An Increased Choroidal Microvasculature Dropout Size is Associated With Progressive Visual Field Loss in Open-Angle Glaucoma

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• PURPOSE: **To investigate whether the choroidal microvasculature dropout (CMvD) increases in size over time among open-angle glaucoma (OAG) eyes presenting with CMvD at baseline and evaluate the association between longitudinal CMvD size increases and subsequent visual field (VF) progression.**

• DESIGN: **Retrospective cohort study.**

• METHODS: **This study enrolled 101 eyes from 101 consecutive patients with OAG with a localized CMvD and glaucomatous VF defects at baseline and a minimum 2-year follow-up. The angular circumference (AC) of the CMvD was determined from choroidal layer images using optical coherence tomography angiography at the baseline and final follow-up. Demographic and ocular characteristics, including the rate of retinal nerve fiber layer thickness loss and amount of CMvD AC increase during follow-up, were compared between OAG eyes with and without VF progression. Cox proportional hazard analysis was performed to identify the clinical factors associated with VF progression. The relationships between CMvD angular enlargement during follow-up and clinical factors were assessed.**

• RESULTS: **CMvD angular enlargement was found in 21.8% of patients while VF progression was observed in 26.7% of the OAG eyes with CMvD during a mean 2.52-year follow-up. OAG eyes with VF progression showed a significantly greater CMvD angular enlargement. A larger increase in the CMvD AC was an independent predictor of VF progression. CMvD AC changes were significantly correlated with the rates of VF deterioration.**

• CONCLUSIONS: **VF progression is significantly associated with a greater longitudinal increase in the CMvD AC in OAG eyes with CMvD. CMvD AC changes have significant correlations with the rate of VF loss. (Am J Ophthalmol 2021;223:205–219. © 2020 Elsevier Inc. All rights reserved.)**

AJO.com Supplemental Material available at AJO.com.
Accepted for publication Oct 22, 2020.

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THE RECENT INTRODUCTION OF OPTICAL COHERENCE tomography angiography (OCTA) has made it possible to visualize and measure retinal and choroidal microvasculature in an objective and quantitative manner. A localized parapapillary choroidal perfusion defect, known as choroidal microvasculature dropout (CMvD), has been extensively studied with OCTA devices in glaucomatous eyes, the presence of which may imply compromised optic nerve head (ONH) perfusion in patients with open-angle glaucoma (OAG).[1,2] Glaucomatous eyes with CMvD typically present with advanced visual field (VF) damage,[1,3,4] in which the size of CMvD is significantly correlated with the severity of VF damage.[5,6] Moreover, CMvD detected during follow-up is associated with progressive retinal nerve fiber layer (RNFL) thinning or VF loss.[7-9] These findings suggest that the presence of CMvD may have a prognostic implication in glaucoma.

The adequate surveillance of VF progression is of paramount importance in patients with glaucoma because the management goal for this condition is centred on halting or reducing the rate of VF progression and thereby maintaining vision-related quality of life. Other than VF testing, structural examinations, such as an RNFL evaluation using optical coherence tomography (OCT), are also used to monitor disease progression. However, in advanced stages of glaucoma with VF defects, detecting changes in structural parameters (ie, RNFL thickness [RNFLT]) may be of limited use because the RNFLT exhibits a measurement floor beyond which no further structural loss is detected despite VF progression.[10-12] There is a need for an alternative metric to monitor eyes with advanced glaucoma. In this regard, OCTA may play an adjunctive role in detecting disease progression because it has shown good reproducibility in both healthy and glaucomatous eyes.[13,14] In addition, progressive microvasculature loss has been detected in the superficial retina using serial OCTA examinations in an eye with advanced glaucoma.[15]

In our current study, we hypothesized that progressive microvasculature loss can also occur in the parapapillary deep layer (ie, choroidal layer), as manifested by the CMvD enlargement, in some patients with OAG with CMvD during follow-up. Moreover, this enlargement of the CMvD may be associated with disease progression. We aimed to investigate the relationship between a longitudinal change in the CMvD size with progressive VF loss

0002-9394/$36.00
https://doi.org/10.1016/j.ajo.2020.10.018

in OAG eyes that initially presented with a localized CMvD and glaucomatous VF damage. We surmised that the clarification of this relationship may enhance our understanding on the role of CMvD in the glaucoma monitoring and provide a rationale for using CMvD size as a potential marker of VF progression in patients with OAG.

METHODS

• **STUDY SUBJECTS:** This study was approved by the Institutional Review Board of Asan Medical Center and followed the tenets of the Declaration of Helsinki. The requirement for written informed consent was waived because of the retrospective design of the study. We reviewed the medical records of consecutive patients with OAG who were treated by a specialist (M.S.K.) at the glaucoma clinic of Asan Medical Center between November 2016 and March 2018. All participants underwent comprehensive ophthalmologic examinations at their initial work-up, which included a review of their medical history, a best-corrected visual acuity (BCVA) assessment, slit-lamp biomicroscopy, intraocular pressure (IOP) measurement using Goldmann applanation tonometry, automated refraction (KR-890; Topcon Corp, Tokyo, Japan), central corneal thickness (CCT) measurement with ultrasonic pachymetry (Tomey SP-3000, Nagoya, Japan), gonioscopy, dilated color fundus photography (Canon, Tokyo, Japan), stereoscopic optic disc photography and red-free RNFL photography (Canon), axial length (AL) measurement with IOL master (Carl Zeiss Meditec, Dublin, California, USA), Humphrey field analyzer (HFA) Swedish Interactive Threshold Algorithm (SITA) 24-2 VF testing (Carl Zeiss Meditec), Cirrus HD spectral-domain OCT (Carl Zeiss Meditec), and OCTA (Angiovue; Optovue Inc, Fremont, California, USA).

The definition of OAG in our present study included all of the following: glaucomatous ONH (ie, generalized or focal rim thinning; vertical cup-to-disc ratio > 0.7; asymmetry in the vertical cup-to-disc ratio between the eyes exceeding 0.2 and not explained by the optic disc size, an optic disc hemorrhage [ODH], or an RNFL defect); open angles on gonioscopy in both eyes; and compatible glaucomatous VF loss[16] in 2 consecutive tests (ie, a cluster of ≥3 nonedged contiguous points with a <5% probability in the hemifield pattern deviation plot and at least 1 point with a <1% probability; a pattern standard deviation with a $P < .05$; or glaucoma hemifield test results outside of normal limits, as confirmed on 2 consecutive reliable VF tests [false-positive errors <15%, false-negative errors <15%, and fixation loss <20% within a month]) irrespective of the IOP level.

For the purposes of our present analyses, the enrolled subjects were required to have all of the following characteristics; 1) BCVA ≥20/40; 2) age ≥18 years at initial presentation; 3) a spherical equivalent of between −8.0 and +3.0 diopters (D), and cylinder correction within +3 D; 4) an OAG with a single localized CMvD within the β-zone parapapillary atrophy (β-PPA) of the parapapillary choroid on choroidal layer OCTA imaging at the initial examination; 5) follow-up for ≥2 years, with availability of ≥5 reliable spectral-domain OCT and VF datasets (after excluding the first VF test to obviate learning effects; and 6) had undergone ≥2 reliable OCTA tests during follow-up. All patients with OAG were followed up every 4-6 months using red-free fundus photography, ONH stereoscopic photography, VF, and spectral-domain OCT with or without OCTA, based on the glaucoma specialist's discretion. The IOP was measured at each visit and the mean follow-up IOP was represented by the average of all the values obtained during the follow-up. The peak follow-up IOP was represented by the highest value of all the values recorded during the follow-up. All ODHs occurring during follow-up visits were identified from stereoscopic optic disc photographs. The affected eye was selected in patients with unilateral disease. If both eyes of a patient were eligible, 1 eye was selected at random.

Patients were excluded from our current analyses if they had severe myopic retinal or macular changes that prevented the accurate ONH/VF evaluation of glaucoma, including posterior staphyloma; any macular or retinal diseases (eg, retinal vascular occlusion or diabetic retinopathy); a history of ocular procedure or surgery including laser treatment, or cataract or glaucoma surgery during follow-up; a history of ocular trauma; cataracts of more than C2, N2, or P2 during follow-up based on the Lens Opacities Classification System III[17]; or a systemic or neurologic disease that could influence the VF tests.

• **ASSESSMENT OF CMVD AND SIZE:** All enrolled subjects had undergone OCTA at baseline, which was repeated every 6-12 months during follow-up, and the final visit. The principles of this system have been well described in previous studies.[1,5,6] In brief, the AngioVue OCTA generates en face images and vascular data at various user-defined retinal layers via an automated layer segmentation algorithm around the ONH.[1] In our current study, the choroidal microvasculature in the parapapillary area was evaluated on en face images that were derived from an en face slab that extended from the retinal pigment epithelium to 390 μm below the Bruch membrane, which was sufficient to include the full thickness of the choroid and the inner border of sclera. All baseline and follow-up OCTA images of the choroidal layer were evaluated using AngioVue software (v 2018.1.0.37). Only good-quality images of high clarity, with no motion artifacts or segmentation errors, and with a scan quality score >6 were used.

CMvD was defined as a complete loss of the choriocapillaries and microvasculature without any visible microvasculature network within the β-PPA, and identified when

the minimum angular width was >200 μm or than the width of the central retinal vein.[1,3-5,9,18] In our current analyses, when the CMvD area included large retinal vessels on the en face images of the choroidal layer, the area covered by the retinal vessels was included as part of the CMvD area if the CMvD extended beyond the vessels. In cases where the retinal vessels were located at the border of the CMvD, the area covered by the vessels was excluded from the CMvD area.

For the determination of a CMvD size, its angular circumference (AC) was measured in our current study using previously described approaches.[4,5,19] In brief, an optimally fitted ellipse around the ONH border was provided automatically by the AngioVue software (v 2018.1.0.37) based on the Bruch membrane opening margin. The CMvDs were manually drawn using ImageJ software (v 1.52; Wayne Rasband, National Institutes of Health, Bethesda, Maryland, USA). The 2 points at which the circumferential borders of the CMvD met the ONH margin were defined as angular circumferential margins. The center of the ONH is also automatically provided by AngioVue software.

The AC (in degrees) was then determined by drawing 2 lines connecting the ONH center to the angular circumferential margins of the CMvD.[4,5,19] The presence and AC of the CMvD were independently assessed by 2 glaucoma specialists (J.Y.L., M.S) during initial screening and after enrollment, who were blind to the clinical data for each patient, including the VF data. Any discrepancies between the 2 observers were resolved by a third specialist (M.S.K.). The AC determined by the 2 observers (J.Y.L., M.S.) was averaged to minimize interobserver variation.

A line was drawn to equally bisect the angular circumferential margins of the CMvD from the ONH center, which is a previously reported method that was used to define the location of the CMvD in our present analyses.[5,18] The CMvD location was represented using a 12-hour clock map. The clock hour was determined based on the location after superimposing and manually aligning the OCTA images on the fundus image provided in the OCTA device. Disagreements between the 2 observers (J.Y.L., M.S.) in determining the clock hour CMvD location were resolved by a third adjudicator (M.S.K.).

• **DEFINITION OF SIGNIFICANT INCREASE IN THE CMVD AC:** All CMvD AC measurements for each study eye at the baseline and final visit were compared. Significant CMvD AC increase was defined by change between the baseline and final measurement of CMvD AC. The Bland-Altman method was used to establish a cutoff for significant CMvD AC increase.[20,21] Change was considered to be significant when it exceeded 1.96 times the intersession standard deviation (SD), which corresponds to the 95% confidence interval (CI) for the true value of the measurement.[22] The intersession SD of the CMvD AC was calculated as the test–retest variability between 2 measurements repeated at 1-week intervals in a separate group of 30 OAG eyes with a localized CMvD, matched to the study eyes (n = 101) by the severity of baseline VF loss (−6 dB < mean deviation [MD] ≤ −12 dB).

• **VISUAL FIELD ASSESSMENT:** The HFA provides various VF summary indices. These include the MD, pattern SD, and visual field index (VFI). The global index for VF sensitivity loss compared with an age-matched control is provided as the VF MD. VFI is expressed as a percentage; 100% represents a normal VF, and 0% represents a perimetrically blind field. The MD and VFI were used as VF summary parameters in the current study. Only reliable VF data were included in the analysis.

• **DEFINITION OF VISUAL FIELD PROGRESSION:** VF progression was determined with the Early Manifest Glaucoma Trial (EMGT) criteria,[23] using HFA-guided progression analysis (GPA; Carl Zeiss Meditec) software. Only "likely progression" was considered VF progression in the current study.

• **SPECTRAL-DOMAIN OCT ASSESSMENT:** The Cirrus spectral-domain OCT system is calibrated on a regular basis by a technician employed by the manufacturer. The optic disc cube scan was used to measure the RNFLT at 6 mm × 6 mm at the circumpapillary region using the Cirrus spectral-domain OCT (software version 10.0; Carl Zeiss Meditec). The circumpapillary RNFLT was measured along a circle of 3.45 mm in diameter centered on the ONH. The circumpapillary RNFLT was measured globally, at 4 quadrants, and at 12 clock hour sectors. The circumpapillary RNFLT of the global area and CMvD-located clock-hour sector were used as RNFLT parameters in our present analyses. Poor quality spectral-domain OCT images with motion artifacts, segmentation failure, or a signal strength <7 were excluded.

• **DATA ANALYSIS:** The interobserver agreement (J.Y.L., M.S.) for the presence and clock-hour location of CMvD and for the measurement of CMvD AC was assessed using the k value and the intraclass correlation coefficient, respectively. A normal distribution was tested using the Kolmogorov-Smirnov test. For comparisons between groups, the independent *t* test or the Mann–Whitney *U* test was performed for continuous variables, based on the normality test. For categorical data, the χ^2 test was performed. GPA software (Carl Zeiss Meditec) for the Cirrus spectral-domain OCT and HFA 24-2 VF testing provides trend-based analysis to estimate the rate of change in the average RNFLT (expressed in μm/year) and VFI (expressed in %/year) over time using linear regression analysis. In addition, linear regression analyses were performed against the patient ages to derive the rate of change in CMvD-located clock-hour RNFLT (expressed in μm/year) and VF MD (expressed in dB/year).

TABLE 1. Demographic Characteristics of Eyes with Open-Angle Glaucoma with Increased Choroidal Microvasculature Dropout Angular Circumference and Stable Choroidal Microvasculature Dropout Angular Circumference

Characteristics	Group A, Entire Group, n = 101	Group B, Increased CMvD AC Group, n = 22	Group C, Stable CMvD AC Group, n = 79	*P* Value[a]
Age (y), mean ± SD	54.81 ± 10.64	56.53 ± 10.92	54.33 ± 11.09	.543[b]
Male, n (%)	47 (46.5)	9 (40.9)	38 (48.10)	.859[c]
CCT (μm), mean ± SD	520.18 ± 23.04	517.55 ± 21.98	520.91 ± 20.41	.666[b]
Axial length (mm), mean ± SD	24.93 ± 2.85	25.12 ± 2.71	24.88 ± 3.24	.631[b]
Spherical equivalent (diopters), mean ± SD	−1.21 ± 2.02	−1.29 ± 2.03	−1.19 ± 1.82	.665[b]
Baseline IOP (mm Hg), mean ± SD	15.38 ± 3.28	15.94 ± 3.18	15.22 ± 3.81	.743[d]
Mean FU IOP (mm Hg), mean ± SD	13.65 ± 1.96	13.71 ± 1.96	13.63 ± 2.05	.369[d]
Peak FU IOP (mm Hg), mean ± SD	17.92 ± 6.95	18.37 ± 7.28	17.79 ± 6.27	.781[d]
No. of antiglaucoma drugs, mean ± SD	1.53 ± 0.58	1.61 ± 0.51	1.51 ± 0.61	.676[b]
Average RNFL thickness at baseline (μm), mean ± SD	66.18 ± 9.31	65.40 ± 8.12	66.40 ± 9.69	.184[d]
Average RNFL thickness at last FU (μm), mean ± SD	64.89 ± 9.26	63.24 ± 8.93	65.35 ± 9.70	.221[d]
Sectoral RNFL thickness at CMvD location at baseline (μm), mean ± SD	64.79 ± 9.19	64.81 ± 9.07	64.78 ± 9.44	.274[d]
Sectoral RNFL thickness at CMvD location at final FU (μm), mean ± SD	62.49 ± 9.28	61.98 ± 8.35	62.63 ± 9.51	.154[d]
Rate of average RNFL thinning (μm/yr), mean ± SD	−0.99 ± 1.66	−1.17 ± 1.33	−0.94 ± 1.50	.784[d]
Rate of sectoral RNFL thinning at CMvD location (μm/y), mean ± SD	−1.23 ± 1.45	−1.58 ± 1.51	−1.13 ± 1.46	.233[d]
VF MD at baseline (dB), mean ± SD	−10.49 ± 6.58	−10.81 ± 6.50	−10.40 ± 6.88	.549[d]
VF MD at last FU (dB), mean ± SD	−11.45 ± 6.76	−13.06 ± 5.93	−11.00 ± 6.13	.045[d,e]
VF VFI at baseline (%), mean ± SD	66.75 ± 12.17	65.41 ± 12.94	67.12 ± 12.59	.249[d]
VF VFI at last FU (%), mean ± SD	65.50 ± 12.31	63.04 ± 11.74	66.19 ± 12.71	.032[d,e]
VF progression (%)	26.7	100	6.3	<.001[c,e]
Rate of VF MD progression (dB/y), mean ± SD	−0.82 ± 1.49	−1.94 ± 1.24	−0.51 ± 1.67	<.001[d,e]
Rate of VFI progression (%/y), mean ± SD	−1.08 ± 1.52	−2.15 ± 1.76	−0.78 ± 1.74	<.001[d,e]
Optic disc hemorrhage, n (%)	15 (14.9)	7 (27.3)	9 (10.1)	.031[c,e]
Hypertension, n (%)	27 (26.7)	7 (27.3)	20 (25.3)	.722[c]
Diabetes mellitus, n (%)	18 (17.8)	4 (18.2)	14 (17.7)	.490[c]
Family history of glaucoma, n (%)	15 (14.9)	3 (13.6)	12 (15.2)	.583[c]
Dyslipidemia, n (%)	8 (7.9)	2 (9.1)	6 (7.6)	.334[c]
Migraine, n (%)	7 (6.9)	2 (9.1)	5 (6.3)	.162[c]
CMvD angular circumference at baseline (degrees), mean ± SD	67.06 ± 20.83	68.89 ± 20.40	66.55 ± 21.14	.587[d]
CMvD angular circumference at last FU (degrees), mean ± SD	68.20 ± 20.91	73.48 ± 20.51	66.73 ± 21.36	.282[d]
Amount of increase in CMvD angular circumference (degrees), mean ± SD	1.14 ± 1.46	4.59 ± 0.45	0.18 ± 0.83	<.001[d,e]
FU period (y), mean ± SD	2.52 ± 0.49	2.53 ± 0.48	2.51 ± 0.49	.927[d]

AC = angular circumference; CCT = central corneal thickness; CMvD = choroidal microvasculature dropout; dB = decibel; FU = follow-up; IOP = intraocular pressure; MD = mean deviation; RNFL = retinal nerve fiber layer; VF = visual field; VFI = visual field index.

[a]Comparison between B and C.

[b]Independent sample *t* test.

[c]χ^2 test.

[d]Mann–Whitney *U* test.

[e]Statistically significant ($P < .05$).

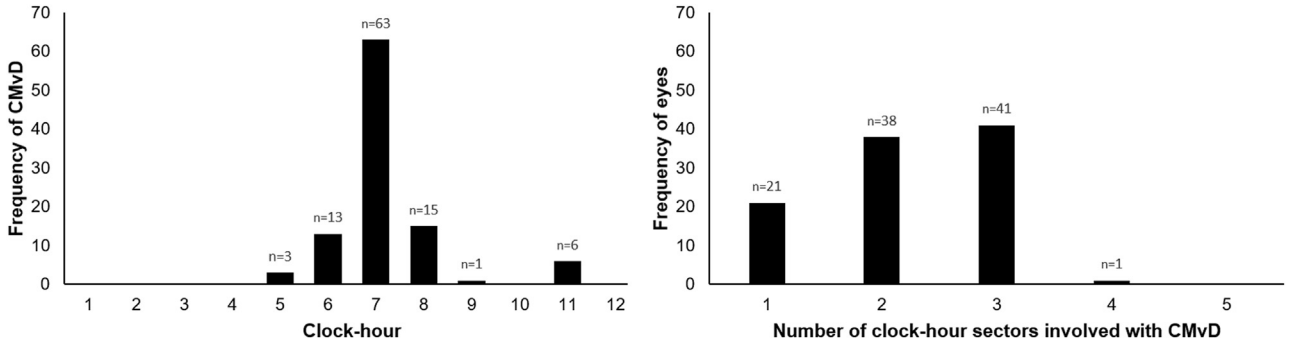


FIGURE 1. Frequency histogram of choroidal microvasculature dropout (CMvD) showing each clock-hour location (left) and number of clock-hour sectors involved with the CMvD (right) at the baseline.

Hazard ratios (HRs) for the association between putative clinical factors and VF progression were determined using Cox proportional hazards models. Univariate Cox proportional hazards analyses were performed separately for all putative variables.

Variables with $P < .10$ by univariate analyses were included in the multivariate Cox proportional hazards models. A backward elimination process was used to develop the final multivariate model, and adjusted HRs with 95% CIs were calculated.

Survival outcomes (time to confirmed VF progression) as a function of the amount of change in CMvD AC and rate of average RNFLT loss were assessed using the Kaplan–Meier survival analyses and compared with log-rank tests. This method was used to compare subjects with the highest and lowest tertiles of the amount of change in the CMvD AC and rate of average RNFLT loss. The time at which VF progression was first observed was regarded as the endpoint in the survival analysis. Patients not showing VF progression were censored. Finally, to evaluate the clinical variables associated with the amount of change in the CMvD AC, univariate and multivariate linear regression analyses were conducted. Multivariate models were built using variables showing $P < .10$ in univariate analyses. Statistical significance was defined as $P < .05$. Statistical analyses were performed using SPSS software (version 21.0; IBM Corp, Chicago, Illinois, USA) and R software (version 3.1.2; R Foundation, Vienna, Austria). Statistical significance was defined as $P < .05$.

RESULTS

A TOTAL OF 125 PATIENTS MET THE INITIAL INCLUSION criteria for this study. Of these cases (ie, 125 eyes), 19 eyes (15.2%) were excluded because of a poor OCTA quality score or motion artifacts in the OCTA images. Five eyes (4.0%) were also excluded because of the misplacement of the ONH margin automatically provided by the software. The demographic characteristics of the remaining study eyes (n = 101) are provided in Table 1. The overall mean follow-up period in this final cohort of 101 study eyes was 2.52 ± 0.49 years, while the baseline VF MD value was −10.49 ± 6.58 dB. There were excellent interobserver agreements for the determination of the presence and location of a CMvD (k = 0.935 and 0.895, respectively). The interobserver intraclass correlation coefficient for the measurements of the CMvD AC was 0.914.

Figure 1 shows the CMvD location on the 12-hour clock map and the number of clock-hour sectors involved with each CMvD at the baseline. The upper and lower 95% Bland-Altman limits of agreement for changes in the CMvD AC were −1.293° and 1.378°, respectively. According to these values, 22 (21.8%) eyes were classified as increased CMvD AC group and 79 (78.2%) eyes were classified as stable CMvD AC group. The mean CMvD AC of increased CMvD AC group was 68.89° at baseline and 73.48° at the final follow-up (difference 4.59° [95% CI 3.71-5.47°]; $P < .001$). The mean AC of the remaining 79 eyes with stable CMvD AC was 66.55° at baseline and 66.73° at the final follow-up (difference 0.18° [95% CI −1.45 to 1.81°]; $P = .29$).

Table 1 summarizes the demographic and ocular characteristics of 2 study groups that were classified according to the status of the CMvD AC increase. Rates of average RNFLT reduction and clock-hour sectoral RNFLT reduction at the CMvD location in the increased CMvD AC group (−1.17 ± 1.33 μm/year and −1.58 ± 1.51 μm/year) were similar to those in the stable CMvD AC group (−0.94 ± 1.50 μm/year and −1.13 ± 1.46 μm/year) without statistical difference ($P = .784$ and $P = .233$, respectively). However, all 22 eyes (100%) in the increased CMvD AC group showed VF progression, while 5 eyes (6.3%) in the stable CMvD AC group showed VF progression during follow-up ($P < .001$). In addition, eyes with CMvD angular enlargement showed significantly higher rates of VF progression as determined using VF MD and VFI ($P < .001$, both) compared with eyes without CMvD

TABLE 2. Demographic Characteristics of Eyes with Open-Angle Glaucoma with and Without Visual Field Progression

Characteristics	Group A, VF Progressor, n = 27	Group B, VF Nonprogressor, n = 74	*P* Value
Age (y), mean ± SD	56.94 ± 10.15	54.03 ± 10.52	.632[a]
Male, n (%)	12 (44.4)	35 (47.3)	.963[c]
CCT (μm), mean ± SD	518.70 ± 22.25	520.72 ± 23.59	.505[a]
Axial length (mm), mean ± SD	25.32 ± 2.28	24.79 ± 2.65	.644[a]
Spherical equivalent (diopters), mean ± SD	−1.28 ± 2.04	−1.18 ± 1.91	.098[a]
Baseline IOP (mm Hg), mean ± SD	16.10 ± 3.69	15.12 ± 3.18	.521[b]
Mean FU IOP (mm Hg), mean ± SD	13.73 ± 1.95	13.62 ± 1.92	.877[b]
Peak FU IOP (mm Hg), mean ± SD	18.49 ± 7.05	17.71 ± 6.68	.185[b]
No. of antiglaucoma drugs, mean ± SD	1.67 ± 0.61	1.47 ± 0.57	.731[a]
Average RNFL thickness at baseline (μm), mean ± SD	65.45 ± 9.86	66.45 ± 9.22	.754[b]
Average RNFL thickness at last FU (μm), mean ± SD	63.25 ± 9.84	65.49 ± 10.54	.511[b]
Sectoral RNFL thickness at CMvD location at baseline (μm), mean ± SD	64.69 ± 9.43	64.83 ± 9.34	.881[b]
Sectoral RNFL thickness at CMvD location at final FU (μm), mean ± SD	62.01 ± 9.09	62.67 ± 10.19	.804[b]
Rate of average RNFL thinning (μm/y), mean ± SD	−1.34 ± 1.59	−0.86 ± 1.64	.431[b]
Rate of sectoral RNFL thinning at CMvD location (μm/y), mean ± SD	−1.62 ± 1.49	−1.09 ± 1.43	.217[b]
VF MD at baseline (dB), mean ± SD	−10.82 ± 6.97	−10.64 ± 6.58	.673[b]
VF MD at last FU (dB), mean ± SD	−13.14 ± 6.46	−10.83 ± 6.04	.004[b,c]
VF VFI at baseline (%), mean ± SD	65.65 ± 13.28	67.15 ± 12.67	.349[b]
VF VFI at last FU (%), mean ± SD	62.84 ± 12.65	66.47 ± 12.13	.012[b,c]
Rate of VF MD progression (dB/y), mean ± SD	−2.10 ± 1.33	−0.35 ± 0.78	<.001[b,c]
Rate of VFI progression (%/y), mean ± SD	−2.28 ± 1.84	−0.64 ± 1.09	<.001[b,c]
Optic disc hemorrhage, n (%)	8 (29.6)	7 (9.5)	.003[c,d]
Hypertension, n (%)	8 (29.6)	19 (25.7)	.293[d]
Diabetes mellitus, n (%)	6 (22.2)	12 (16.2)	.082[d]
Family history of glaucoma, n (%)	6 (22.2)	9 (12.2)	.342[d]
Dyslipidemia, n (%)	5 (18.5)	3 (4.1)	.466[d]
Migraine, n (%)	4 (14.8)	3 (4.1)	.738[d]
CMvD angular circumference at baseline (degrees), mean ± SD	69.25 ± 22.20	66.27 ± 18.57	.459[b]
CMvD angular circumference at last FU (degrees), mean ± SD	72.56 ± 22.16	66.61 ± 18.33	.259[b]
Amount of increase in CMvD angular circumference (degrees), mean ± SD	3.31 ± 0.87	0.34 ± 0.52	<.001[b,c]
FU period (y), mean ± SD	2.52 ± 0.50	2.52 ± 0.48	.921[b]

CCT = central corneal thickness; CMvD = choroidal microvasculature dropout; dB = decibel; FU = follow-up; IOP = intraocular pressure; MD = mean deviation; RNFL = retinal nerve fiber layer; VF = visual field; VFI = visual field index.

[a]Independent sample *t* test.

[b]Mann–Whitney *U* test.

[c]Statistically significant ($P < .05$).

[d]χ^2 test.

angular enlargement, despite the fact that both groups had similar glaucoma severity at baseline ($P > .05$). In consequence, VF MD and VFI values at last follow-up were significantly lower in the increased CMvD AC than in the stable CMvD AC group ($P = .045$ and $P = .032$, respectively). Moreover, eyes with CMvD angular enlargement showed significantly higher incidence of ODH and greater extent of the CMvD AC increase during follow-up compared with eyes without CMvD angular enlargement ($P < .05$, both, Table 1).

TABLE 3. Clinical Factors Associated with Visual Field Progression in Eyes with Open-Angle Glaucoma Using the Cox Proportional Hazards Model

	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age (y), per 1 increase	0.980 (0.954-1.009)	.177		
CCT (μm), per 1 increase	1.003 (0.994-1.013)	.447		
AL (mm), per 1 increase	1.291 (0.909-1.675)	.108		
Baseline IOP (mm Hg), per 1 increase	1.077 (0.902-1.251)	.164		
Mean FU IOP (mm Hg), per 1 increase	1.039 (0.895-1.205)	.619		
Peak FU IOP (mm Hg), per 1 increase	1.031 (0.998-1.063)	.067		
Average RNFL thickness at baseline (μm), per 1 increase	1.003 (0.975-1.030)	.882		
Sectoral RNFL thickness at CMvD location at baseline (μm), per 1 increase	0.998 (0.975-1.023)	.903		
Rate of average RNFL thinning (μm/y), per 1 increase	0.742 (0.519-1.059)	.100		
Rate of sectoral RNFL thinning at CMvD location (μm/year), per 1 increase	0.890 (0.714-1.112)	.307		
VF MD at baseline (dB), per 1 increase	0.995 (0.951-1.039)	.794		
VF VFI at baseline (%), per 1 increase	0.993 (0.978-1.011)	.503		
CMvD angular circumference at baseline (degrees), per 1 increase	1.018 (1.009-1.025)	.021[a]		
Amount of increase in CMvD angular circumference (degrees), per 1 increase	1.454 (1.269-1.664)	<.001[a]	1.515 (1.310-1.747)	<.001[a]
Presence of ODH	1.503 (1.267-1.945)	.033[a]		

AL = axial length; CCT = central corneal thickness; CI = confidence interval; CMvD = choroidal microvasculature dropout; dB = decibel; FU = follow-up; HR = hazard ratio; IOP = intraocular pressure; MD = mean deviation; ODH = optic disc hemorrhage; RNFL = retinal nerve fiber layer; VF = visual field; VFI = visual field index.

[a]Statistically significant ($P < .05$).

Table 2 lists the baseline characteristics of 2 subject groups that were stratified according to their VF progression status. VF MD and VFI values at last follow-up were significantly lower in the VF progressed than in the VF stable group (both $P < .05$). The rates of VF progression as determined using VF MD and VFI were also significantly higher in the VF progressed than in the VF stable group (both $P < .05$). Furthermore, the incidence of ODH and extent of the CMvD angular enlargement during follow-up were also significantly greater in the VF progressed cases than in the VF stable subjects (both $P < .05$).

Table 3 presents the results of univariate and multivariate Cox regression analyses of putative clinical factors for VF progression during follow-up. The factors found to be significantly associated with VF progression by univariate analyses included the CMvD AC at baseline (HR = 1.018 [95% CI 1.009-1.025]; $P = .021$), amount of CMvD angular enlargement during follow-up (HR = 1.454 [95% CI 1.269-1.664]; $P < .001$), and the presence of ODH (HR = 1.503 [95% CI 1.267-1.946]; $P = .033$). In multivariate Cox regression analyses incorporating all variables that showed $P < .01$ in the univariate analyses, the amount of CMvD angular enlargement (HR = 1.515 [95% CI 1.310-1.747]; $P < .001$) was found to be a consistent risk factor for subsequent VF progression.

Table 4 presents the clinical factors associated with the amount of CMvD angular enlargement during follow-up based on linear regression analyses. By univariate analysis, a faster rate of VF MD loss (dB/year) ($\beta = -0.198$ [95% CI −0.328 to −0.066]; $P = .006$), a faster rate of VFI loss (%/year) ($\beta = -0.131$ [95% CI −0.266 to −0.001]; $P = .041$), and a larger CMvD AC at baseline ($\beta = 0.044$ [95% CI 0.000-0.086]; $P = .048$) were associated with a greater amount of CMvD angular enlargement during follow-up. Multivariate analyses were separately performed with 2 models to avoid multicollinearity between 2 associated VF parameters (ie, VF MD and VFI). In these 2 sets of multivariate analyses, the amount of CMvD angular enlargement during follow-up was significantly associated with the rate of VF MD change ($\beta = -0.194$ [95% CI −0.353 to −0.037]; $P = .011$), rate of VFI change ($\beta = -0.161$ [95% CI −0.312 to −0.012]; $P = .029$), and CMvD AC at baseline (model 1: $\beta = 0.146$ [95% CI 0.012-0.282]; $P = .034$, model 2: $\beta = 0.157$ [95% CI 0.019-0.293]; $P = .030$).

TABLE 4. Linear Regression Analyses of Clinical Factors Associated with the Amount of Choroidal Microvasculature Dropout Angular Circumference Increase During Follow-Up in Eyes with Open-Angle Glaucoma

	Univariate Analysis		Multivariate Analysis			
			Model 1		Model 2	
	β Coefficient (95% CI)	*P* Value	β Coefficient (95% CI)	*P* Value	β Coefficient (95% CI)	*P* Value
Age (y)	−0.011 (−0.030 to 0.007)	.232				
CCT (μm)	0.006 (−0.003 to 0.014)	.184				
AL (mm)	0.024 (−0.054 to 0.100)	.589				
Baseline IOP (mm Hg)	0.020 (−0.031 to 0.069)	.461				
Mean FU IOP (mm Hg)	0.025 (−0.106 to 0.158)	.690				
Peak FU IOP (mm Hg)	0.002 (−0.033 to 0.035)	.973				
Average RNFL thickness at baseline (μm)	−0.018 (−0.039 to 0.005)	.111				
Average RNFL thickness at last FU (μm)	−0.029 (−0.059 to 0.005)	.160				
Rate of average RNFL thinning (μm/y)	−0.020 (−0.280 to 0.242)	.890				
Sectoral RNFL thickness at CMvD location at baseline (μm)	−0.011 (−0.029 to 0.007)	.232				
Sectoral RNFL thickness at CMvD location at final FU (μm)	−0.017 (−0.041 to 0.002)	.065				
Rate of sectoral RNFL thinning at CMvD location (μm/y)	−0.025 (−0.334 to 0.324)	.661				
VF MD at baseline (dB)	−0.004 (−0.030 to 0.040)	.791				
VF MD at last FU (dB)	−0.017 (−0.050 to 0.018)	.331				
Rate of VF MD progression (dB/y)	−0.198 (−0.328 to −0.066)	.006	−0.194 (−0.353 to −0.037)	.011[a]		
VF VFI at baseline (%)	−0.005 (−0.017 to 0.009)	.525				
VF VFI at last FU (%)	−0.006 (−0.018 to 0.007)	.384				
Rate of VFI progression (%/y)	−0.131 (−0.266 to −0.001)	.041			−0.161 (−0.312 to −0.012)	.029[a]
CMvD angular circumference at baseline (degrees)	0.044 (0.000-0.086)	.048	0.146 (0.012-0.282)	.034[a]	0.157 (0.019-0.293)	.030[a]
FU (y)	0.006 (−0.008 to 0.022)	.363				

AL = axial length; CCT = central corneal thickness; CI = confidence interval; CMvD = choroidal microvascular dropout; dB = decibel; FU = follow-up; IOP = intraocular pressure; MD = mean deviation; ODH = optic disc hemorrhage; RNFL = retinal nerve fiber layer; VF = visual field; VFI = visual field index.

Model 1: rate of VF progression (dB/y), CMvD angular circumference at baseline (degrees).

Model 2: rate of VF progression (%/y), CMvD angular circumference at baseline (degrees).

[a]Statistically significant ($P < .05$).

Figure 2 shows Kaplan–Meier survival curves for the 2 putative clinical factors for VF progression. The likelihood of VF progression was significantly greater for eyes in the highest tertile for the amount of CMvD angular enlargement during follow-up compared with those in the lowest tertile for this variable (log-rank test; $P < .001$).

However, there was no statistically significant difference in terms of the likelihood of VF progression between the highest and lowest tertiles for the average RNFL thinning rate during follow-up (log-rank test; $P = .106$).

Figure 3 shows the associations between the rates of VF progression, as determined by dB per year, amount of CMvD angular enlargement, and the rate of average RNFL thinning during follow-up. These scatter plots showed that the rate of VF progression was significantly associated with the amount of CMvD angular enlargement ($P < .001$) during follow-up, but not with the rate of average RNFL thinning ($P = .338$).

Representative cases from our current study cohort are shown in Figures 4 and 5. A 70-year-old woman with

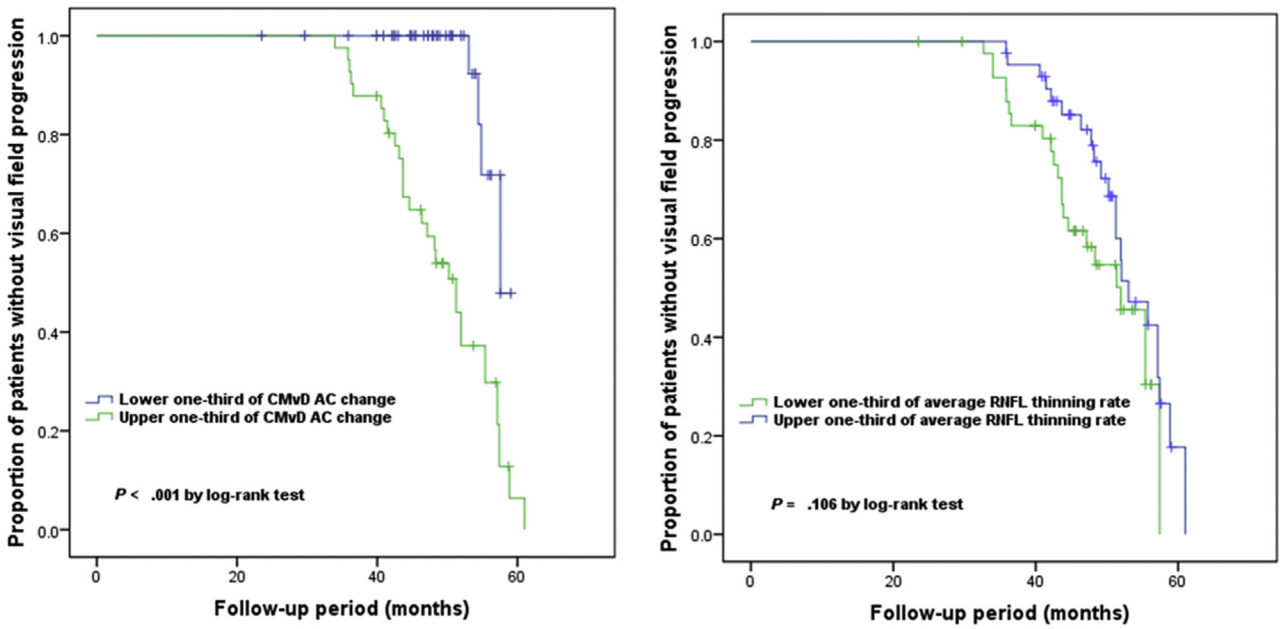


FIGURE 2. Kaplan–Meier survival curves of the effects of 2 putative clinical factors (the choroidal microvasculature dropout [CMvD] angular circumference [AC] change and average retinal nerve fiber layer [RNFL] thinning rate) on visual field (VF) progression in eyes with open-angle glaucoma. Survival curves of the upper and lower tertiles of each group were compared using log-rank tests. (Left) Differences in the probability of VF progression were statistically significant between eyes in the upper third of CMvD AC increases and those in the lower third ($P < .001$, log-rank test). (Right) There were no statistically significant differences, however, between the cases in the highest and lowest tertiles for the average RNFL thinning rate ($P = .106$, log-rank test).

OAG and inferotemporal CMvD in her left eye had a VF defect of MD −3.81 dB and VFI 95% at baseline. While she showed persistent inferior RNFL defects without significant RNFLT loss according to spectral-domain OCT GPA analysis during follow-up, OCTA images revealed a CMvD angular enlargement in the amount of 3.91° from November 2016 to February 2019, which was consistent with VF progression in the superior hemifield, as confirmed by HFA GPA analysis (Figure 4). In contrast, a 68-year-old man with OAG and inferotemporal CMvD in his right eye had a VF defect of MD −13.77 dB and VFI 53% at baseline. During follow-up, he showed persistent inferior RNFL defects without significant RNFLT loss based on spectral-domain OCT GPA analysis. His OCTA images also showed a minimal change of 0.49° in the amount of CMvD AC from August 2017 to August 2019, during which time there was no VF progression (Figure 5).

DISCUSSION

THE CLINICAL IMPLICATIONS OF CMVD ANGULAR ENLARGEMENT during follow-up in OAG eyes has remained unclear. Our present study findings, however, demonstrate that a larger CMvD angular enlargement is significantly associated with subsequent VF progression as well as a higher rate of VF loss during follow-up. We have recently reported that the extent of the CMvD AC was positively associated with the severity of a parafoveal VF defect based on the findings of our cross-sectional study,[5] and we speculated that the size of the impaired choroidal perfusion, as represented by the CMvD, might increase over time with disease progression. Kim and associates[24] found in their previous study that the longitudinal enlargement of the CMvD area (mm^2) was associated with progressive RNFL thinning in eyes with primary OAG during a mean follow-up of 2.5 years. While our current study results are in part consistent with those of Kim and associates,[24] our study differs in that we measured the CMvD size based on the AC (in degrees). Moreover, because eyes with CMvD typically present with advanced VF damage,[1,3,4] our study cohort consisted of OAG eyes with more advanced glaucoma severity at baseline (VF MD = −10.62 dB) compared with those examined by Kim and associates[23] (MD = −6 dB).

Consequently, VF progression was assessed as our main endpoint in association with a CMvD angular enlargement, because it is difficult to monitor disease progression using structural parameters such as RNFLT because of the floor effect in patients with advanced glaucoma.[10-12] On the basis of our work, it would be of benefit for clinicians to obtain baseline OCTA images of parapapillary choroidal layer to monitor the appearance of CMvD or CMvD angular enlargement in association with subsequent VF progression.

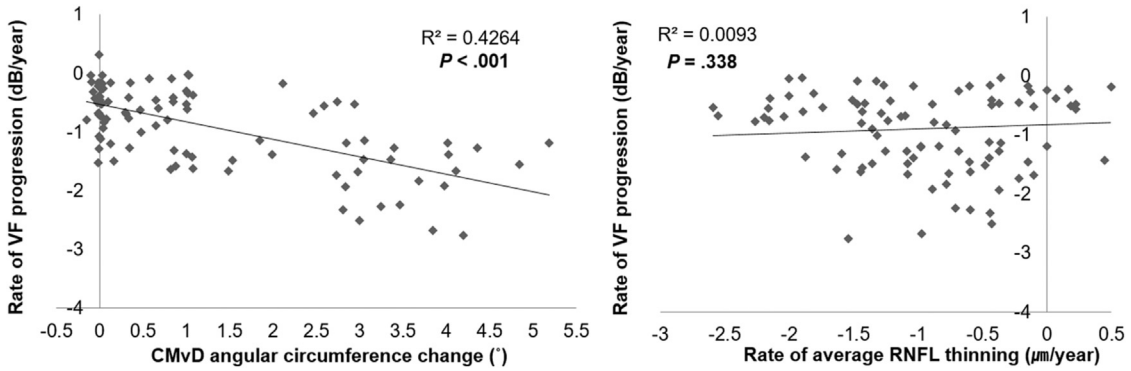


FIGURE 3. Scatter plots showing the association between the rate of visual field progression and the extent of the choroidal microvasculature dropout angular circumference change (left), and the rate of average retinal nerve fiber layer thinning (right).

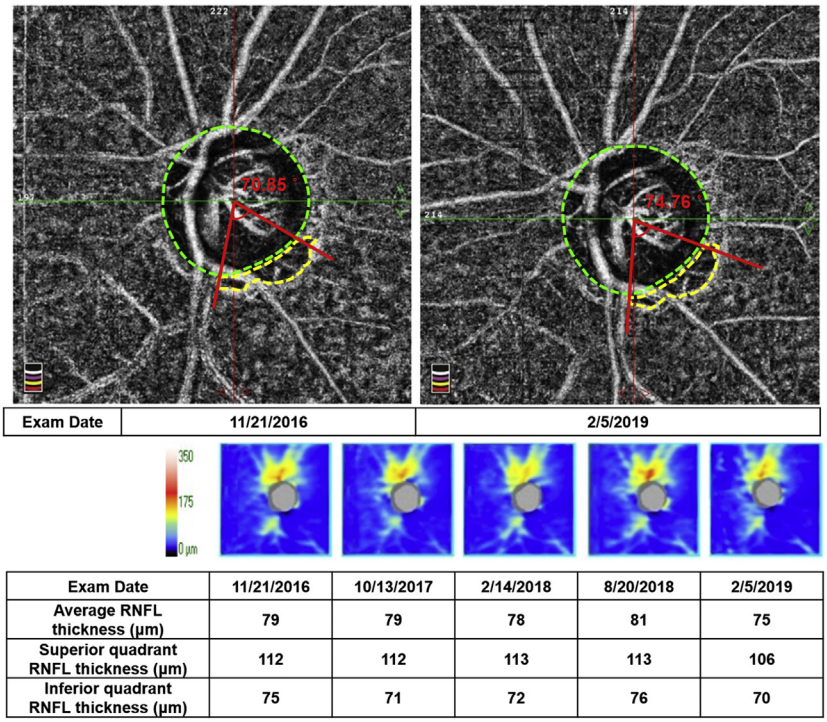
Although the pathogenesis of CMvD remains unclear, its detection during follow-up is associated with progressive RNFL thinning or VF loss in patients with OAG.[7-9] Because CMvD represents a localized perfusion defect of the choriocapillaries and choroidal microvasculature in the β-PPA region,[1,2] its presence may indicate a compromised or lack of perfusion to deep layer structures of the ONH, such as the prelaminar or lamina tissue. Given that vascular insufficiency to the ONH may play an important role in the prognosis of OAG,[25-30] CMvD may be closely associated with future glaucoma progression. In our current study series, because CMvD angular enlargement was possibly suggestive of a worsening of compromised perfusion to the ONH, it can be closely linked to the progression of existing VF damage. Indeed, the eyes in our current cohort with CMvD angular enlargement exhibited significantly higher rates of VF progression as determined using VF MD or VFI compared with eyes without CMvD angular enlargement during follow-up (Table 1).

Because glaucoma is a progressive structural and functional disease, assessing the VF progression or the rates of RNFLT reduction is undoubtedly important in the management of patients. Analyses of the longitudinal CMvD angular enlargement in the current study showed a significantly greater extent of CMvD angular enlargement in the VF progressor than in the VF nonprogressor group (3.31 vs 0.34°, $P < .001$), indicating the potential role of CMvD AC in monitoring VF progression among patients with OAG with CMvD. By contrast, rates of average RNFLT reduction and clock-hour sectoral RNFLT reduction at the CMvD location did not differ significantly in these 2 groups during follow-up (average RNFL thinning −1.34 vs −0.86 μm/year, $P = .431$; Table 2).

Our observation of a greater CMvD angular enlargement in the eyes showing VF progression has several possible explanations. First, the increased CMvD may be the result of a secondary change associated with progressive VF loss. A diminished metabolic need associated with progressive retinal ganglion cell damage and associated VF loss is accompanied by reduced perfusion in the deep layer ONH structures, resulting in the angular enlargement of the CMvD. Second, given that a CMvD may be associated with risk factors closely linked to vascular insufficiency at the ONH, such as a low diastolic blood pressure,[1,19] glaucoma pathogenesis in at least some patients with OAG with CMvD may involve a vascular mechanism. Consequently, eyes with signs of an increased hypoperfusion to the ONH, such as an angular enlargement of the CMvD, may show a higher prevalence of VF progression compared with those without a CMvD angular enlargement. Prospective longitudinal studies are needed in the future to clarify the temporal relationship between the CMvD AC increase and VF progression, which cannot be answered with the current study design.

When we considered all of the independent clinical factors together using Cox proportional hazards models, we found that a larger increase in the CMvD AC was the most consistent prognostic factor for VF progression in both univariate and multivariate analyses ($P < .05$, Table 3). The associations we found between the CMvD AC at baseline and ODH and VF progression were significant by univariate analyses but not in the multivariate analyses. Moreover, Kaplan–Meier survival analyses revealed that OAG eyes in the highest tertile for a CMvD angular enlargement were at greater risk of progressive VF loss than those in the lowest tertile (log-rank test, $P < .001$; Figure 2).

Our findings are in line with those of a recent study by Bak and associates,[31] who showed that the increment of angular extent in the β-PPA region was associated with glaucomatous damage after following 153 primary OAG and 105 normal eyes for ≥10 years. Therefore, our present findings may demonstrate the nature of the relationship between the longitudinal change in CMvD AC during follow-up and progressive VF loss, as well as provide important insights into the feasibility of using a longitudinal change in the CMvD AC as a potential marker of VF



Exam Date	11/21/2016	10/13/2017	2/14/2018	8/20/2018	2/5/2019
Average RNFL thickness (µm)	79	79	78	81	75
Superior quadrant RNFL thickness (µm)	112	112	113	113	106
Inferior quadrant RNFL thickness (µm)	75	71	72	76	70

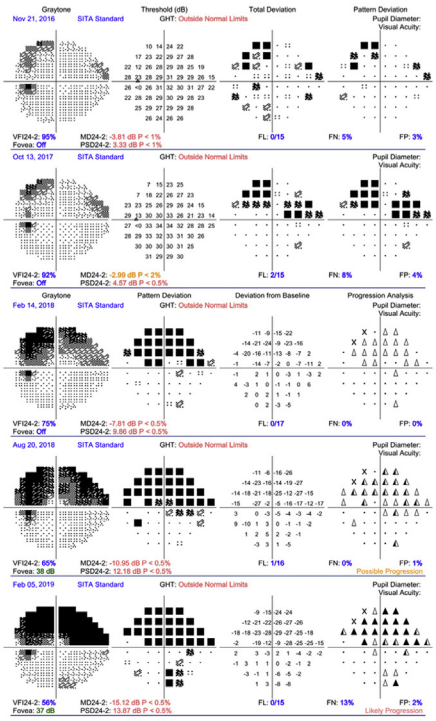


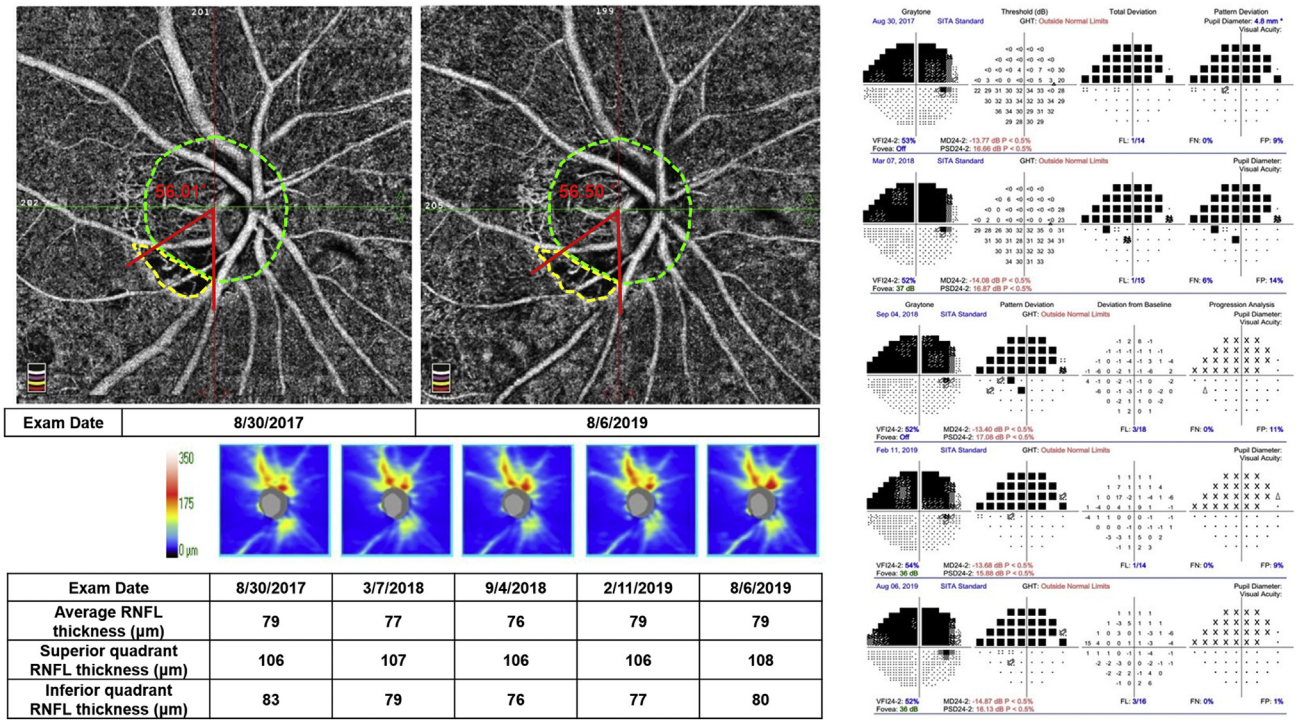
FIGURE 4. Representative optical coherence tomography angiography en face images of the choroidal layer in a left eye showing increased choroidal microvasculature dropout (CMvD) angular circumference (AC) during follow-up (top left), and corresponding stable retinal nerve fiber layer thickness images of spectral-domain optical coherence tomography (bottom left), and progressive visual field loss (right). The ellipse demarcated by the green dotted line indicates the optic nerve head (ONH) border based on the Bruch membrane opening margin. The area within the yellow dotted line is the area of the CMvD, whilst the angles denoted by the two red lines from the center of ONH indicate the ACs of the CMvD. The AC of the CMvD at baseline and at the final visit was 70.85 and 74.76°, respectively.

progression in OAG eyes presenting with CMvD and VF defects at baseline.

It is noteworthy from our present study findings that a CMvD AC at baseline was not significantly associated with VF progression in the multivariate Cox regression model, despite its significance by univariate analyses (Table 3). Previous studies have found that CMvD detected during follow-up was a significant predictor of progressive RNFL thinning or VF loss in patients with OAG,[7-9] suggesting that CMvD may be an important indicator of a poor prognosis. However, this discrepancy between previous studies can be explained by differences in study design and sample populations used. Our current series consisted of OAG eyes with CMvD at baseline that were analyzed for an association with VF progression during follow-up. Our present findings are supported by those of a recent study by Kim and associate,[24] who reported that the CMvD area (mm^2) at baseline and at the final follow-up was not significantly associated by linear regression analysis with the global RNFL thinning rate during follow-up.

Among the putative clinical factors considered in our current investigation, RNFL loss or thinning has been associated with the development and progression of glaucomatous VF defects in previous studies.[32,33] Nonetheless, the relationship between RNFL thinning and VF progression in glaucoma may be affected by the baseline glaucoma severity of OAG eyes in a given study population. The measurement floor of RNFL thickness has been estimated at a VF loss of −10 to −14 dB, beyond which additional RNFL thinning is unlikely to occur despite VF progression.[12] In our current study cohort, the baseline VF MD of the 101 OAG eyes was −10.49 dB. As a result, the rates of average RNFL thinning and CMvD-located clock-hour sector RNFL thinning had no significant associations with VF progression (Table 2). This was further confirmed by our Kaplan–Meier analysis showing that while OAG eyes in the highest tertile of average RNFL thinning rate appeared to be at greater risk of progressive VF loss than those in the lowest tertile for this variable, this difference was not statistically significant (log-rank test, $P = .106$; Figure 2).

Multivariate linear regression revealed that a greater increase in CMvD AC had a significant correlation with a faster rate of VF progression, as assessed by the rates of change in the VF MD and VFI (Table 4, Figure 3; $P <$



Exam Date	8/30/2017	3/7/2018	9/4/2018	2/11/2019	8/6/2019
Average RNFL thickness (µm)	79	77	76	79	79
Superior quadrant RNFL thickness (µm)	106	107	106	106	108
Inferior quadrant RNFL thickness (µm)	83	79	76	77	80

FIGURE 5. Representative optical coherence tomography angiography en face images of choroidal layer in a right eye with a stable choroidal microvasculature dropout (CMvD) angular circumference (AC) during follow-up (top left), and corresponding stable retinal nerve fiber layer thickness images based on spectral-domain optical coherence tomography (bottom left), and stable visual field test results (right). The ellipse demarcated by the green dotted line indicates the optic nerve head (ONH) border based on the Bruch's membrane opening margin. The area within the yellow dotted line is the area of the CMvD, whilst the angles denoted by the two red lines from the center of the ONH indicate the ACs of the CMvD. The AC of the CMvD at baseline and at the final visit was 56.01 and 56.50°, respectively.

.05 for both). Our present findings suggest that although the causal relationship between the longitudinal change in CMvD AC and glaucomatous VF progression remains unknown based on our study design, impaired parapapillary choroidal perfusion in the β-PPA region in the form of CMvD may increase with advancing glaucomatous VF damage over time, and that the rate of VF progression is significantly positively correlated with the increase in the CMvD AC. Of interest in this regard also, the amount of CMvD angular enlargement during follow-up was found in our present analyses to be significantly influenced by the extent of the baseline CMvD AC (Table 4). A higher CMvD AC at baseline may thus indicate more compromised perfusion in the ONH. This may further aggravate ischemic damage to the ONH by reducing the axonal transport of neurotrophic factors by mitochondria due to hypoxia and by releasing toxic substances that may have negative effects on axonal function.[34] This "vicious cycle" may result in the apoptosis of remaining RGCs and contribute to an increase in CMvD AC during follow-up. In line with the poor association between the rate of RNFLT loss and subsequent VF progression noted in Table 3, we found also that the rate of RNFLT loss had no correlation with rate of VF progression assessed by VF MD change (Figure 3, $P > .05$). Again, the lack of a relationship between the RNFL thinning rate (µm/year) and rate of VF progression (dB/year) observed in our study can be explained by the glaucoma severity, ie, advanced disease, of the OAG eyes (MD = −10.49 dB) enrolled in our cohort.

IOP is a well-known risk factor for glaucomatous progression.[35-37] Higher IOP values during follow-up increased the risk of VF progression when the treatment was compared with observation alone among OAG eyes in the Early Manifest Glaucoma Trial.[35] In the current study, none of the IOP-related parameters during follow-up, including the mean and peak, were related to VF progression. One explanation for our finding is that both groups maintained relatively well-controlled IOP level during follow-up with antiglaucoma treatment (mean IOP 13.73 mm Hg for the VF progressed group vs 13.62 mm Hg for the VF stable group). Therefore, our findings should not be regarded as discounting the importance of IOP lowering in patients with OAG.

The CMvD size was estimated quantitatively in our present study by measuring the AC on a 2-dimensional plane.

Measuring the area of the CMvD, as described by Kim and associates,[24] is a viable alternative method of quantitatively determining the CMvD size. There are multiple advantages of measuring the AC to estimate the CMvD size, however.

Subjectivity can be reduced using the AC as the area measurement requires drawing the entire CMvD border manually and the possibility of human error. In addition, the AC (in degrees) is less affected by the ocular magnification effect from different ALs of OAG eyes than the area (mm^2). Since the vascular networks in the parapapillary choroidal region are positioned in a radial pathway and enter the ONH in a centripetal direction,[38] measuring the AC by drawing 2 lines connecting the ONH center to the circumferential margins of the CMvD at the ONH margin may better reflect the anatomy of perfusion dropout in the parapapillary choroid. Finally, the pattern of the RNFL orientation at the optic disc would render the existing CMvD to undergo angular enlargement with progressive VF loss. In the future, a computer algorithm with OCTA device that automatically aligns the baseline choroidal layer scan images and compares the size of follow-up CMvDs to that of baseline CMvD images are needed for easier clinical application of our findings.

Our current study had several limitations. First, we examined OAG eyes with CMvD that had been identified at a referral tertiary care–based practice, in a retrospective manner rather than through population-based screening. Thus, they were subject to selection bias and may represent a subgroup of patients with OAG with CMvD in Korea that do not have the same characteristics as similar patients in the general population. Our findings may therefore not be generalizable to other populations of different ethnicities. In particular, these results may not be applicable to OAG eyes without CMvD. Second, CMvD was identified and measured from en face OCTA images of the choroidal layer, which is itself subject to several limitations. For example, large overlying retinal vessels or ODH may project onto en face choroidal layer images, inducing projection artifacts and rendering it difficult to detect or define CMvD boundaries. These projection artifacts of the superficial retinal vessels, or a shadow effect from ODH, may lead to false negative or false positive results in the evaluation of the CMvD and AC measurements in the choroidal layer images. However, CMvD in our present analyses was defined and measured by 3 examiners using a method that has been validated in previous studies.[4,5,19] We attempted to minimize any subjectivity effects by using 2 independent examiners and a third adjudicator to determine the CMvD presence and CMvD AC, and found excellent interobserver agreements ($k = 0.935$ for detection, intraclass correlation coefficient = 0.914 for AC measurement). Furthermore, the assessment of change in the CMvD AC in the same eyes could have minimized the effect of projection artifacts during the measurement of the CMvD AC. Third, we did not have a control group without CMvD and glaucomatous VF defects at baseline for comparison. Since CMvD can occur in glaucoma suspects or preperimetic glaucoma eyes that initially do not show this defect, the manner in which the occurrence of CMvD is related to disease progression in these eyes would be of great interest and help us to understand its pathogenic role in very early-stage OAG eyes or suspected OAG cases. Since OCTA is a relatively new technology, our present study was limited by a short follow-up duration (mean 2.52 years), which could have affected the change in CMvD AC and the detection rate of VF progression during follow-up. Our observation of a relatively small degree of CMvD angular enlargement in the VF progressor group compared with that in the VF stable group (3.31 vs 0.34°, $P < .05$) might have been influenced by this relatively short follow-up duration. Since the amount of CMvD AC is likely to increase over time, long-term prospective studies with larger numbers of study and control cases are needed to better understand the role of CMvD development or its angular enlargement in the glaucoma progression. Finally, because CMvD is often found in OAG eyes with advanced VF damage, our study subject eyes had moderate to advanced stage glaucoma (MD = −10.49 dB).[16] Thus, it may be difficult to apply our findings to eyes with mild stage glaucoma.

In conclusion, a CMvD angular enlargement is a significant predictor of subsequent VF progression in OAG eyes that initially present with CMvD and VF defects. The extent of this CMvD angular enlargement is significantly positively associated with the rate of VF progression, as assessed by the VF MD and VFI. Our findings enhance the current understanding of the role of CMvD in glaucoma pathogenesis and provide an additional strategy for monitoring VF progression in OAG eyes with CMvD using OCTA technology.

ALL AUTHORS HAVE COMPLETED AND SUBMITTED THE ICMJE FORM FOR DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST. Funding/Support: This study received no funding. Financial Disclosures: The authors indicate no financial support or conflicts of interest. All authors attest that they meet the current ICMJE criteria for authorship.

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