Parapapillary Deep-Layer Microvasculature Dropout and Visual Field Progression in Glaucoma

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• PURPOSE: To evaluate the association between optical coherence tomography angiography (OCT-A)-derived parapapillary deep-layer microvasculature dropout and glaucomatous visual field (VF) progression.

• DESIGN: Retrospective, cohort study.

• METHODS: A total of 138 eyes of 138 patients with primary open-angle glaucoma (mean follow-up, 5.5 years) and with ≥5 VFs prior to OCT-A imaging were included. VF progression was defined as either a Guided Progression Analysis–based "likely progression" event or a significant VF index (VFI) slope. Microvasculature dropout was defined as parapapillary deep-layer microvasculature dropout based on a qualitative analysis of OCT-A. Prevalence of dropout was compared between eyes with and without VF progression.

• RESULTS: Fifty-five eyes (39.9%) demonstrated VF progression. A higher proportion of eyes with dropout progressed than those without dropout (50/84 eyes [59.5%] vs 5/54 eyes [9.3%]; $P < .001$). In multivariable logistic regression analysis, mean and standard deviation intraocular pressure, optic disc hemorrhage, focal lamina cribrosa defect, and dropout were significantly associated with prior VF progression ($P < .05$). The VFI progression rate was significantly faster in eyes with dropout than in those without dropout (−2.23% ± 3.22%/year vs −0.05% ± 1.24%/year, respectively; $P < .001$), and the location of dropout and VF progression were spatially correlated.

• CONCLUSIONS: Eyes with parapapillary deep-layer microvasculature dropout detected by OCT-A had a significantly higher rate of VF progression than eyes without dropout. These findings implicate dropout as a structural parameter suggestive of past glaucomatous VF progression. Further prospective longitudinal studies are needed to elucidate the role of deep-layer microvasculature damage in the pathogenesis of glaucoma. (Am J Ophthalmol 2019;200:65–75. © 2018 Elsevier Inc. All rights reserved.)

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GLAUCOMA IS AN OPTIC NEUROPATHY CHARACTERIZED by progressive damage to the optic nerve head (ONH).[1] It is well established that functional impairment owing to retinal ganglion cell (RGC) damage can have a serious impact on an individual's quality of life.[2] In this regard, elucidation of the factors associated with glaucomatous visual field (VF) progression is of clinical importance. Key risk factors for VF progression include elevated intraocular pressure (IOP),[3–8] older age,[3,4,6] lower central corneal thickness (CCT),[3,4,6,7] decreased ocular perfusion pressure,[6,9] and the presence of optic disc hemorrhages (DH),[8,10,11] ß-zone parapapillary atrophy (ßPPA),[12,13] and focal lamina cribrosa (LC) defects.[14] Structural loss and dysfunction in the microvasculature of the retina, choriocapillaris, and ONH also are factors that have been hypothesized to be associated with glaucomatous progression.

Recent advances in optical imaging with optical coherence tomography angiography (OCT-A) have enabled the visualization of microvasculature in both superficial retinal layer and deep-layers including choriocapillaris, and these vascular factors were shown to be associated with the severity of VF damage.[15–18] Specifically, a recent study reported that parapapillary deep-layer microvasculature dropout, the complete dropout of the parapapillary choriocapillaris or microvasculature within the sclera, measured by OCT-A, is associated with worse VF sensitivity even after controlling for the degree of axonal loss and focal LC damage.[19] Furthermore, a recent study showed that parapapillary deep-layer microvasculature dropout occurred more frequently in eyes with retinal nerve fiber layer (RNFL) thinning, especially in eyes with DH compared to those without both deep-layer microvasculature dropout and DH.[20] However, whether parapapillary deep-layer microvasculature dropout is associated with glaucomatous VF progression remains to be determined.

The purpose of the present study was to evaluate the association between OCT-A-based parapapillary deep-layer microvasculature dropout and glaucomatous VF progression.

METHODS

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Informed consent was obtained from all subjects. This study included primary open-angle glaucoma (POAG) patients who had been followed up for at least 3 years and had undergone at least 5 serial VF measurements prior to the present OCT-A and spectral-domain OCT (SDOCT) imaging. Final VF testing and OCT-A/SDOCT imaging were conducted within a 6-month period. POAG was defined as the presence of glaucomatous optic nerve damage (ie, the presence of focal thinning, notching, or localized or diffuse atrophy of the RNFL) with an open angle, and compatible repeatable VF damage. Glaucomatous VF damage was defined as (1) a VF outside the normal limits on a glaucoma hemifield test; or (2) 3 abnormal points with $P < 5\%$ probability of being normal, 1 with $P < 1\%$ by pattern deviation; or (3) pattern standard deviation (PSD) outside 95% normal limits as confirmed on 2 consecutive, reliable (≤33% fixation losses and false-negatives, ≤15% false-positives) tests.

For inclusion in the study, POAG patients were required to have visible βPPA of a temporal width ≥ 100 μm on fundus photographs of at least 1 radial scan measured by the built-in caliper of SDOCT, open angle by gonioscopy, and best-corrected visual acuity ≥ 20/40. Only eyes with ßPPA were included, since the deep-layer microvasculature including choriocapillaris cannot be properly appreciated owing to projection artifacts from the high reflectivity of retinal pigment epithelium (RPE).[15] Patients with a history of ocular surgery other than uncomplicated cataract or glaucoma surgery, intraocular diseases other than glaucoma (eg, diabetic retinopathy or nonglaucomatous optic neuropathy) or neurologic diseases (eg, stroke or pituitary tumor) that could cause VF loss were excluded. Those with diabetes mellitus and/or systemic hypertension were included unless they had been diagnosed with diabetic or hypertensive retinopathy. Those with poor-quality imaging or unreliable VF tests also were excluded.

• **CLINICAL PARAMETERS:** Initial ophthalmologic examinations included measurement of best-corrected visual acuity (BCVA), refraction tests, slit-lamp biomicroscopy, IOP by Goldmann applanation tonometry, gonioscopy, CCT measured with the Pentacam Scheimpflug imaging system (Oculus Optikgeräte GmbH, Wetzlar, Germany), axial length (AXL) measured by IOL Master (Carl Zeiss Meditec, Dublin, California, USA), dilated stereoscopic examination of the optic disc, simultaneous color and red-free fundus photography (TRC-NW8; Topcon, Tokyo, Japan), and standard automated perimetry (Humphrey Field Analyzer; 30-2 Swedish Interactive Threshold Algorithm; Carl-Zeiss Meditec). The examination intervals prior to OCT-A and SDOCT imaging ranged from 3 to 6 months. The examinations included slit-lamp biomicrosopy, Goldmann applanation tonometry, optic disc examinations, and fundus photography. Presence of DH, defined as an isolated splinter- or flame-shaped hemorrhage on the ONH, was determined by 2 masked observers (M.H.S. and J.M.K.) based on their review of fundus photographs and clinical examinations performed at intervals of 3–6 months.[15,19] Baseline IOP was measured before initiation of the IOP-lowering treatment. The mean IOP and standard deviation (SD) IOP during the entire follow-up period were calculated. To avoid the undesired effect that numerous sequential IOP measurements during a short period would have on the final average, the average IOP for each 6-month period was used to calculate the mean follow-up IOP.[14,21] All IOPs measured 4 weeks after any type of incisional surgery or laser procedure were excluded to avoid the effect of transitory IOP changes during this period.[14] At the time of the imaging, we measured the systolic and diastolic blood pressure (BP) of a patient at the height of the heart with an automatic BP instrument (Model Easy X 800 (R/L), JAWON Medical Co. Ltd., Kyungsan, Korea). Mean ocular perfusion pressure (MOPP) was calculated according to the following formula: MOPP = 2/3 (mean arterial pressure [MAP] – IOP), where MAP = diastolic BP + 1/3 (systolic BP − diastolic BP).

• **EVALUATION OF PARAPAPILLARY ATROPHY AND FOCAL LAMINA CRIBROSA DEFECT:** Presence and width of the ßPPA with and without BM was determined by synchronous viewing of the infrared fundus image and ONH radial circle (ONH-RC) scans consisting of 24 consecutive radial B-scans and 3 ONH-RC scans aligned to the fovea-to–Bruch membrane (BM) opening center axis obtained using Spectralis OCT2 Glaucoma Module Premium Edition (GMPE) software (version 1.9.17.0) (Spectralis; Heidelberg Engineering GmbH, Heidelberg, Germany). ßPPA with BM ($ßPPA_{+BM}$) was defined as PPA without RPE but with BM, and ßPPA without BM ($ßPPA_{-BM}$) was defined as PPA with exposed scleral flange without BM, with a temporal width ≥ 100 μm on at least 1 radial scan, as measured by the built-in caliper of the SDOCT. The average width of $ßPPA_{+BM}$ and $ßPPA_{-BM}$ was calculated from 6 radial scans of which the center was located at the fovea-BM opening.[22,23] If the temporal margin of ONH or βPPA was not well visualized, adjacent radial scans 15 degrees apart were used for the measurement. Focal LC defects, defined as laminar holes or laminar disinsertions violating the normal U- or W-shaped contour of the anterior laminar surface, were determined by review of enhanced depth imaging SD-OCT ONH 20 × 20-degree scans consisting of 48 radial B-scans (Figure, A and B).[14,24–29] Two masked observers (H.R.K. and J.W.P.) evaluated the presence of ßPPA, $ßPPA_{-BM}$, and focal LC defects in a masked fashion. Disagreements were resolved by a third adjudicator (M.H.S.).

• **PARAPAPILLARY DEEP-LAYER MICROVASCULATURE DROPOUT:** The Spectralis OCT Angiography Module (Spectralis; Heidelberg Engineering GmbH, Heidelberg, Germany) incorporated into the OCT2 platform, with a central wavelength of 880 nm, an acquisition speed of 85

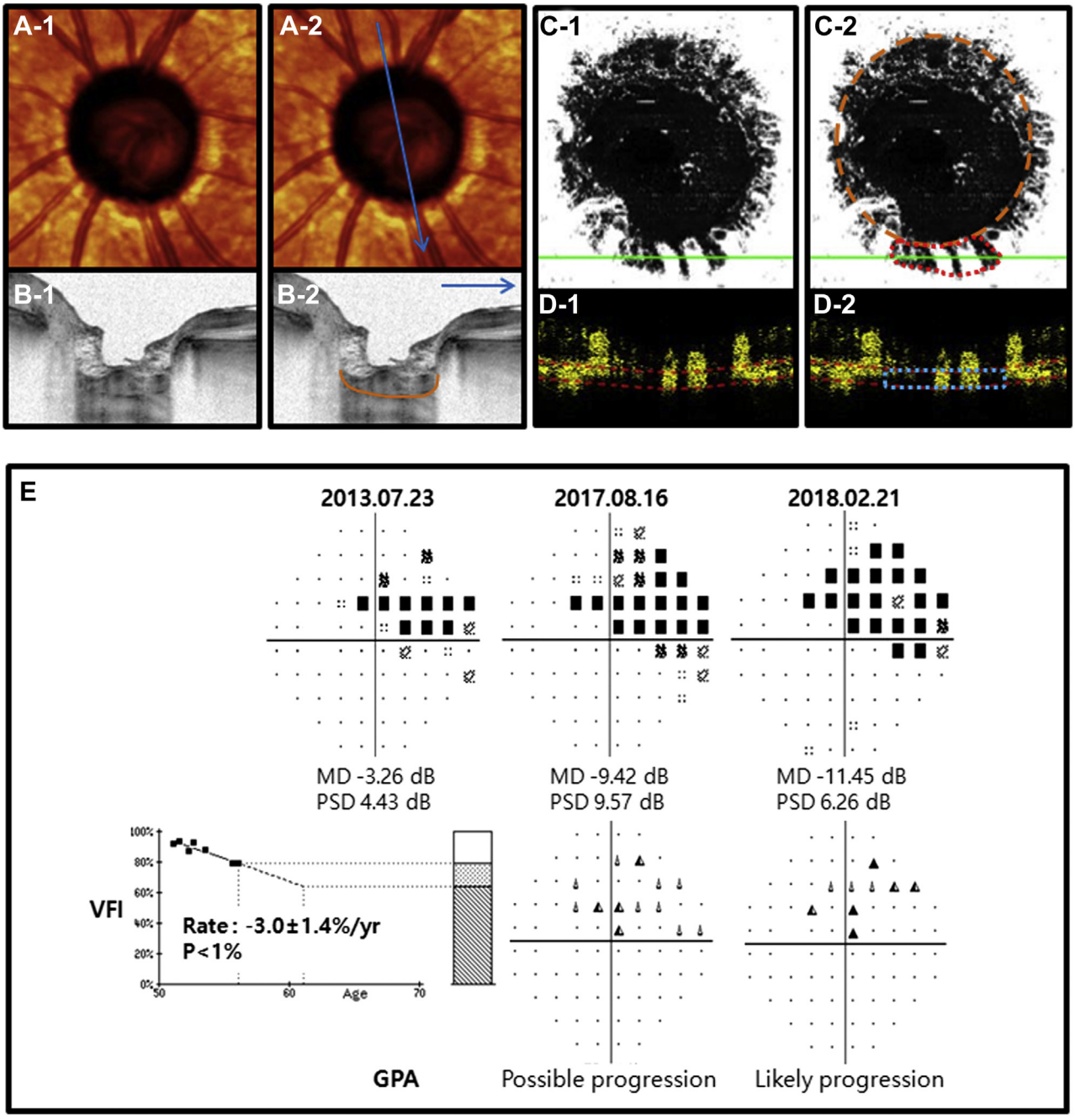

FIGURE. Representative case of eye with parapapillary deep-layer microvasculature dropout showing both event-based and rate-based visual field (VF) progression. The left eye of a 55-year-old woman with parapapillary deep-layer microvasculature dropout, with baseline intraocular pressure (IOP), mean IOP, and standard deviation (SD) IOP of 15.0 mm Hg, 11.9 mm Hg, and 1.5 mm Hg, respectively, did not have optic disc hemorrhages detected on her regular follow-up examinations over 4.5 years. (A, B) Enhanced-depth-imaging spectral-domain optical coherence tomography (SDOCT). A-2 and B-2 are the same images as A-1 and B-1 but are additionally labeled to indicate the horizontal scan locations (large blue arrows) and anterior surface of the lamina cribrosa (orange lines). The contours of the anterior laminar surface were preserved (orange lines), with no evidence of LC defects (A and B). (C, D) OCT angiography. C-2 and D-2 are the same images as C-1 and D-1 but are additionally labeled to indicate the horizontal scan locations (green lines), optic disc margins (orange dotted lines), and location of parapapillary deep-layer microvasculature dropout (red and blue dotted lines). Deep-layer microvasculature dropout showing complete dropout of the parapapillary deep-layer microvasculature (blue dotted lines) was observed in the inferior area (red and blue dotted lines) (C and D). (E) Note the clear VF progression in the superior hemifield corresponding to the location of dropout, based both on Guided Progression Analysis (GPA) and the VF index (VFI) (−3.0%/year) criteria during a 4.5-year follow-up period ($P < .10$).

kHz, and lateral and axial resolutions of 5.7 μm and 3.9 μm per pixel, respectively, was used to visualize the parapapillary deep-layer microvasculature.[19] Scans were obtained according to the 15 × 10-degree scan pattern, consisting of 256 clusters of 5 repeated B-scans. OCT-A images judged to be of poor quality by 2 observers (M.H.S. and J.W.P.) according to the following criteria were excluded: (1) quality score < 25; (2) poor clarity; (3) residual motion artifacts visible as an irregular vessel pattern or disc boundary on the en face angiogram; (4) local weak signal, including floater or posterior vitreous detachment; (5) choroidal-layer segmentation errors.[19]

The 2 independent observers (M.H.S. and J.W.P.), masked to the patients' characteristics and optic disc features, identified parapapillary deep-layer microvasculature dropout. Details on the determination of the presence of parapapillary deep-layer microvasculature dropout has been described elsewhere.[15,19,30,31] Briefly, βPPA was delineated manually as an area between the optic disc margin and RPE tip.[30] A dropout of parapapillary deep-layer microvasculature within the βPPA was defined as a complete loss of the choriocapillaris or microvasculature contained within the upper and lower margin of the choroid or the scleral flange, respectively, on both horizontal and en face OCT-A vessel-density maps (Figure, C and D).[31] Deep-layer microvasculature dropout was required be present on at least 4 consecutive horizontal B-scans and also to be ≥ 200 μm in diameter on at least 1 scan.[15] To evaluate the spatial correlation between VF progression and the dropout, the location of the dropout was categorized into superior and inferior hemiretinas. Discrepancies between the 2 observers were resolved by consensus, or, if consensus could not be reached, the subject was excluded from the analysis.[15]

• **VISUAL FIELD PROGRESSION ANALYSIS:** Trend- and event-based VF progression was defined using VF index (VFI) and Guided Progression Analysis (GPA) criteria. Specifically, an eye was classified as progressing if a statistically significant negative VFI slope ($P < .05$) was detected[32] or "likely progression by GPA criteria of at least 3 test locations showing significant deterioration in visual sensitivity compared with 2 baseline examinations on 3 consecutive VF tests was found (Figure, E).[32,33] VF change based on the GPA criteria was required be observed at the latest follow-up visit.

Eyes for which the follow-up GPA results failed to provide any information owing to severely depressed fields or severe baseline defect where the pattern deviation plot did not display any information were excluded. Eyes showing GPA-based "possible progression," when at least 3 test points in the same location on 2 consecutive field tests showed significant deterioration without a significant negative VFI slope, also were excluded in order to avoid uncertainty of VF progression determination. When 1 eye showed VF progression and the other eye did not, the eye with progression was selected. When both eyes showed VF progression or both did not, 1 eye was randomly selected.

The global VF progression rate was determined based on the VFI. The VF progression rate of the superior and inferior hemifields was determined by calculating their respective rates of change of average retinal sensitivity.

• **STATISTICAL ANALYSIS:** Baseline characteristics and test results were compared between the eyes with and without VF progression using the independent t test or Mann-Whitney test, depending on the normality test results. Categorical variables were compared using the χ^2 test. To identify factors associated with VF progression, each variable was first assessed in a univariable logistic regression analysis. A subsequent multivariable logistic regression analysis was performed for parameters that had a P value < .1 in the univariable regression analysis. To measure the interobserver agreement for the determination of parapapillary deep-layer microvasculature dropout, focal LC defect, presence of the βPPA_{-BM}, and DH, kappa value was derived. Interobserver reproducibility of the measurement of βPPA_{+BM} and βPPA_{-BM} was assessed by the Bland-Altman plot. The analyses were conducted using MedCalc (MedCalc, Inc, Mariakerke, Belgium), and P values < .05 were considered statistically significant.

RESULTS

AMONG THE TOTAL OF 175 EYES OF 168 POAG PATIENTS that met the eligibility criteria, 29 eyes (16.6%) of 22 patients (13.1%) without βPPA and 8 eyes (4.6%) of 8 patients (4.8%) with poor-quality OCT-A images were excluded, thus leaving 138 eyes for an analysis. Eyes with and without βPPA did not differ in terms of age and VF MD (58.3 ± 14.2 years vs 59.7 ± 18.7 years; $P = .685$ for age; −6.57 ± 5.15 dB vs −6.72 ± 8.41 dB; $P = .929$ for VF MD). There was excellent interobserver agreements for determination of the parapapillary deep-layer microvasculature dropout (kappa = 0.91), focal LC defect (kappa = 0.88), presence of the βPPA_{-BM} (kappa = 0.92), and DH (kappa = 0.84). There was good interobserver reproducibility for the measurement of βPPA_{+BM} (Bland-Altman 95% limits of agreement, −56.5 μm to 51.6 μm) and βPPA_{-BM} width (Bland-Altman 95% limits of agreement, −47.4 μm to 48.3 μm).

Age and follow-up period at time of OCT-A were 56.9 ± 14.8 (range: 15–88) years and 5.5 ± 1.4 (range: 3.0–10.6) years, respectively. Eighty eyes (58.0%) had mild (mean deviation [MD], ≥−6 dB) and 58 (42.3%) had moderate-to-advanced (MD, <−6 dB) VF loss at baseline.

Among the 138 eyes included in the study, 55 (39.9%) had VF progression and 83 (60.1%) did not. Among the 55 eyes showing VF progression, 35 fulfilled both the GPA and VFI criteria, 8 met the GPA criteria

TABLE 1. Clinical Characteristics of Progressing and Nonprogressing Glaucomatous Eyes

Variables	Progression (N = 55)	No Progression (N = 83)	*P* Value
Age (y), mean ± SD (range)	58.3 ± 16.2 (24–88)	58.1 ± 13.3 (23–87)	.946[a]
Sex (n, male/female)	29/26	40/43	.606[b]
Spherical equivalent (D)	−2.7 ± 3.6	−2.3 ± 3.4	.643[c]
Axial length (mm)	24.9 ± 2.0	25.0 ± 1.6	.570[c]
Central corneal thickness (μm)	527.6 ± 43.2	533.8 ± 33.4	.360[a]
Self-reported diabetes, n (%)	10 (18.2%)	9 (10.8%)	.222[b]
Self-reported hypertension, n (%)	15 (27.3%)	18 (21.7%)	.453[b]
Diabetes medication, n (%)	9 (16.4%)	9 (10.8%)	.347[b]
Antihypertensive medication, n (%)	14 (25.5%)	17 (20.5%)	.495[b]
Number of topical glaucoma medications, n (%)			.011[b]*
0	3 (5.4%)	5 (6.0%)	
1	4 (7.3%)	23 (27.7%)	
>1	48 (87.3%)	55 (66.3%)	
Topical medications, n			.620[b]
Prostaglandin analogues	33	40	
Beta-antagonists	46	51	
Carbonic anhydrase inhibitors	46	52	
Alpha-1-agonists	22	16	
Follow-up period (y)	5.5 ± 1.6	5.5 ± 1.0	.837[a]
IOP(mm Hg)			
Baseline	19.1 ± 9.9	16.4 ± 4.3	.043[a]*
Mean	13.6 ± 2.5	12.8 ± 2.1	.068[a]
SD	2.9 ± 2.0	2.1 ± 0.7	.001[a]*
IOP at the time of the testing	12.2 ± 2.7	11.9 ± 2.3	.468[a]
VF measurements			
Number, n	8.1 ± 1.9	7.6 ± 2.0	.137[c]
Baseline MD (dB)	−7.1 ± 5.4	−5.8 ± 4.5	.145[a]
Baseline PSD (dB)	7.2 ± 4.4	5.7 ± 4.3	.046[a]*
Final MD (dB)	−10.7 ± 5.5	−4.8 ± 4.6	<.001[a]*
Final PSD (dB)	9.9 ± 3.1	5.6 ± 4.2	<.001[c]*
Systolic BP (mm Hg)	123.8 ± 16.6	122.2 ± 17.1	.625[a]
Diastolic BP (mm Hg)	74.3 ± 12.0	73.7 ± 12.7	.786[a]
MOPP (mm Hg)	48.1 ± 9.4	48.3 ± 9.0	.879[a]
ßPPA$_{+BM}$ width (μm)	247.6 ± 156.8	189.5 ± 74.9	.004*
ßPPA$_{-BM}$ width (μm)	202.4 ± 229.3	170.8 ± 214.7	.412
Presence of ßPPA$_{-BM}$	31 (56.4%)	47 (56.6%)	.849[b]
Disc hemorrhage, n (%)	17 (30.9%)	10 (12.0%)	.006[b]*
Focal LC defect, n (%)	30 (54.5%)	21 (25.3%)	<.001[b]*

ßPPA$_{+BM}$ = ß-zone parapapillary atrophy with Bruch membrane; ßPPA$_{-BM}$ = ß-zone parapapillary atrophy without Bruch membrane; BP = blood pressure; D = diopter; IOP = intraocular pressure; LC = lamina cribrosa; MD = mean deviation; MOPP = mean ocular perfusion pressure; PSD = pattern standard deviation; SD = standard deviation; VF = visual field.

P values < .05 are noted by an asterisk (*).

[a]The comparison was performed by independent sample *t* test.

[b]The comparison was performed by χ^2 test.

[c]The comparison was performed by Mann-Whitney *U* test.

only, and 12 met the VFI criteria only. Table 1 compares the clinical characteristics of the progressing and nonprogressing eyes. Age, sex, spherical equivalent, AXL, CCT, presence of diabetes and hypertension, diabetes medication, antihypertensive medication, mean follow-up period, baseline IOP, SD IOP, IOP at time of testing, mean number of VFs, baseline MD, systolic BP, diastolic BP, MOPP, and presence of ßPPA$_{-BM}$ did not differ between the 2 groups ($P > .1$ for all comparisons). Progressing eyes had a higher mean IOP during follow-up than nonprogressing eyes, with marginal significance ($P = .068$). Progressing eyes had significantly larger numbers of glaucoma medications, a higher baseline IOP and SD IOP, worse baseline PSD, worse final

TABLE 2. Distribution of Parapapillary Deep-Layer Microvasculature Dropout in Eyes With and Without Visual Field Progression

	No Progression (N = 83 Eyes)	Progression (N = 55 Eyes)	*P* Value[a]
Dropout (n = 84 eyes)	34 (40.5%)	50 (59.5%)	<.001*
No dropout (n = 54 eyes)	49 (90.7%)	5 (9.3%)	

VF progression was defined as a likely progression on Guided Progression Analysis having at least 3 test points showing a significant deterioration in visual sensitivity compared with 2 baseline examinations on 3 consecutive visual field tests or a significant negative slope between visual field index and age.

P values < .05 are noted by an asterisk (*).

[a]The comparison was performed by χ^2 test.

MD and PSD, and higher prevalence of DH and focal LC defects ($P < .05$ for all comparisons).

The progression analysis results (the numbers of progressing and nonprogressing eyes) for the groups with and without deep-layer microvasculature dropout are summarized in Table 2. VF progression was more common in eyes with dropout than in those without dropout (50/84 eyes [59.5%] vs 5/54 eyes [9.3%]; $P < .001$).

Table 3 shows the univariable and multivariable logistic regression analysis results of factors associated with VF progression. Based on the univariable analysis, VF progression was significantly associated with higher baseline IOP (odds ratio [OR]: 1.06 per 1 mm Hg higher; $P = .044$), higher SD IOP (OR: 1.56 per 1 mm Hg higher; $P = .001$), worse baseline VF PSD (OR: 1.08 per 1 dB worse; $P = .046$), higher prevalence of DH (OR: 2.84; $P = .011$), higher prevalence of focal LC defect (OR: 3.54; $P < .001$), wider ßPPA$_{+BM}$ width (OR: 1.25 per 50 μm wider; $P = .004$), and higher prevalence of parapapillary deep-layer microvasculature dropout (OR: 15.15; $P < .001$). Higher mean IOP showed a significant association with VF progression, with marginal significance (OR: 1.15 per 1 mm Hg higher; $P = .066$). Age, CCT, AXL, baseline VF MD, and presence and width of ßPPA$_{-BM}$ were not significantly associated with VF progression ($P > .1$ for all comparisons). Baseline IOP, mean IOP, and SD IOP were significantly associated with each other ($P < .001$, respectively); thus, these 3 IOP parameters were included in separate multivariable models to avoid multicollinearity. In each of the 3 multivariable models using different IOP variables (baseline IOP, mean IOP during follow-up, and SD IOP), VF progression was significantly associated with higher prevalence of parapapillary deep-layer microvasculature dropout (OR: 5.04, $P = .019$; OR: 5.68, $P = .008$; OR: 3.64, $P = .043$, respectively) (Table 3). VF progression was also significantly associated with higher prevalence of focal LC defects, with OR ranging from 3.06 to 3.69, all $P < .05$, and a higher prevalence of DH, with OR ranging from 5.14 to 7.02, all $P < .05$, and wider ßPPA$_{+BM}$ width per 50 μm wider, with OR 1.33 and 1.28 with mean IOP and SD IOP included.

The VF progression rates of eyes with and without parapapillary deep-layer microvasculature dropout are compared in Table 4. The mean VF index change rate of eyes with dropout (−2.23 %/year) was significantly faster than that of eyes without dropout (−0.05 %/year) ($P < .001$). The subgroup of 45 eyes with deep-layer microvasculature dropout located only in the inferior hemiretinas had a significantly faster rate of change of VF index (−1.37 %/year vs −0.05 %/year; $P < .001$) and of VF sensitivity in the superior hemifield (−0.43 dB/year vs 0.27 dB/year; $P < .001$) than did those without dropout. Meanwhile, the differences in the rate of VF progression between eyes with dropout only in the inferior hemiretinas and those without dropout were marginally significant for the inferior hemifield (0.04 dB/year vs 0.20 dB/year, respectively; $P = .057$). When the within-subject analysis was performed for eyes with dropout only in the inferior area, the superior hemifield had significantly faster VF progression rate than the inferior hemifield (−0.43 ± 0.98 dB/year vs 0.04 ± 0.44 dB/year, respectively; $P < .001$). The subgroup of 14 eyes with dropout located only in the superior hemiretinas had a significantly faster rate of change of VF index (−1.36%/year vs −0.05%/year; $P = .005$) and of VF sensitivity in the inferior hemifield (−0.45 dB/year vs 0.20 dB/year; $P < .001$) than did those without dropout. Although eyes with dropout only in the superior hemiretinas tended to have a faster VF progression rate in the superior hemifield than did those without dropout, the differences did not reach statistical significance (−0.05 dB/year vs 0.27 dB/year; $P = .102$). When the within-subject analysis was performed for eyes with dropout only in the superior area, the inferior hemifield had faster VF progression rate than the superior hemifield with marginal significance (−0.05 ± 0.76 dB/year vs −0.45 ± 1.08 dB/year, respectively; $P = .065$).

The Figure illustrates a patient with parapapillary deep-layer microvasculature dropout showing VF progression. The left eye of the 55-year-old woman with early low-tension glaucoma (baseline MD = −3.26 dB, baseline IOP = 15.0 mm Hg) and well-controlled IOP (mean IOP = 11.9 mm Hg, SD IOP = 1.5 mm Hg) did not show any DH or focal LC defect. During the 4.5 years of follow-up, the eye with dropout in the inferior area showed significant VF progression in the corresponding superior hemifield on both the GPA and VF index criteria (Figure).

DISCUSSION

IN THE CURRENT STUDY, THE PRESENCE OF PARAPAPILLARY deep-layer microvasculature dropout was independently

TABLE 3. Univariable and Multivariable Regression Analysis Evaluating Factors Associated With Visual Field Progression

	Univariable Model		Multivariable Model 1[a] With Baseline IOP Included		Multivariable Model 2[a] With Mean IOP Included		Multivariable Model 3[a] With SD IOP Included	
Variables	Odds Ratio, 95% CI	*P* Value	Odds Ratio, 95% CI	*P* Value	Odds Ratio, 95% CI	*P* Value	Odds Ratio, 95% CI	*P* Value
Age, per 1 year older	1.00 (0.98–1.02)	.946						
CCT, per 40 μm thinner	1.19 (0.82–1.74)	.356						
Axial length, per 1 mm longer	0.96 (0.78–1.17)	.667						
Baseline IOP, per 1 mm Hg higher	1.06 (1.00–1.12)	.044*	1.05 (0.98–1.13)	.167				
Mean IOP, per 1 mm Hg higher	1.15 (0.99–1.35)	.066			1.51 (1.17–1.95)	.002*		
SD IOP, per 1 mm Hg higher	1.56 (1.15–2.10)	.001*					1.94 (1.20–3.12)	.006*
Baseline visual field MD, per 1 dB worse	1.05 (0.98–1.13)	.145						
Baseline visual field PSD, per 1 dB worse	1.08 (1.00–1.17)	.046*	1.19 (1.04–1.37)	.013*	1.26 (1.10–1.45)	.001*	1.24 (1.08–1.42)	.002*
Disc hemorrhage, presence	2.84 (1.26–6.40)	.011*	5.14 (1.67–15.75)	.004*	6.71 (2.05–21.97)	.002*	7.02 (2.20–22.37)	.001*
Focal lamina cribrosa defect, presence	3.54 (1.71–7.32)	<.001*	3.69 (1.34–10.15)	.012*	3.06 (1.14–8.23)	.027*	3.64 (1.32–10.09)	.013*
ßPPA$_{+BM}$ width, per 50 μm wider	1.25 (1.06–1.48)	.004*	1.24 (0.97–1.59)	.088	1.33 (1.05–1.69)	.018*	1.28 (1.02–1.61)	.030*
ßPPA$_{-BM}$ width, per 50 μm wider	1.03 (0.96–1.12)	.410						
ßPPA$_{-BM}$, presence	0.93 (0.47–1.87)	.848						
Parapapillary deep-layer microvasculature dropout, presence	15.15 (5.47–42.02)	<.001*	5.04 (1.30–19.53)	.019*	5.68 (1.58–20.45)	.008*	3.64 (1.04–12.72)	.043*

ßPPA$_{+BM}$ = ß-zone parapapillary atrophy with Bruch membrane; ßPPA$_{-BM}$ = ß-zone parapapillary atrophy without Bruch membrane; CCT = central corneal thickness; IOP = intraocular pressure; LC = lamina cribrosa; MD = mean deviation; PSD = pattern standard deviation; SD = standard deviation; VF = visual field.

P values < .05 are noted by an asterisk (*).

[a]Adjusted for all variables with $P < .10$ in the univariable model.

TABLE 4. Comparison of the Visual Field Progression Rate Between Eyes With and Without Parapapillary Deep-Layer Microvasculature Dropout

Variables	Eyes Without Dropout (N = 54)	Eyes With Dropout (N = 84)	*P* Value[a]	Eyes With Dropout Only in the Inferior Hemiretinas (n = 45)	*P* Value[a]	Eyes With Dropout Only in the Superior Hemiretinas (N = 14)	*P* Value[a]
VFI progression rate (%/y)	−0.05 ± 1.24	−2.23 ± 3.22	<.001[b]*	−1.37 ± 2.37	<.001[b]*	−1.36 ± 2.44	.005[b]*
Superior VF sensitivity progression rate (dB/y)	0.27 ± 0.63	−0.45 ± 0.98	<.001[b]*	−0.43 ± 0.98[d]	<.001[c]*	−0.05 ± 0.76[e]	.102[c]
Inferior VF sensitivity progression rate (dB/y)	0.20 ± 0.39	−0.41 ± 1.27	<.001[b]*	0.04 ± 0.44[d]	.057[c]	−0.45 ± 1.08[e]	<.001[c]*

VF = visual field; VFI = visual field index.

P values < .05 are noted by an asterisk (*).

[a]*P* value compared to eyes without parapapillary deep-layer microvasculature dropout.

[b]The comparison was performed by Mann-Whitney *U* test.

[c]The comparison was performed by independent sample *t* test.

[d]Superior hemifield had significantly faster VF progression rate than the inferior hemifield among eyes with parapapillary deep-layer microvasculature dropout only in the inferior area (*P* < .001).

[e]Inferior hemifield had faster VF progression rate than the superior hemifield among eyes with parapapillary deep-layer microvasculature dropout only in the superior area with marginal significance (*P* = .065).

associated with prior VF progression; ORs ranged from 3.64 to 5.68 even after adjusting for known factors related with VF progression, including focal LC defects,[14] DHs,[4,21] width of the βPPA with BM,[22,23,34] and IOP parameters.[3,4,6,21] Furthermore, eyes with deep-layer microvasculature dropout showed a significantly faster rate of VF progression rate than those without deep-layer microvasculature dropout, and the locations of dropout and VF progression were spatially correlated. These findings suggest that deep-layer microvasculature dropout may serve as an important structural parameter associated with progressive damage of RGC function.

Recently, Park and associates suggested that deep-layer microvasculature dropout is associated with progressive RNFL thinning.[20] Moreover, our group reported that VF sensitivity was worse in eyes with dropout than in those without dropout for a similar degree of LC damage and axonal loss.[19] The current results demonstrate that parapapillary deep-layer microvasculature dropout may be an important factor associated with the past VF progression. Given that VF progression plays a pivotal role in patients' quality of life and treatment strategy, this result has clinical significance for the management of glaucoma.

However, it is still unclear whether parapapillary deep-layer microvasculature dropout plays a causative role in VF progression or is simply an epiphenomenon of progression. A possible hypothesis is that parapapillary deep-layer microvasculature damage disrupts the blood–optic nerve barrier, and thereby accelerates the release of vasoactive substances that damage ONH axons.[35–42] Deep-layer microvasculature damage might be associated with hypoperfusion and subsequent reduction of the retrograde axoplasmic transport of neurotrophic factors to the RGC cell body.[35–42] Alternatively, parapapillary deep-layer microvasculature dropout might be merely an epiphenomenon of progressive RGC damage that includes RNFL thinning and subsequent VF progression. However, the current study cannot directly address these issues owing to its retrospective nature. Further longitudinal prospective studies are warranted with OCT-A microvasculature dropout assessed at baseline.

It is noteworthy that a considerable number of eyes with parapapillary deep-layer microvasculature dropout (34/84; 40.48%) did not progress, and that 90.74% (49/54) of those without dropout had no VF progression. These findings suggest that absence of dropout is highly suggestive of stable disease, whereas presence of dropout does not guarantee detectable VF progression. The clinical implications of these findings are not clear. Possible explanations include the relatively short follow-up period (approximately 5.52 years) for detection of VF progression. Indeed, over the course of a longer follow-up period, eyes with dropout and without VF progression might ultimately progress. Second, conservative VF progression determination may have attributed a considerable number of eyes with dropout showing no VF progression. VF progression was determined, in an event analysis, according to the GPA-based likely progression criteria, and, in a trend analysis, according to the VFI slope. Although these strict criteria carry the advantage of relatively low rates of false positivity,[43,44] conversely, they might lead to lower sensitivity for detection of subtle VF progression. Third, we can hypothesize that dropout may need to be accompanied by other factors influencing glaucoma progression. In this study, focal LC defect, DH, and mean IOP were factors associated with VF progression among eyes with dropout

(data not shown). These speculations can be elucidated only by prospective longitudinal studies with longer follow-up periods in participants with serial SDOCT and OCT-A testing.

In this study, the VF progression rate of eyes with dropout was significantly greater than that of those without dropout, both globally and locally in areas corresponding to the location of dropout. These findings are suggestive of a topographic relationship between parapapillary deep-layer microvasculature dropout and VF progression. Interestingly, faster VF deterioration of eyes with dropout also was observed in an area without dropout, though the differences did not reach statistical significance. As a result of these findings, clinicians should be aware of VF progression not only at the hemifield corresponding to the deep-layer microvasculature dropout, but also at the opposite hemifield. However, it remains to be determined whether these observations support the hypothesis that focal compromise of deep-layer microvasculature can propagate to an area with intact deep-layer microvasculature, or are merely coincidental findings.

In this study, IOP parameters remained as important factors associated with VF progression, and mean IOP and SD IOP were higher in the progression group than in the nonprogression group. These results do not necessarily mean that IOP was not controlled in the progression group. Mean IOP of the progression group was ~29% lower than mean baseline IOP, while mean IOP of the nonprogression group was ~22% lower than mean baseline IOP. In addition, IOP at the time of the testing did not differ between the 2 groups (12.2 ± 2.7 vs 11.9 ± 2.3; $P = .468$). Therefore, we consider that IOP differences between the 2 groups appear to be mainly owing to the high baseline IOP of the progression group, and not their poorly controlled IOP. Meanwhile, one may argue that eyes with progression are more likely to have surgery to lower IOP, and that the progression rate may be influenced by the surgery. In this study, 7 eyes (12.7%) of the progression group and 1 eye (1.2%) of the nonprogression group had glaucoma surgery. None of the eyes, except 1 in the progression group, had notable change of VFI slope. Therefore, it appears that the influence of surgery on VF progression is insignificant.

As already noted above, the present study is limited by a relatively short follow-up period, its retrospective nature, and the conservative criteria applied for determination of VF progression.[43,44] Because OCT-A is a new technology, VF progression was determined before the OCT-A imaging. Therefore, the clinical implication of the current results should be limited to the notion that parapapillary deep-layer microvasculature dropout was associated with the prior VF progression. The population in this study was relatively young, perhaps owing to the relatively young age of our sample population. This may limit the generalizability of the current results to older patients with glaucoma. In addition, age, CCT, glaucoma severity, and presence of ßPPA$_{-BM}$, all of which are important factors associated with glaucoma progression, were unrelated to VF progression in our dataset. Second, determination of deep-layer microvasculature dropout was based on the qualitative assessment of the 2 observers, and its extent was not considered. Further improvement of the OCT-A analytics that enable user-defined regional quantitative analysis of the deep-layer microvasculature is necessary.

In conclusion, OCT-A-based parapapillary deep-layer microvasculature dropout was independently associated with prior VF progression. Moreover, there was a spatial correlation between deep-layer microvasculature dropout location and that of VF progression. These findings implicate parapapillary deep-layer microvasculature dropout as a structural parameter associated with the prior glaucomatous VF progression. Further prospective longitudinal studies are needed to elucidate the causative role of deep-layer microvasculature damage in the pathophysiology of glaucoma.

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