemic and ocular factors are thought to contribute to MvD

development. However, the frequency was about twofold higher in OAG compared to BRVO eyes in this study, suggesting that ONH-related mechanical factors are mainly responsible for MvD development. In our previous study, a higher baseline IOP was significantly associated with the extent of MvD in glaucoma patients.²⁷ Therefore it is possible that mechanical factors contribute to MvD, which could explain why MvD is a prominent feature of glaucoma patients but is less common in BRVO (31.8%) and compressive optic neuropathy (34.1%).¹⁰ Mechanical damage within the LC by glaucoma usually involves the inferotemporal region where the lamina pores are larger and have less tissue support. This could explain why MvD location was predominant in the inferior region in OAG. However, the location was predominant in the superior region in BRVO. Vessel occlusion usually involves the superior region due to the effect of gravity, and this may contribute to axonal damage in the superior region. Therefore MvD found in the superior region in BRVO may be a finding secondary to RGC loss in the superior region, suggesting different pathogenic mechanism of MvD found in two diseases.

Studies have demonstrated that OAG eyes with MvD were significantly more myopic than eyes without MvD.^{2,12} In our previous study, we found that the extent of MvD correlated significantly with the degree of myopia.³ Previous studies have suggested that increased mechanical stress on the ONH and peripapillary sclera may compromise the parapapillary microvasculature during eyeball elongation in myopia.²⁸ Both deformation and strain are notably concentrated in the parapapillary region, where the scleral flange is located.²⁹ Thus scleral vessels may be subjected to tensile stress, causing deep layer MvD.² Myopic eyes undergo axial elongation and scleral deformation in the parapapillary region, which may trigger MvD. If mechanical stress is further increased by an elevated IOP, development of MvD will be exacerbated.^{30,31} This could partly explain the relationship between scleral deformation, detected by OCT, and the presence of MvD in our previous study.³² MvD in the parapapillary region compromises the blood supply to the RNFL and optic disc rim, which leads to further progression. All of these findings indicate that mechanical processes within the ONH, such as elevated IOP, LC changes, ONH changes caused by myopia, and scleral deformation may contribute to MvD development.

Although less frequent compared to OAG, the presence of MvD in BRVO eyes and compressive optic neuropathy suggest that it may occur as a result of RGC loss. Direct compression of the optic nerve axons in compressive optic neuropathy may lead to RGC loss and focal dropout of the choroidal lobules supplying the axons, because the local metabolic demand is reduced.¹⁰ A similar phenomenon may occur in BRVO. Vein occlusion causes edema and hemorrhage around the axons, which leads to RGC loss in the area, resembling RNFL defects seen in glaucoma. Vessel occlusion occurs in the inner retinal layer; however, reduced metabolic demand to the axons may reduce deep-layer choroidal microcirculation. Altogether, MvD could be found in eyes with mechanical damage to the ONH as in glaucoma and secondary reduction due to axonal loss in various diseases that compromise the RGCs. Secondary change due to axonal loss may also occur in glaucoma; therefore presence of MvD could be a mixed-up finding of glaucomatous process within the ONH and secondary changes after axonal loss in glaucoma. The findings of the present study

add that various pathogenic mechanism may underlie the development of MvD.

The factors associated with MvD in this study were also different between the BRVO and OAG eyes. BRVO eyes with MvD tended to have worse baseline MD of the VF, which was associated with the presence and extent of MvD, along with worse BCVA and reduced macular superficial VD. This could indicate that factors that contribute to RNFL loss contributes to MvD in BRVO. These findings support our hypothesis that the presence of MvD in BRVO may be related to reduced metabolic demands secondary to RGC loss. BRVO eyes with greater vessel occlusion have more extensive ischemia of the inner retinal layer, resulting in greater RNFL loss. These eyes tend to have worse MD of the VF, decreased BCVA, and reduced macular superficial VD after BRVO onset.

Although not clinically significant (mean MD slope, -0.03 dB/y), BRVO eyes with greater MvD angles were at risk of faster MD change of the VF. A greater MvD angle, rather than the presence of MvD, indicates the amount of RGC loss following vein occlusion, and the risk for functional loss. Comparison of the MvD angles between BRVO and OAG eyes showed that the former eyes had significantly greater MvD angles despite a lower incidence of MvD. A greater extent of MvD could indicate greater RNFL loss and reduced metabolic demand resulting MvD in BRVO. On the other hand, OAG with MvD was significantly associated with a history of systemic hypertension. The presence of MvD was associated with worse baseline MD of the VF and reduced macular superficial VD in glaucoma, while it was associated with a greater change of MD of the VF in OAG eyes. However, there were no significant associations with the MvD angle and the MD change of the VF. This indicates that MvD may precede the development of glaucoma and contribute to its progression. Because MvD could be related to the mechanical process underlying glaucoma within the ONH, it may be an important factor in VF progression in OAG.

Our study had several limitations. First, OCT-A imaging is an emerging technique, and the retinal vessel signals evident on en face, deep-layer OCT-A images make it difficult to precisely define the MvD boundaries. Therefore only eyes with clear dropout were considered to have MvD. However, the prevalence of β -PPA did not differ between BRVO and OAG eyes, and the fact that MvD is located within the β -PPA, which has few superficial retinal vessels, reduces the risk of artifacts. Comparison of MvD between BRVO and OAG eyes could be useful in this situation. We excluded BRVO eyes with edema, as it can obscure MvD. Finally, OCT-A imaging was performed several months after the occurrence of MvD, which could have affected our findings.

In conclusion, MvD was a more prominent finding in OAG compared to BRVO eyes. The MvD frequencies were 31.8% and 63.1% in age, spherical equivalent, and the baseline MD of the VF matched BRVO and OAG eyes, respectively. This suggests that the glaucomatous process contributes to MvD development. Presence of MvD was associated with different factors in BRVO and OAG. The presence of MvD was important in OAG, while the extent of MvD was important in BRVO, in terms of its association with MD change of the VF. These findings suggest that the pathogenesis of MvD may differ between BRVO and OAG. Longitudinal studies are required to confirm our findings.

Acknowledgments

Supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (NRF-2021R1A2C2093617).

Disclosure: **J. Baek**, None; **H.-Y.L. Park**, None; **S.A. Kim**, None; **K.E. Hong**, None; **S.J. Jeon**, None; **D.Y. Shin**, None; **Y. Jung**, None; **C.K. Park**, None

References

- Suh MH, Zangwill LM, Manalastas PI, et al. Deep retinal layer microvasculature dropout detected by the optical coherence tomography angiography in glaucoma. *Ophthalmology*. 2016;123:2509–2518.
- Lee EJ, Lee SH, Kim JA, Kim TW. Parapapillary deep-layer microvasculature dropout in glaucoma: topographic association with glaucomatous damage. *Invest Ophthalmol Vis Sci*. 2017;58:3004–3010.
- Park HL, Jeon SJ, Park CK. Features of the choroidal microvasculature in peripapillary atrophy are associated with visual field damage in myopic patients. *Am J Ophthalmol*. 2018;192:206–216.
- Lee EJ, Kim S, Hwang S, Han JC, Kee C. Microvascular compromise develops following nerve fiber layer damage in normal-tension glaucoma without choroidal vasculature involvement. *J Glaucoma*. 2017;26:216–222.
- Suh MH, Zangwill LM, Manalastas PI, et al. Optical coherence tomography angiography vessel density in glaucomatous eyes with focal lamina cribrosa defects. *Ophthalmology*. 2016;123:2309–2317.
- Kim GN, Lee EJ, Kim TW. Parapapillary choroidal microvasculature dropout in nonglaucomatous healthy eyes. *Acta Ophthalmologica*. 2020;98(6):e754–e760.
- Park HL, Kim JW, Park CK. Choroidal microvasculature dropout is associated with progressive retinal nerve fiber layer thinning in glaucoma with disc hemorrhage. *Ophthalmology*. 2018;125:1003–1013.
- Lee EJ, Kim TW, Kim JA, Kim JA. Central visual field damage and parapapillary choroidal microvasculature dropout in primary open-angle glaucoma. *Ophthalmology*. 2018;125:588–596.
- Shin JW, Jo YH, Song MK, Won HJ, Kook MS. Nocturnal blood pressure dip and parapapillary choroidal microvasculature dropout in normal-tension glaucoma. *Sci Rep*. 2021;11:206.
- Lee EJ, Kim JA, Kim TW, Kim H, Yang HK, Hwang JM. Glaucoma-like parapapillary choroidal microvasculature dropout in patients with compressive optic neuropathy. *Ophthalmology*. 2020;127:1652–1662.
- Mastropasqua R, D'Aloisio R, Agnifili L, et al. Functional and structural reliability of optic nerve head measurements in healthy eyes by means of optical coherence tomography angiography. *Medicina (Kaunas)*. 2020;56:44.
- Kim CS, Shin KS, Lee HJ, Jo YJ, Kim JY. Sectoral retinal nerve fiber layer thinning in branch retinal vein occlusion. *Retina*. 2014;34:525–530.
- Woo JM, Cha JB, Lee CK. Comparison of lamina cribrosa properties and the peripapillary vessel density between branch retinal vein occlusion and normal-tension glaucoma. *PLoS One*. 2020;15(10):e0240109.
- Fernandez-Vigo JI, Kudsieh B, Shi H, et al. Normative database and determinants of macular vessel density measured by optical coherence tomography angiography. *Clin Exp Ophthalmol*. 2020;48:44–52.
- Barnett EM, Fantin A, Wilson BS, Kass MA, MO Gordon. The incidence of retinal vein occlusion in the ocular hypertension treatment study. *Ophthalmology*. 2010;117:484–488.
- McGrath MA, Wechsler F, Hunyor AB, Penny R. Systemic factors contributory to retinal vein occlusion. *Arch Intern Med*. 1978;138:216–220.
- Peduzzi M, Debbia A, Guerrieri F, Bolzani R. Abnormal blood rheology in retinal vein occlusion. A preliminary report. *Graefes Arch Clin Exp Ophthalmol*. 1986;24:83–85.
- David R, Zangwill L, Badarna M, Yassur Y. Epidemiology of retinal vein occlusion and its association with glaucoma and increased intraocular pressure. *Ophthalmologica*. 1988;197:69–74.
- Rath EZ, Frank RN, Shin DH, Kim C. Risk factors for retinal vein occlusions. A case-control study. *Ophthalmology*. 1992;99:509–514.
- Glacet-Bernard A, Coscas G, Chabanel A, Zourhani A, Lelong F, Samama MM. Prognostic factors for retinal vein occlusion: prospective study of 175 cases. *Ophthalmology*. 1996;103:551–560.
- Mitchell P, Smith W, Chang A. Prevalence and associations of retinal vein occlusion in Australia. The Blue Mountains Eye Study. *Arch Ophthalmol*. 1996;114:1243–1247.
- Klein R, Klein BE, Moss SE, Meuer SM. The epidemiology of retinal vein occlusion: the Beaver Dam Eye Study. *Trans Am Ophthalmol Soc*. 2000;98:133–141; discussion 141–143.
- Cugati S, Wang JJ, Rochtchina E, Mitchell P. Ten-year incidence of retinal vein occlusion in an older population: the Blue Mountains Eye Study. *Arch Ophthalmol*. 2006;124:726–732.
- Klein BE, Meuer SM, Knudtson MD, Klein R. The relationship of optic disk cupping to retinal vein occlusion: the Beaver Dam Eye Study. *Am J Ophthalmol*. 2006;141:859–862.
- Barnett EM, Fantin A, Wilson BS, Kass MA, MO Gordon. The incidence of retinal vein occlusion in the ocular hypertension treatment study. *Ophthalmology*. 2010;117:484–488.
- Stewart RM, Clearkin LG. Insulin resistance and autoregulatory dysfunction in glaucoma and retinal vein occlusion. *Am J Ophthalmol*. 2008;145:394–396.
- Lee J, Park CK, Park HL. Determinants of vessel defects in superficial and deep vascular layers in normal-tension glaucoma using optical coherence tomography angiography. *Sci Rep*. 2021;11(1):9941.
- Cahane M, Bartov E. Axial length and scleral thickness effect on susceptibility to glaucomatous damage: a theoretical model implementing Laplace's law. *Ophthalmic Res*. 1992;24:280–284.
- Eilaghi A, Flanagan JG, Simmons CA, Ethier CR. Effects of scleral stiffness properties on optic nerve head biomechanics. *Ann Biomed Eng*. 2010;38:1586–1592.
- Wang YX, Jiang R, Wang NL, Xu L, Jonas JB. Acute peripapillary retinal pigment epithelium changes associated with acute intraocular pressure elevation. *Ophthalmology*. 2015;122:2022–2028.
- Jiang R, Xu L, Liu X, Chen JD, Jonas JB, Wang YX. Optic nerve head changes after short-term intraocular pressure elevation in acute primary angle-closure suspects. *Ophthalmology*. 2015;122:730–737.
- Shin DY, Jeon SJ, Kim EK, Jung KI, Park HYL, Park CK. Association between peripapillary scleral deformation and choroidal microvascular circulation in glaucoma. *Sci Rep*. 2019;9(1):18503.