Check for updates

ARTICLE

Clinical characteristics of open-angle glaucoma progression with peripapillary microvasculature dropout in different locations

Jihei Sara Lee[1], Youngmin Park[1], Sungeun Park[1], Mijeong Kim[1], Chan Yun Kim [1], Wungrak Choi[1], Sang Yeop Lee[1,2] and Hyoung Won Bae [1]✉

OBJECTIVE: The study attempted to identify clinical characteristics associated with structural progression in open-angle glaucoma (OAG) in the presence of MvD in different locations.

METHODS: A total of 181 consecutive OAG eyes (follow-up 7.3 ± 4.0 years), which demonstrated peripapillary choroidal MvD (defined as a focal capillary loss with no visible microvascular network in choroidal layer) on optical coherence tomography (OCT) angiography (OCTA), were divided based on the location of MvD. Structural progression was determined using trend-based analysis of the Guided Progression Analysis software of Cirrus OCT.

RESULTS: MvD was identified in the temporal quadrant in 110 eyes (temporal MvD; 60.5 ± 12.6 years), and in the inferior quadrant in 71 eyes (inferior MvD; 60.3 ± 11.1 years). After adjusting for age, average intraocular pressure (IOP) and baseline retinal nerve fibre layer (RNFL) thickness and visual field mean deviation, inferior MvD eyes showed faster rates of thinning in the inferior RNFL (mean (95% CI); −0.833 (−1.298 to −0.367)) compared to temporal MvD eyes (−0.144 (−0.496 to 0.207)) when long-term IOP fluctuation was larger than the median value (1.7 mmHg; $P = 0.022$). Long-term IOP fluctuations were independently associated with inferior RNFL thinning in eyes with inferior MvD ($P = 0.002$) but not in eyes with temporal MvD.

CONCLUSIONS: In OAG eyes, the rates of RNFL and GCIPL thinning were comparable regardless of MvD locations. However, inferior MvD is associated with faster RNFL and GCIPL thinning in the same quadrant when long-term IOP fluctuation is present. Structural progression in the presence of temporal MvD was less associated with IOP fluctuation.

INTRODUCTION

Microvascular changes of the optic nerve head are considered a potential factor in the pathogenesis of open-angle glaucoma (OAG) [1, 2]. This proposition has been supported by studies which showed that in eyes with glaucomatous damage, peripapillary choroidal microvasculature was more impaired than contralateral healthy eyes [3]. In this regard, peripapillary choroidal microvasculature dropout (MvD) has been of particular interest. This regional vasculature loss as shown on optical coherence tomography angiography (OCTA) exactly mirrors perfusion defect on indocyanine green angiography [4], and many investigators have previously argued that it may be a sign of impaired juxtapapillary choroidal blood flow and compromised perfusion in the prelaminar tissue [5]. This view is further strengthened by literature that show a higher prevalence of concurrent systemic risk factors, such as low diastolic blood pressure (DBP), cold extremities, and migraine, in eyes with MvD compared to eyes without the dropout [6, 7].

Its significance in the development and progression of glaucoma has been actively investigated. Studies that prove its association with retinal nerve fibre layer (RNFL) thinning and visual field (VF) defect abound [8–10]. However, while numerous studies reported that MvD is most frequently present in areas spanning from the inferior to temporal sectors [3, 11], few studies have analysed its locational significance. Of note, MvD's have been observed in non-glaucomatous optic neuropathy, such as compressive optic neuropathy (CON) and non-arteritic ischemic optic neuropathy (NAION), chiefly clustered in the temporal sector [12, 13]. If the location of MvD in these diseases is any indication, the tendency of a MvD to be present in certain sectors over others suggests that the location of MvD in glaucomatous eyes may be related to specific pathoetiology. We hypothesized that different locations of MvD are associated with different patterns of primary neuronal damage in glaucoma. The purpose of this study was to compare and identify clinical characteristics associated with glaucoma progression in eyes with MvD in different locations.

MATERIALS AND METHODS

Patient population

The study protocol was approved by the Institutional Review Board of Severance Hospital at Yonsei University (IRB approval number 4-2022-

---

[1]Department of Ophthalmology, Severance Hospital, Institute of Vision Research, Yonsei University College of Medicine, Seoul, Korea. [2]Department of Ophthalmology, Yongin Severance Hospital, Yonsei University College of Medicine, Yongin-si, Korea. ✉email: baekwon@yuhs.ac

0985) and the study was conducted in adherence to the tenets of the Declaration of Helsinki. Informed consent was waivered due to the retrospective nature of the study. A total of 181 consecutive eyes with diagnosis of OAG were enrolled following a retrospective review of patients who were referred to the Department of Ophthalmology, Severance Hospital between March 2017 and December 2020. Patients who were 40 years or older at the time of OAG diagnosis were considered eligible for inclusion. OAG was diagnosed when glaucomatous optic disc changes (such as localized or diffused neuroretinal rim thinning, a difference of cup-to-disc ratio greater than 0.2 between 2 eyes) were noted on stereo-disc photographs, RNFL defect was identified on either red-free fundus photographs or Cirrus OCT (Carl Zeiss Meditec, Inc., Dublin, California) and open angle was confirmed with gonioscopy. Two glaucoma specialists (JSL and WC) re-evaluated the diagnosis of OAG and any discrepancy was resolved by a third adjudicator (HWB). Standard automated perimetry (SAP; 24-2 SITA standard, Humphrey Field Analyzer II; Carl Zeiss Meditec, Inc., Dublin, California) was also performed. Patients with advanced stages of glaucoma as per Hodapp-Parrish-Anderson criteria (VF defects with mean deviation (MD) <-12 dB and either ≥50 points on the pattern standard deviation (PSD) plot depressed below the 5% level and ≥25 but <50% of points depressed below the 1% level, or points within the central 5° with a sensitivity <15 dB in both hemifields on reliable VF tests) were excluded from the analysis in order to avoid a "floor effect" in measurements of RNFL and ganglion cell-inner plexiform layer (GCIPL) thicknesses [14, 15]. A VF test was considered reliable when fixation losses were less than 33% and false positive rates were below 33%. A VF defect was considered to be associated with glaucoma if the glaucoma hemifield test results were abnormal or if 3 contiguous VF locations on PSD were below 5% significance levels and if the defects were reproduced in the same location on 2 consecutive tests. A minimum of 5 'reliable' VF tests per eye was required for evaluation of VF defect progression. On average, 7.5 ± 2.3 VF tests were performed for each eye over 7.3 ± 4.0 years of follow-up (7.6 ± 2.5 tests for inferior MvD eyes vs. 7.1 ± 2.2 tests for temporal MvD eyes; $P = 0.093$). A total of 6 eyes (3 with temporal MvD and 3 with inferior MvD) were excluded from analysis due to insufficient numbers of reliable VF tests.

Subjects satisfying any of the following criteria were excluded from the study: 1) eyes without β-peripapillary atrophy (PPA) on fundus photographs or OCT; 2) eyes with parapapillary γ-zone with a maximum horizontal width exceeding 200 μm on infrared imaging (because a wide parapapillary γ-zone may be associated with peripapillary microvascular impairment from scleral stretching) [16]; 3) refractive error less than −8.00 D or greater than +3.00 D; 4) significant media opacity such as cataract; 5) clinical evidence of intracranial lesion, neurologic disorder, rheumatologic disease or systemic vasculitis; 6) systemic medication known to induce optic neuropathy (e.g. ethambutol, digoxin and vigabatrin); 7) history of optic neuritis or NAION; 8) history of intraocular surgery other than uncomplicated cataract surgery; 9) history of ocular disease that may increase IOP and cause secondary glaucoma; 10) ocular manifestation of systemic disease known to affect optic disc such as diabetic retinopathy and retinal vessel occlusion; 11) presence of pseudoexfoliation or pigment dispersion; 12) history of ocular trauma; 13) failure to produce 2 consecutive reliable VF tests at baseline; and 14) less than 5 high signal strength (high signal strength was defined as ≥ 7/10) cirrus OCT tests. When both eyes were eligible, the right eye was chosen.

Ophthalmologic examinations
All subjects underwent complete ophthalmologic examinations at baseline, including medical history, visual acuity, intraocular pressure (IOP; measured with Goldmann applanation tonometer (GAT), Haag-Streit model BQ-900; Haag-Streit, Inc., Bern, Switzerland), refraction, slit-lamp examinations, gonioscopy, central corneal thickness (CCT), axial length, dilated fundus examinations, colour disc stereophotography, red free fundus photography, SAP, cirrus OCT and cirrus OCT angiography (AngioPlex; Carl Zeiss Meditec, Inc., Dublin, CA). Patients were followed every 6 months, undergoing visual acuity, IOP measurements, slit-lamp examinations, colour disc stereophotography, red free fundus photography, SAP and cirrus OCT each visit. Zeiss Forum software (Carl-Zeiss Meditec, Dublin, California, USA) was used to calculate progression rates for MD (dB/year) and visual field index (VFI; %/year). The average value of 2 repeated IOP measurements taken during the first 2 consecutive visits were considered the baseline IOP. The mean IOP is the average value of IOP's collected every 6 months. IOP fluctuations were defined as the standard deviation (SD) of IOP's collected every 6 months.

Optical coherence tomography and angiography
The thicknesses of RNFL and GCIPL were obtained using the 200×200 optic disc cube and 512×128 macular cube protocols of cirrus OCT version 6.0 software. The rates at which RNFL and GCIPL thicknesses changed during follow-up were determined using the trend-based algorithm of Guided Progression Analysis of Cirrus OCT. The trend-based algorithm is designed to align superpixels (4×4 pixels), measure the thickness of each superpixel and perform linear regression analyses in order to calculate changes in the thickness over the follow-up period. The 2 initial examinations were set as the baseline. All OCT scans were evaluated for image quality by a single investigator (JSL) and those with any artifacts were excluded from analysis.

The retinal vessel density (rVD) of the peripapillary and macular areas were obtained using a commercially available OCT angiography device. The angiography algorithm is described in detail elsewhere [17]. The AngioPlex software employed in this study calculated rVD by adding the total length of perfused vasculature per unit area of a 6mm-diameter circle placed on en face images of peripapillary and macular inner-retinal layer, which was automatically segmented by the OCT software. Any segmentation error was manually corrected and all scans were examined for quality by a single investigator (JSL). Those scans with any motion artifacts or low signal strength (<7/10) were excluded.

Determination of peripapillary choroidal MvD
An MvD was defined as a focal and complete loss of choriocapillaries or microvasculature within β-PPA on en face images of the choroid. The choroidal layer was manually generated by creating an en-face slab that extends from the retinal pigment epithelium to 390 μm below, which is a distance considered sufficient to include both the choroid and the inner scleral layer [12]. A microvasculature loss was defined as the absence of choriocapillaries adjoining the disc margin for a circumferential width greater than a half clock-hour. The location of MvD was determined based on the 4 circumferential quadrants of sectoral RNFL thickness measurements of the cirrus OCT. If an MvD spanned over more than 1 neighbouring sector, the sector that included larger portions of the MvD was assigned. The presence and the location of MvD were determined by 2 independent observers (JSL and SP), who were blinded to the clinical information of subjects. Any discrepancy was resolved by a third adjudicator (HWB). Based on the location of the peripapillary choroidal MvD, patients were assigned to either inferior MvD or temporal MvD groups.

Statistical analysis
Interobserver agreement on the presence and location of MvD was analysed using the κ statistics. The distribution of data was determined with Wilk-Shapiro test. Continuous data are presented as mean ± SD, and categorical data as number (percentage). Independent samples t-test and Mann-Whitney U test were used for comparisons of normally distributed and non-normally distributed continuous data, respectively. Chi-square test was used for comparisons of categorical variables. The mean rates of change in RNFL and GCIPL thicknesses between inferior and temporal MvD groups were compared using a linear mixed model that adjusted for age, average IOP, baseline VF MD, baseline GCIPL and RNFL thicknesses. Univariate linear regression analyses were performed separately for each variable. To build a multivariate model, a stepwise selection method was adopted with the entry P-value of <0.1 and a stay P-value of <0.05. All statistical analyses were conducted using SPSS version 23 (SPSS Inc., Chicago, Illinois). A p-value < 0.05 was considered statistically significant.

RESULTS
Baseline characteristics
The clinical characteristics of OAG eyes with inferior and temporal MvD are illustrated in Table 1. MvD was identified mainly in the temporal quadrant in 110 eyes (temporal MvD; 60.5 ± 12.6 years, 39.1 % males), and in the inferior quadrant in 71 eyes (inferior MvD; 60.3 ± 11.1 years, 39.4 % males). The κ coefficient for interobserver agreement on the presence of MvD was 0.918. The intraclass correlation coefficient (ICC) for interobserver reproducibility in determining the location of the MvD was 0.899. The follow-up duration was comparable between the 2 groups ($P = 0.871$). The 2 groups were similar in age, gender, axial length

Table 1. Baseline characteristics of patient population depending on the location of MvD.

	Inferior MvD (n = 71)	Temporal MvD (n = 110)	P
Age, years	60.3 ± 11.1	60.5 ± 12.6	0.924
Males, n (%)	28 (39.4)	43 (39.1)	0.889
AXL, mm	24.7 ± 1.4	24.6 ± 1.3	0.545
CCT, μm	538.8 ± 32.8	535.0 ± 32.4	0.441
IOP, mmHg			
Baseline	17.9 ± 4.2	16.8 ± 3.1	0.102
Average	14.1 ± 2.2	13.9 ± 1.9	0.449
Fluctuation	2.0 ± 0.9	1.9 ± 1.0	0.796
Initial VF			
MD, dB	−6.1 ± 6.8	−6.7 ± 7.0	0.572
PSD, dB	6.7 ± 4.7	5.9 ± 4.5	0.271
VFI, %	83.1 ± 17.7	85.6 ± 16.9	0.361
Final VF			
MD, dB	−6.9 ± 6.6	−6.9 ± 7.5	0.937
PSD, dB	7.4 ± 4.1	6.6 ± 4.4	0.245
VFI, %	80.0 ± 19.4	80.0 ± 22.3	0.968
Initial RNFL thickness, μm			
Average	73.3 ± 12.4	72.7 ± 13.6	0.773
Superior	95.4 ± 21.6	91.2 ± 24.1	0.234
Temporal	61.5 ± 12.4	58.1 ± 13.2	0.077
Inferior	73.8 ± 19.0	80.3 ± 21.9	0.041
Nasal	62.3 ± 9.2	61.7 ± 11.1	0.733
Final RNFL thickness, μm			
Average	72.6 ± 10.9	72.4 ± 13.3	0.927
Superior	93.8 ± 20.8	88.2 ± 22.9	0.102
Temporal	60.4 ± 12.4	58.1 ± 13.1	0.251
Inferior	70.0 ± 16.5	78.9 ± 22.2	0.004
Nasal	65.4 ± 9.6	64.1 ± 10.8	0.417
Initial GCIPL thickness, μm			
Average	56.0 ± 10.4	61.4 ± 28.4	0.131
Superior	75.1 ± 10.9	70.7 ± 11.2	0.010
Superotemporal	72.9 ± 10.0	68.8 ± 11.2	0.014
Inferotemporal	58.4 ± 9.3	63.1 ± 11.4	0.005
Inferior	60.8 ± 8.9	63.2 ± 10.6	0.116
Inferonasal	70.9 ± 9.7	68.3 ± 11.9	0.128
Superonasal	78.9 ± 10.4	73.2 ± 11.5	0.001
Final GCIPL thickness, μm			
Average	53.1 ± 8.3	56.7 ± 11.6	0.028
Superior	73.9 ± 10.9	69.7 ± 11.9	0.017
Superotemporal	79.9 ± 70.2	67.1 ± 11.6	0.062
Inferotemporal	55.3 ± 8.2	61.0 ± 11.5	<0.001
Inferior	68.3 ± 10.0	66.2 ± 12.1	0.018
Inferonasal	68.3 ± 10.0	66.2 ± 12.1	0.223
Superonasal	77.3 ± 10.4	71.5 ± 12.3	0.001
BMI, kg/m	22.1 ± 2.7	23.5 ± 3.8	0.162
SBP, mmHg	124.1 ± 17.2	125.4 ± 17.3	0.740
DBP, mmHg	73.8 ± 11.0	74.2 ± 11.4	0.865
Hypertension, n (%)	21 (29.6)	33 (30.0)	0.720
Diabetes, n (%)	3 (4.2)	10 (9.1)	0.376
Family history, n (%)	12 (16.9)	12 (10.9)	0.256

Table 1. continued

	Inferior MvD ($n = 71$)	Temporal MvD ($n = 110$)	P
Disc OCT angiography			
Signal strength	9.2 ± 1.0	9.0 ± 1.1	0.175
Center, mm^{-1}	0.6 ± 1.6	0.6 ± 1.3	0.891
Inner, mm^{-1}	13.8 ± 2.9	13.9 ± 2.9	0.740
Outer, mm^{-1}	19.5 ± 21.0	16.9 ± 2.1	0.222
Full, mm^{-1}	15.7 ± 2.3	15.8 ± 2.1	0.867
Macula OCT angiography			
Signal strength	9.1 ± 1.1	9.0 ± 1.7	0.629
Center, mm^{-1}	9.1 ± 3.8	8.4 ± 4.0	0.296
Inner, mm^{-1}	17.3 ± 2.5	16.8 ± 2.9	0.314
Outer, mm^{-1}	16.1 ± 2.6	16.0 ± 3.0	0.863
Full, mm^{-1}	16.2 ± 2.5	16.0 ± 2.9	0.706
Follow-up, years	7.3 ± 4.3	7.4 ± 3.9	0.871

MvD microvasculature dropout, *AXL* axial length, *CCT* central corneal thickness, *IOP* intraocular pressure, *VF* visual field, *MD* mean deviation, *PSD* pattern standard deviation, *VFI* visual field index, *RNFL* retinal nerve fiber layer, *GCIPL* ganglion cell inner plexiform layer, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *OCT* optical coherence tomography.
$P < 0.05$ was considered statistically significant.

and CCT. The 2 groups did not show significant differences in IOP at baseline or during follow-up. Baseline VF parameters were also comparable. Inferior RNFL of the inferior MvD group (73.8 ± 19.0 μm) was thinner than that of the temporal MvD group (80.3 ± 21.9 μm; $P = 0.041$) at baseline. Superior ($P = 0.010$), superonasal ($P = 0.001$) and superotemporal ($P = 0.014$) GCIPL was thicker for the inferior MvD group than the temporal MvD group at baseline. No significant differences were found in underlying systemic medical conditions such as hypertension and diabetes mellitus.

Comparison of rates of RNFL and GCIPL thinning
The rates of global and regional RNFL and GCIPL thinning were comparable between eyes with inferior and temporal MvD (Supplemental Table 1). The 2 groups were further divided into small and large long-term IOP fluctuations using the median value of 1.7 mmHg (Table 2). IOP fluctuations were defined as the SD of IOP collected during office visits every 6 months. Significantly faster mean rates of RNFL and GCIPL thinning were found in the inferior hemifield in eyes with inferior MvD compared to temporal MvD eyes when the long-term IOP fluctuations were above the median value after adjusting for confounding factors, including age, baseline VF MD, mean IOP, baseline RNFL thickness and baseline GCIPL thickness (mean difference (95% CI); −0.833 (−1.298 to −0.367) μm/year, $P = 0.022$; −0.741 (−0.952 to −0.530) μm/year, $P = 0.020$, respectively). However, the difference was not noted in comparisons of VF progression rates between the 2 groups (Supplemental Table 2). The rates of RNFL and GCIPL thinning were comparable between the 2 groups when IOP fluctuations were small. The mean rates of RNFL and GCIPL thinning were also similar when the groups were divided using baseline IOP or average IOP (Supplemental Table 3).

Factors contributing to RNFL thinning in MvD eyes
Factors associated with RNFL thinning in superior and inferior hemifields in eyes with MvD were identified (Table 3). According to the multivariable analysis, large IOP fluctuations were significantly associated with faster rates of RNFL thinning in the inferior hemifield in inferior MvD eyes ($β$ −0.463, 95% CI −1.111 - −0.264; $P = 0.002$), but not in temporal MvD eyes ($P = 0.549$). Elevated baseline IOP was associated instead with RNFL thinning

in the inferior hemifield of eyes with temporal MvD ($β$ 0.279, 95% CI 0.014–0.228; $P = 0.027$).

DISCUSSION
The present study demonstrated that the rates of RNFL and GCIPL thinning in the inferior and superior hemifields were comparable between eyes with temporal and inferior MvD. However, the thinning rates in the inferior RNFL and GCIPL were significantly faster in eyes with inferior MvD in comparison to eyes with temporal MvD in the presence of large long-term IOP fluctuations. Long-term IOP fluctuations were independently associated with inferior RNFL thinning in eyes with MvD in the inferior quadrant. The findings of this study suggest that MvD in different locations may be associated with different patterns of glaucomatous progression.

Numerous studies in the past have linked MvD to glaucoma severity and progression [18, 19]. For instance, MvD has shown significant associations with thinner RNFL and worse VF MD in one study [6]. Another study found that the dropout was more frequently present in eyes with central VF defect [20]. Its presence as well as its area and angular circumference were found to be independently related with faster RNFL thinning [19, 21]. Increases in size of the dropout over time were also significant markers of faster rates of RNFL thinning as well as VF loss [22, 23]. Previous studies have not come to terms on whether MvD is a primary pathogenic phenomenon or a secondary consequence of glaucomatous damage [5, 24], but these studies do generally agree that MvD helps identify high-risk glaucoma. We believe the present study, by comparing the rates of RNFL and GCIPL thinning among eyes with MvD in different locations, adds to the current literature that MvD location may be relevant to glaucoma pathogenesis.

The results suggest that the location of MvD may reveal different primary pathogenic mechanisms of glaucomatous damage. Although the site of MvD did not affect the thinning rates in general, eyes with inferior MvD showed faster RNFL and GCIPL thinning in the same hemifield than eyes with temporal MvD when large long-term IOP fluctuations were present. With respect to OAG in general, there exist 2 major theories on the pathogenesis: the mechanical and vascular theories. The mechanical theory posits that elevated IOP puts mechanical stress on retinal ganglion cells to cause irreversible damage [25]. This

Table 2. Comparison of rates of structural progression between inferior and temporal MvD depending on long-term IOP fluctuation.

IOP Fluctuation		Inferior MvD Mean (95% CI)	Temporal MvD Mean (95% CI)	Difference Mean (95% CI)	P*
Small (<1.7 mmHg)	RNFL rate, µm/year				
	Mean global	−0.205 (−0.535 to 0.124)	−0.090 (−0.288 to 0.109)	0.115 (−0.276 to 0.507)	0.558
	Hemi-superior	−0.527 (−1.085 to 0.030)	−0.362 (−0.698 to 0.026)	0.166 (−0.497 to 0.828)	0.618
	Hemi-inferior	−0.580 (−1.206 to 0.047)	−0.473 (−0.850 to 0.095)	0.107 (−0.637 to 0.852)	0.774
	GCIPL rate, µm/year				
	Mean global	−0.439 (−0.680 to 0.199)	−0.528 (−0.672 to 0.383)	0.088 (−0.198 to 0.374)	0.539
	Hemi-superior	−0.439 (−0.689 to 0.190)	−0.473 (−0.623 to 0.323)	0.034 (−0.263 to 0.330)	0.820
	Hemi-inferior	−0.439 (−0.747 to 0.130)	−0.581 (−0.767 to 0.396)	0.143 (−0.224 to 0.509)	0.438
Large (≥1.7 mmHg)	RNFL rate, µm/year				
	Mean global	−0.338 (−0.564 to 0.112)	−0.262 (−0.432 to 0.091)	0.076 (−0.209 to 0.362)	0.595
	Hemi-superior	−0.618 (−0.970 to 0.266)	−0.852 (−1.117 to 0.586)	0.234 (−0.211 to 0.679)	0.298
	Hemi-inferior	−0.833 (−1.298 to 0.367)	−0.144 (−0.496 to 0.207)	0.688 (0.101 to 1.276)	**0.022**
	GCIPL rate, µm/year				
	Mean global	−0.595 (−0.746 to 0.444)	−0.446 (−0.560 to 0.332)	0.149 (−0.042 to 0.340)	0.124
	Hemi-superior	−0.466 (−0.646 to 0.286)	−0.470 (−0.605 to 0.334)	0.004 (−0.223 to 0.231)	0.973
	Hemi-inferior	−0.741 (−0.952 to 0.530)	−0.424 (−0.583 to 0.265)	0.317 (0.051–0.0583)	**0.020**

MvD microvasculature dropout, *IOP* intraocular pressure, *CI* confidence interval, *RNFL* retinal nerve fiber layer, *GCIPL* ganglion cell inner plexiform layer, *VF* visual field, *MD* mean deviation.
P < 0.05 was considered statistically significant. Statistically significant *P*-values are in bold.
*Adjusted for age, mean IOP, baseline VF MD, baseline RNFL thickness, baseline GCIPL thickness.

theory may be especially applicable to damages in the superior and inferior hemispheres because the superior and inferior portions of the lamina cribrosa tend to have larger pores and less connective tissue support compared to the nasal and temporal portions [26], and mechanical insult from elevated IOP is likely exaggerated in these regions. According to the results of our study, eyes with MvD in this susceptible region showed faster RNFL and GCIPL thinning in the same hemisphere when large IOP fluctuations were also present. The relationship between the localized choroidal perfusion defect (MvD) and IOP fluctuations is not entirely clear. However, previous studies have shown that MvDs are more susceptible to large IOP fluctuations than elevated mean IOP. For instance, Jo et al. described that glaucoma eyes with MvD tended to experience greater long-term IOP fluctuations [10]. Micheletti et al. have reported faster MvD enlargement in both area and angular circumference when in the presence of large IOP fluctuation, and not in that of high average IOP [23]. In the same study, eyes that developed MvD during follow-up tended to show large IOP fluctuations compared to eyes that did not develop any MvD during the same period. Other studies have also found that peak IOP tended to be higher in eyes with MvD [7]. Based on these studies, we can extrapolate that repeated loading and unloading of stresses on the fibroelastic tissues of the lamina cribrosa from IOP fluctuations, when combined with impaired choroidal perfusion, resulted in more rapid structural progression in our patient population. It is also possible that the damaging effect of IOP fluctuations may be more apparent in a study population with low mean IOP such as our own, whose average IOP was in the low teens [27]. However, further investigations are necessary to establish the relationship between choroidal perfusion, IOP fluctuations and structural progression in glaucoma.

The vascular theory, on the other hand, states that some of glaucoma are associated with alterations in ocular blood flow [2]. In other words, retinal hypoperfusion results in reduced oxygen supply and predisposes metabolically active retinal ganglion cells to injury. A number of optic neuropathy in part share this

pathogenic mechanism with glaucoma, namely CON and NAION [12, 13]. They involve acute hypoperfusion of the short posterior ciliary artery, resulting in severe ischemia in the distal branches [28, 29]. MvD has also been reported in these diseases, and interestingly enough, it was most frequently observed in the temporal parapapillary sector in association with thinner RNFL and reduced retinal vessel density. We speculate that the temporal MvD may be present in glaucoma in association with this mechanism. However, while the temporal MvD eyes were relatively less affected by IOP fluctuations in the present study, they did not show characteristic features of the subtypes of glaucoma thought to be affected by impaired perfusion to affirm our speculation. For instance, past investigations have related these subtypes of glaucoma with predominant macular GCIPL loss and more central VF defect [30, 31]. Furthermore, when Yum et al. compared clinical characteristics between temporal and inferotemporal RNFL defect among normal-tension glaucoma (NTG), eyes with temporal RNFL defect tended to show lower best-corrected visual acuity and more prevalent central scotoma [32]. The temporal MvD eyes in the present study did not show significantly lower VFI values and GCIPL thicknesses than those of the inferior MvD eyes. However, we do suspect that temporal MvD was more prevalent than inferior MvD in our study population in part due to the equally high prevalence of NTG, which is generally believed to result from regional vascular insufficiency. Nonetheless, larger samples with greater variations in baseline IOP are necessary to assess our speculations regarding the temporal MvD.

According to our analysis, the difference in structural progression rates between inferior MvD and temporal MvD eyes did not result in different functional deterioration rates (Supplemental Table 2). With regards to these results, we propose following explanations. First, damaged retinal ganglion cells might have been compensated by a complex network of neural cells, resulting in a VF test that does not directly reflect the amount of nerve damage [33]. Furthermore, it is possible that current OCT provides incomplete information on cells that are intact in

Table 3. Linear regression analysis to identify factors associated with RNFL thinning in different MvD groups.

RNFL location		Inferior MvD				Temporal MvD			
		Univariable		Multivariable		Univariable		Multivariable	
		β (95% CI)	P	β (95% CI)	P	β (95% CI)	P	β (95% CI)	P
Inferior	Age	−0.038 (−0.038 to 0.029)	0.638	−0.188 (−0.053 to 0.011)	0.191	0.054 (−0.014 to 0.025)	0.598	0.072 (−0.016 to 0.030)	0.548
	Baseline IOP	0.016 (−0.086 to 0.094)	0.406			0.305 (0.031–0.234)	0.011	0.279 (0.014 to 0.228)	0.027
	IOP fluctuation	−0.279 (−0.844 to −0.011)	0.049	−0.463 (−1.111 to −0.264)	0.002	0.062 (−0.178 to 0.333)	0.549		
	Baseline VF MD	−0.361 (−0.120 to −0.017)	0.010	−0.296 (−0.110 to 0.001)	0.053	−0.168 (−0.061 to 0.005)	0.099	−0.051 (−0.068 to 0.047)	0.711
	Baseline RNFLT	−0.273 (−0.061 to 0.001)	0.055	−0.241 (−0.062 to 0.010)	0.150	−0.167 (−0.032 to 0.003)	0.101	−0.101 (−0.036 to 0.017)	0.465
	Baseline GCIPLT	−0.259 (−0.063 to 0.0003)	0.070	−0.024 (−0.038 to 0.032)	0.876	−0.008 (−0.009 to 0.008)	0.935		
	Hypertension	−0.178 (−1.188 to 0.393)	0.313			0.073 (−0.385 to 0.754)	0.520		
	Diabetes mellitus	−0.359 (−3.145 to 0.075)	0.400			−0.068 (−1.130 to 0.618)	0.561		
	SBP	0.377 (−0.010 to 0.079)	0.123			−0.097 (−0.028 to 0.014)	0.516		
	DBP	0.125 (−0.047 to 0.077)	0.622			−0.173 (−0.052 to 0.014)	0.244		
	BMI	0.096 (−0.191 to 0.247)	0.779			−0.048 (−0.129 to0.099)	0.791		
Superior	Age	0.082 (−0.018 to 0.031)	0.574	0.234 (−0.011 to 0.050)	0.199	0.126 (−0.008 to 0.033)	0.222	0.023 (−0.245 to 0.250)	0.979
	Baseline IOP	0.061 (−0.068 to 0.095)	0.741			−0.262 (−0.226 to −0.010)	0.032	−0.128 (−0.478 to 0.425)	0.863
	IOP fluctuation	0.069 (−0.210 to 0.345)	0.628			−0.182 (−0.494 to 0.027)	0.078	−0.163 (−3.454 to 2.961)	0.822
	Baseline VF MD	−0.193 (−0.067 to 0.001)	0.059	0.063 (−0.039 to 0.053)	0.749	−0.119 (−0.054 to 0.022)	0.399		
	Baseline RNFLT	−0.175 (−0.037 to 0.008)	0.214			−0.298 (−0.044 to −0.009)	0.003	−0.138 (−0.236 to 0.209)	0.856
	Baseline GCIPLT	−0.044 (−0.031 to 0.023)	0.759			0.107 (−0.004 to 0.013)	0.299		
	Hypertension	−0.165 (−1.038 to 0.373)	0.345			0.042 (−0.509 to 0.736)	0.718		
	Diabetes mellitus	−0.329 (−2.826 to 0.048)	0.058	−0.426 (−3.342 to −0.069)	0.042	0.138 (−0.342 to 1.330)	0.243		
	SBP	0.018 (−0.039 to 0.042)	0.939			−0.099 (−0.028 to 0.014)	0.506		
	DBP	−0.280 (−0.083 to 0.022)	0.232			−0.455 (−0.081 to −0.021)	0.001	−0.438 (−0.334 to 0.188)	0.438
	BMI	−0.151 (−0.101 to 0.065)	0.640			−0.272 (−0.198 to 0.026)	0.126		

RNFL retinal nerve fiber layer, *MvD* microvasculature dropout, *CI* confidence interval, *IOP* intraocular pressure, *VF* visual field, *MD* mean deviation, *RNFLT* retinal nerve fiber layer thickness, *GCIPLT* ganglion cell inner plexiform layer thickness, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *BMI* body mass index.
$P < 0.05$ was considered statistically significant.

structure, but damaged in function, and vice versa [34]. Second, a more sensitive test of vision performance might have been necessary to identify any correlation between VF defect and different structural damage rates between the 2 groups. Inter-individual variabilities in structure-function relationships, and discordance between the region of retina tested by a VF stimulus and measured by OCT may further contribute to the lack of difference in VF in our analysis [15, 35, 36]. Third, a significant difference in VF damage might have been noted if the data were collected for a longer period. Previously, a time lag was reported to exist between initial nerve fibre damage and resultant VF defect [37]. Further studies with a longer follow-up are necessary to prove our speculations.

There are several limitations to the study. First of all, the study is limited by its retrospective design. Second, the study includes a small number of subjects, and the small sample size may have affected the results. Third, the study results may not be generalized as the study population consisted of Koreans, among whom NTG is more prevalent. Fourth, projection artifacts of superficial vessels may have created false images of vascularity in the deep retinal layers, resulting in false negative detection of MvD. Lastly, the study results may not be generalizable to glaucomatous eyes without β-PPA, and further investigations are necessary to identify whether certain regions of RNFL or GCIPL are more prone to damage in the presence of large IOP fluctuations over others.

In conclusion, the rates of RNFL and GCIPL thinning are comparable between glaucomatous eyes with temporal and inferior MvD. However, structural progression is more rapid in eyes with MvD in the inferior hemifield when accompanied by long-term IOP fluctuations, but not in eyes with MvD in the temporal sector. These findings suggest that progression of glaucoma in association with MvD in different locations are affected by different risk factors. MvD may be useful for detection of patients at a high risk of rapid progression who require close observation and strict IOP control.

SUMMARY

What was known before

- Choroidal microvasculature dropout (MvD) as shown on optical coherence tomography angiography (OCTA) exactly mirrors perfusion defect on indocyanine green angiography.
- MvD may be a sign of impaired juxtapapillary choroidal blood flow and compromised perfusion in the prelaminar tissue.

What this study adds

- Eyes with inferior MvD showed faster RNFL and GCIPL thinning in the same hemifield than eyes with temporal MvD when large long-term IOP fluctuations were present.
- The location of MvD in glaucomatous eyes may be related to specific pathoetiology.

DATA AVAILABILITY
The datasets generated during and/or analysed during the current study are not publicly available due to patient confidentiality but are available from the corresponding author on reasonable request.

REFERENCES
1. Weinreb RN. Ocular blood flow in glaucoma. Can J Ophthalmol. 2008;43:281–3.
2. Flammer J, Orgul S, Costa VP, Orzalesi N, Krieglstein GK, Serra LM, et al. The impact of ocular blood flow in glaucoma. Prog Retin Eye Res. 2002;21:359–93.
3. Kim JA, Son DH, Lee EJ, Kim H, Kim TW. Intereye comparison of the characteristics of the peripapillary choroid in patients with unilateral normal-tension glaucoma. Ophthalmol Glaucoma. 2021;4:512–21.
4. Lee EJ, Lee KM, Lee SH, Kim TW. Parapapillary choroidal microvasculature dropout in glaucoma: a comparison between optical coherence tomography angiography and indocyanine green angiography. Ophthalmology. 2017;124:1209–17.
5. Lee EJ, Lee SH, Kim JA, Kim TW. Parapapillary deep-layer microvasculature dropout in glaucoma: topographic association with glaucomatous damage. Investig Ophthalmol Vis Sci. 2017;58:3004–10.
6. Suh MH, Zangwill LM, Manalastas PI, Belghith A, Yarmohammadi A, Medeiros FA, et al. Deep retinal layer microvasculature dropout detected by the optical coherence tomography angiography in glaucoma. Ophthalmology. 2016;123:2509–18.
7. 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.
8. Lee EJ, Kim TW, Kim JA, Kim JA. Central visual field damage and parapapillary choroidal microvasculature dropout in primary open-angle glaucoma. Ophthalmology. 2018;125:588–96.
9. 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;125:1003–13.
10. Jo YH, Kwon J, Jeong D, Shon K, Kook MS. Rapid central visual field progression rate in eyes with open-angle glaucoma and choroidal microvasculature dropout. Sci Rep. 2019;9:8525.
11. Kwon JM, Weinreb RN, Zangwill LM, Suh MH. Juxtapapillary deep-layer microvasculature dropout and retinal nerve fiber layer thinning in glaucoma. Am J Ophthalmol. 2021;227:154–65.
12. 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;127:1652–62.
13. Shin JW, Lee JY, Lee BJ, Lim HT, Kook MS. Clinical characteristics of choroidal microvasculature dropout in normal-tension glaucoma versus nonarteritic anterior ischemic optic neuropathy: an optical coherence tomography angiography study. Sci Rep. 2021;11:21391.
14. Mwanza JC, Kim HY, Budenz DL, Warren JL, Margolis M, Lawrence SD, et al. Residual and dynamic range of retinal nerve fiber layer thickness in glaucoma: comparison of three OCT platforms. Investig Ophthalmol Vis Sci. 2015;56:6344–51.
15. Hood DC, Kardon RH. A framework for comparing structural and functional measures of glaucomatous damage. Prog Retin Eye Res. 2007;26:688–710.
16. Lee EJ, Kim TW, Kim JA, Kim JA. Parapapillary deep-layer microvasculature dropout in primary open-angle glaucoma eyes with a parapapillary gamma-zone. Investig Ophthalmol Vis Sci. 2017;58:5673–80.
17. Lee T, Bae HW, Seong GJ, Kim CY, Lee SY. HigH Pulse Wave Velocity Is Associated with Decreased Macular Vessel Density in Normal-tension Glaucoma. Investig Ophthalmol Vis Sci. 2021;62:12.
18. Lee EJ, Kim JA, Kim TW. Influence of choroidal microvasculature dropout on the rate of glaucomatous progression: a prospective study. Ophthalmol Glaucoma. 2020;3:25–31.
19. Lin S, Cheng H, Zhang S, Ye C, Pan X, Tao A, et al. Parapapillary choroidal microvasculature dropout is associated with the decrease in retinal nerve fiber layer thickness: a prospective study. Investig Ophthalmol Vis Sci. 2019;60:838–42.
20. Kwon J, Shin JW, Lee J, Kook MS. Choroidal microvasculature dropout is associated with parafoveal visual field defects in glaucoma. Am J Ophthalmol. 2018;188:141–54.
21. Micheletti E, Moghimi S, El-Nimri N, Nishida T, Suh MH, Proudfoot JA, et al. Relationship of macular ganglion cell complex thickness to choroidal microvasculature drop-out in primary open-angle glaucoma. Br J Ophthalmol. 2022;107:809–15.
22. Lee JY, Shin JW, Song MK, Hong JW, Kook MS. An increased choroidal microvasculature dropout size is associated with progressive visual field loss in open-angle glaucoma. Am J Ophthalmol. 2021;223:205–19.
23. Micheletti E, Moghimi S, Nishida T, El-Nimri N, Mahmoudinedzah G, Kamalipour A, et al. Factors associated with choroidal microvascular dropout change. Br J Ophthalmol. 2022. Epub ahead of print.
24. Son KY, Han JC, Kee C. Parapapillary deep-layer microvasculature dropout is only found near the retinal nerve fibre layer defect location in open-angle glaucoma. Acta Ophthalmol. 2022;100:e174–80.
25. Weinreb RN, Aung T, Medeiros FA. The pathophysiology and treatment of glaucoma: a review. JAMA. 2014;311:1901–11.
26. Quigley HA, Addicks EM. Regional differences in the structure of the lamina cribrosa and their relation to glaucomatous optic nerve damage. Arch Ophthalmol. 1981;99:137–43.
27. Kim JH, Caprioli J. Intraocular Pressure Fluctuation: Is It Important? J Ophthalmic Vis Res. 2018;13:170–4.

28. Hayreh SS. Ischemic optic neuropathy. Prog Retin Eye Res. 2009;28:34–62.
29. Kaup M, Plange N, Arend KO, Remky A. Retrobulbar haemodynamics in non-arteritic anterior ischaemic optic neuropathy. Br J Ophthalmol. 2006;90:1350–3.
30. Marshall HN, Andrew NH, Hassall M, Qassim A, Souzeau E, Ridge B, et al. Macular ganglion cell-inner plexiform layer loss precedes peripapillary retinal nerve fiber layer loss in glaucoma with lower intraocular pressure. Ophthalmology. 2019;126:1119–30.
31. Park HY, Jung KI, Na KS, Park SH, Park CK. Visual field characteristics in normal-tension glaucoma patients with autonomic dysfunction and abnormal peripheral microcirculation. Am J Ophthalmol. 2012;154:466–75.e461.
32. Yum HR, Park HL, Park CK. Characteristics of normal-tension glaucoma patients with temporal retinal nerve fibre defects. Sci Rep. 2020;10:6362.
33. Denniss J, Turpin A, McKendrick AM. Relating optical coherence tomography to visual fields in glaucoma: structure-function mapping, limitations and future applications. Clin Exp Optom. 2019;102:291–9.
34. Fry LE, Fahy E, Chrysostomou V, Hui F, Tang J, van Wijngaarden P, et al. The coma in glaucoma: retinal ganglion cell dysfunction and recovery. Prog Retin Eye Res. 2018;65:77–92.
35. Malik R, Swanson WH, Garway-Heath DF. 'Structure-function relationship' in glaucoma: past thinking and current concepts. Clin Exp Ophthalmol. 2012;40:369–80.
36. Harwerth RS, Wheat JL, Fredette MJ, Anderson DR. Linking structure and function in glaucoma. Prog Retin Eye Res. 2010;29:249–71.
37. Miki A, Medeiros FA, Weinreb RN, Jain S, He F, Sharpsten L, et al. Rates of retinal nerve fiber layer thinning in glaucoma suspect eyes. Ophthalmology. 2014;121:1350–8.

AUTHOR CONTRIBUTIONS

Conception and design: HWB. Analysis and interpretation: JSL and HWB. Data collection: JSL, YMP, SP, WC, SYL, and CYK. Obtained funding: HWB. Overall responsibility: JSL and HWB.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41433-023-02675-w.

Correspondence and requests for materials should be addressed to Hyoung Won Bae.

Reprints and permission information is available at http://www.nature.com/reprints

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.