Choroidal Microvascular Dropout in Primary Angle Closure Glaucoma

HARSHA L. RAO, SHRUTHI SREENIVASAIAH, MOHAMMED RIYAZUDDIN, SRILAKSHMI DASARI, SHIVANI DIXIT, JAYASREE P. VENUGOPAL, ZIA S. PRADHAN, NARENDRA K. PUTTAIAH, SATHI DEVI, ROBERT N. WEINREB, KAWEH MANSOURI, AND CARROLL A.B. WEBERS

• PURPOSE: **To determine the prevalence and factors associated with the presence of choroidal microvascular dropout (CMvD) in primary angle-closure glaucoma (PACG) eyes compared to primary open-angle glaucoma (POAG) eyes.**

• DESIGN: **Cross-sectional study.**

• METHODS: **Thirty-six POAG eyes (36 patients) and 28 PACG eyes (28 patients) underwent optical coherence tomography angiography (OCTA). Presence of CMvD was evaluated on choroidal OCTA slabs. Visual field (VF) defects in the glaucoma eyes were classified into initial nasal defect (IND), initial parafoveal scotoma (IPFS), and combined nasal and parafoveal defect, and the association between type of VF defect and CMvD was evaluated.**

• RESULTS: **CMvD was detected in 21 POAG (58.3%) and 10 PACG (35.7%) eyes (P = .07). CMvD in POAG eyes was associated with pretreatment intraocular pressure (odds ratio [OR] = 0.91/mm Hg higher intraocular pressure, P = .06), VF mean deviation (MD, OR = 0.75/dB higher MD, P = .007), retinal nerve fiber layer thickness (OR = 0.92/μm increase in thickness, P = .02), and peripapillary vessel density (OR = 0.80/unit increase in density, P = .01). CMvD in PACG eyes was associated only with VF MD (OR = 0.90/dB higher MD, P = .05). When analyzed in the entire cohort of glaucoma patients (64 eyes), CMvD was significantly associated with POAG (OR > 3.5, P < .05) after accounting for glaucoma severity. CMvD was seen in 6 of 7 eyes with IPFS and 1 of 13 with IND in the POAG group (P < .05) and 1 of 2 eyes with IPFS and 0 of 10 with IND in the PACG group (P < .05).**

• CONCLUSIONS: **Prevalence of CMvD was significantly lower in PACG compared to POAG. As in POAG, CMvD in PACG was associated with advanced VF damage and with IPFS on VF.** **(Am J Ophthalmol 2019;199: 184–192.**

PRIMARY OPEN-ANGLE GLAUCOMA (POAG) AND primary angle closure glaucoma (PACG) are the 2 major subtypes of glaucoma. A recent systematic review and meta-analysis estimated that 64.3 million people aged between 40 and 80 years had glaucoma worldwide, of which 44.1 million had POAG and 20.2 million had PACG.[1]

Although increased intraocular pressure (IOP) is the predominant risk factor for glaucoma,[2] reduced ocular perfusion has also been proposed to have a role in the pathogenesis of glaucoma.[3,4] Blood supply to the eye occurs largely through the retinal and the choroidal circulations, each of which has certain unique characteristics.[5,6] Optical coherence tomography angiography (OCTA) is a relatively recent, noninvasive and dye-less technique that enables visualization of the retinal and choroidal vasculature of the eye in vivo. The superficial retinal vessels are branches of the central retinal artery and supply the inner retinal layers (mainly the nerve fiber layer). Multiple studies have used OCTA to demonstrate a reduction in the superficial retinal vessel densities of the peripapillary and macular regions in eyes with POAG[7–13] and PACG.[14,15] In contrast, choroidal vessels of the peripapillary region arise from the short posterior ciliary artery and supply the prelaminar and laminar regions of the optic nerve head (ONH). Therefore, it has been proposed that the choroidal vasculature has a role in the pathogenesis of glaucomatous ONH damage.[16]

Recently, choroidal microvasculature dropout (CMvD), defined as the complete loss of choriocapillaris in localized regions of parapapillary atrophy (PPA), has been observed using OCTA in POAG eyes.[17,18] Studies have also reported a topographic association between the location of CMvD and structural defects (retinal nerve fiber layer, RNFL thinning, and lamina cribrosa defects) as well as functional defects (visual field, VF loss) in POAG eyes.[17,19,20]

To date, there have not been any publications that evaluated the peripapillary choroidal vasculature in PACG eyes. The purpose of the current study was to determine the

AJO.com Supplemental Material available at AJO.com.
Accepted for publication Nov 28, 2018.

From Narayana Nethralaya, Rajajinagar, Bangalore, India (H.L.R., S.S., S.Dixit, J.P.V., Z.S.P., N.K.P., S.Devi); Narayana Nethralaya, Hulimavu, Bangalore, India (H.L.R., M.R., S.Dasari, N.K.P.); Shiley Eye Institute, Hamilton Glaucoma Center and Department of Ophthalmology, University of California, San Diego, La Jolla, California, USA (R.N.W.); Glaucoma Center, Montchoisi Clinic, Swiss Vision Network, Lausanne, Switzerland (K.M.); Department of Ophthalmology, University of Colorado, Denver, Colorado, USA (K.M.); and University Eye Clinic Maastricht, University Medical Center, Maastricht, Netherlands (C.A.B.W.).

Inquiries to Harsha L. Rao, Narayana Nethralaya, 63, Bannerghatta Road, Hulimavu, Bangalore 560076, India; e-mail: harshalaxmanarao@gmail.com

0002-9394/$36.00
https://doi.org/10.1016/j.ajo.2018.11.021

prevalence of CMvD and evaluate the factors associated with its presence in eyes with PACG. Additionally, these findings were compared with the prevalence and factors associated with CMvD in POAG patients. As PACG presents with higher IOP compared to POAG, the glaucomatous damage in PACG is more likely to be attributable to IOP-related factors than non-IOP related factors (such as reduced blood flow). We therefore hypothesized that the prevalence of CMvD would be lower in PACG compared to POAG.

METHODS

THIS WAS A PROSPECTIVE, CROSS-SECTIONAL STUDY conducted at Narayana Nethralaya, a tertiary eye care center in Bengaluru, South India, between July 2017 and February 2018. The methodology adhered to the tenets of the Declaration of Helsinki for research involving human subjects. Written informed consent was obtained from all participants and the study was approved by the Institute's Ethics Committee.

Participants of the study included consecutively enrolled POAG and PACG patients. Both POAG and PACG patients had glaucomatous changes on ONH examination (focal or diffuse neuroretinal rim thinning, localized notching, or retinal nerve fiber layer defects), as documented by glaucoma experts, and correlating visual field (VF) defects. POAG patients had open angles on gonioscopy. PACG patients had occludable anterior chamber angles on gonioscopy (before iridotomy) and presence of goniosynechiae in the angle and had patent peripheral iridotomy prior to the optical coherence tomography (OCT) imaging. The anterior chamber angle was examined with indentation gonioscopy; it was considered occludable if, in primary position, the posterior trabecular meshwork was not seen in 3 or more quadrants.[21] Pretreatment (before medication or iridotomy) IOP was documented for all glaucoma patients, but was not used in the definition of either POAG or PACG. Inclusion criteria for all participants were age ≥18 years, corrected distance visual acuity of 20/40 or better, and refractive error within ±5 diopters (D) sphere and ±3 D cylinder. Exclusion criteria were presence of any media opacities that prevented good-quality OCT scans, or any retinal or neurologic disease, other than glaucoma, that could confound the evaluation. All participants underwent a comprehensive ocular examination, which included a detailed medical history, corrected distance visual acuity measurement, slit-lamp biomicroscopy, Goldmann applanation tonometry, gonioscopy, dilated fundus examination, stereoscopic optic disc photography, visual field (VF) examination, and OCT imaging with RTVue-XR spectral-domain OCT (SDOCT; Optovue Inc, Fremont, California, USA).

VF examination was performed using a Humphrey Field Analyzer II, model 720i (Zeiss Humphrey Systems, Dublin, California, USA), with the Swedish interactive threshold algorithm (SITA) standard 24-2 program. VFs were considered reliable if the fixation losses were less than 20% and the false-positive and false-negative response rates were less than 15%. VF was considered glaucomatous if the pattern standard deviation was abnormal at $P < 5\%$, glaucoma hemifield test was outside normal limits, or the pattern deviation probability plot contained ≥3 points in a cluster depressed to $P < 5\%$ level with 1 or more of these points depressed to $P < 1\%$ level. The type of VF defect was also determined based on a previously described classification.[22] An initial parafoveal scotoma (IPFS) was defined as a glaucomatous VF defect within 12 points of the central 10 degrees of fixation and no VF defect in the nasal periphery (12 points) outside 10 degrees of fixation. An initial nasal defect (IND) was defined as a glaucomatous VF defect in the nasal periphery outside the central 10 degrees of fixation, with no VF defect within the central 10 degrees. A combined nasal defect (ND) and parafoveal scotoma (PFS) was defined as a glaucomatous defect involving both the parafoveal and the nasal regions. Criteria for a VF defect were the presence of 3 or more points with $P < .05$, 1 of which had $P < .01$, among 12 points in each area (IPFS or IND) on the pattern deviation plot.

Stereoscopic optic disc photographs were obtained by trained technicians using a digital fundus camera (Kowa nonmyd WX; Kowa Company, Ltd, Tokyo, Japan). Each optic disc photograph was evaluated independently by 2 glaucoma experts (H.L.R. and N.K.P.) in a masked manner to determine the presence of glaucomatous changes (focal or diffuse neuroretinal rim thinning, localized notching, or RNFL defects) and the presence of disc hemorrhage. The experts were masked to all the clinical data, the visual field data, and the fellow-eye data. Discrepancy in the classification between the 2 experts was resolved by consensus.

OCTA imaging of the ONH was performed using RTVue-XR SDOCT (AngioVue, v2016.2.0.35). The ONH scan covers an area of 4.5 mm × 4.5 mm. One high-density (HD) scan of the ONH was performed by the same technician in all these subjects. Each B-scan in the HD mode consists of 400 A-scans, providing a resolution of 400 × 400 pixels. The manufacturer's 2-level motion correction procedure was used to minimize the artifacts in the scans; the first level was by using an eye tracker for real-time correction of saccades, blinks, and drifting of the eye during scanning, and the second was by using a proprietary software, motion correction technology (MCT).[23] The software compares 2 consecutive B-scans at the same location and, using motion of the blood column as the contrast, delineates blood vessels.[24] In the ONH scan, the peripapillary region is defined as a 0.75-mm-wide elliptical annulus extending from the optic disc boundary. Average peripapillary vessel density was calculated automatically by the OCTA software from the "Radial Peripapillary Capillary (RPC) slab," which extends from the internal limiting membrane (ILM) to the posterior boundary of the nerve fiber layer.

Peripapillary CMvD was evaluated on the en face images of the choroidal slabs segmented automatically by the OCTA software (Figure, Left panel). CMvD was defined as a focal sectoral capillary dropout, the circumferential width of which was more than one half clock hour of the disc circumference, with no visible microvascular network identified on the choroidal en face images (Figure, Right panel).[19] Two independent observers (S.S. and M.R.), masked to the clinical, VF, and RNFL details of the patients, identified CMvD. Disagreements between the observers were resolved by a third adjudicator (H.L.R.).

• **MEASUREMENTS FROM THE CHOROIDAL OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY SLAB:** The following measurements were performed on the choroidal OCTA slab using ImageJ software (version 1.51; National Institutes of Health, Bethesda, Maryland, USA): optic disc area, area of PPA, CMvD area, and angular extent of CMvD. All these measurements were done by 2 examiners (S.S. and M.R.) independently and in a masked manner. The optic disc and the PPA margins were marked by simultaneously viewing the stereoscopic optic disc photographs and the scanning laser ophthalmoscopic (SLO) images that were simultaneously obtained with the OCTA images (Figure, Middle panel). CMvD was delineated by marking its borders and the area measured (Figure, Right panel). To measure the angular extent of the CMvD, the long axis and short axis of the disc were drawn and the point where the axes crossed was determined as the optic disc center. Two lines were then drawn connecting the disc center to the circumferential margins of CMvD and the angle between these 2 lines was defined as the angular extent of CMvD in degrees (Figure, Right panel). In an eye showing more than 1 CMvD, the area and the angular extent of each CMvD was added to determine the total area and total angular extent of CMvD for the eye. Average values of these measurements from the 2 independent examiners were used in analyses. Poor-quality choroidal slab images, defined as those with a signal strength index < 45 or blurred images that hampered the delineation of the disc margins, PPA, or CMvD, were excluded from the analysis.

All subjects also underwent the peripapillary RNFL thickness measurements on RTVue-XR SDOCT using the ONH scan. This scan protocol has been explained in detail previously.[25,26] Poor-quality ONH scans, defined as those with a signal strength index < 35 or scans with motion artifacts and segmentation errors, were excluded from the analysis. All the examinations for a particular subject were performed on the same day.

• **STATISTICAL ANALYSIS:** Descriptive statistics included mean and standard deviation for normally distributed continuous variables and median and interquartile range (IQR) for non-normally distributed variables. Shapiro-Wilk test was used to test the distribution of continuous variables. Student *t* test (if normally distributed) or the Mann-Whitney *U* test (if non-normally distributed) was used to compare the continuous variables between the POAG and the PACG groups. Categorical variables were described using percentages. The χ^2 test was used to compare the frequency of categorical variables between the glaucoma groups. Interexaminer agreement regarding the presence of CMvD and the measurements from the choroidal OCTA slab were assessed using kappa statistics and intraclass correlation coefficients (ICC). Factors associated with the presence of CMvD in POAG and PACG eyes were initially evaluated using univariate logistic regression analysis. Factors associated with CMvD with a P value of $\leq .10$ were evaluated in multivariate logistic regression models. Before introducing into the multivariate analysis, collinearity between independent variables was evaluated using correlation analysis and variables showing a correlation coefficient > 0.5 were analyzed in separate multivariate models. Frequency of different types of VF defects was compared between eyes with and without CMvD. Statistical analyses were performed using Stata version 13.1 (StataCorp, College Station, Texas, USA) statistical software. A P value of $\leq .05$ was considered statistically significant for the final analysis.

RESULTS

THIRTY-NINE POAG PATIENTS (53 EYES) AND 29 PACG patients (42 eyes) underwent OCTA imaging during the study period. Of these, 3 eyes with poor-quality choroidal slab images (1 POAG and 2 PACG eyes) and 2 eyes (with POAG) with unreliable VF results were excluded. If both eyes of any glaucoma patient were eligible for inclusion, 1 eye was selected for final analysis with the intention of matching the severity of VF loss (based on the mean deviation, MD) between the POAG and PACG groups. The final analysis included 36 eyes of 36 POAG patients and 28 eyes of 28 PACG patients. The clinical features, VF parameters, type of VF defect, average peripapillary vessel density, and average RNFL thickness of the included eyes are shown in Table 1. The pretreatment IOP was significantly greater in PACG compared to POAG eyes. Global indices on VF, type of VF defect, average peripapillary vessel density, and RNFL thickness measurements were comparable between the POAG and PACG eyes. Table 1 also shows the parameters evaluated on the choroidal OCTA slabs in these eyes. Interexaminer agreement in detection of the CMvD was excellent (kappa: 0.91). ICC for the measurements of the choroidal OCTA slab were also excellent (0.92 for disc area, 0.85 for PPA area, 0.87 for CMvD area, and 0.91 for the angular extent of CMvD). Optic disc area was significantly larger in

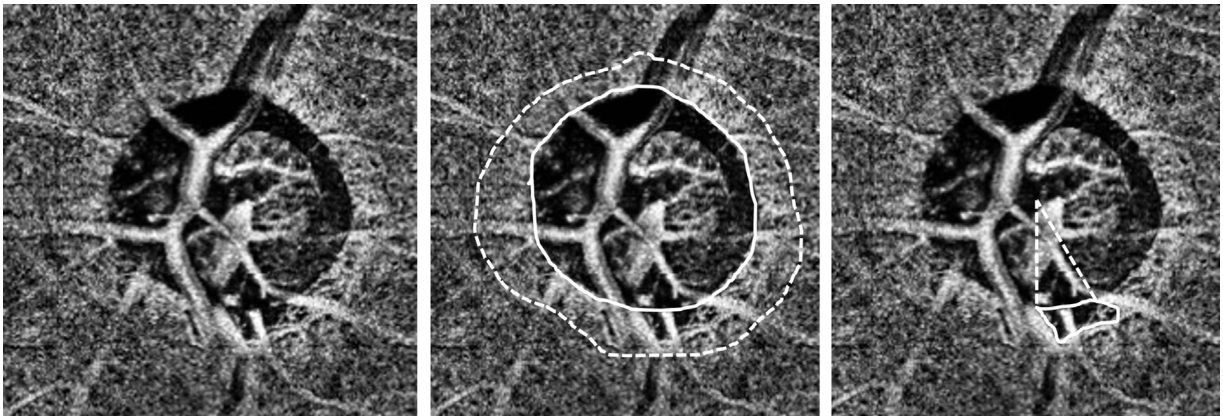

FIGURE. Analysis of the choroidal optical coherence tomography angiography slab (Left panel) of an eye showing choroidal microvascular dropout (CMvD). (Middle panel) Optic disc margin (solid line) and the region of parapapillary atrophy (dashed line) marked on the choroidal slab. (Right panel) CMvD (solid line) and the angular extent of CMvD (dashed lines) marked on the slab.

PACG eyes compared to POAG eyes. Area of PPA was comparable between the glaucoma groups. Prevalence of CMvD was lower in PACG compared to POAG eyes, although this was not statistically significant. In the POAG group, CMvD was detected in 21 eyes (58.3%); of these, 17 eyes showed dropout in the inferior or inferotemporal sectors, 3 eyes showed dropout in the superior or superotemporal sectors, and 1 eye had CMvD at both the superior and inferior poles. In the PACG group, CMvD was detected in 10 eyes (35.7%); of these, 9 eyes showed dropout in the inferior or inferotemporal sectors and 1 eye had CMvD at both the superior and inferior poles. Area of CMvD and its angular extent was similar between the 2 glaucoma groups.

Table 2 shows the factors associated with the presence of CMvD in POAG eyes. On univariate analysis, pretreatment IOP, VF MD, average RNFL thickness, and average peripapillary vessel density were significantly associated with the presence of CMvD. CMvD was more frequently seen in POAG eyes with lower pretreatment IOP and in eyes with more severe glaucomatous damage (lower or more negative MD, RNFL thickness, and vessel density). As MD, RNFL thickness, and peripapillary vessel density were strongly correlated to each other (pairwise correlation coefficients, $r > 0.65$), 3 separate multivariate models were built to evaluate the factors associated with CMvD. In multivariate model 1 (Table 2), which included pretreatment IOP and VF MD as independent variables, CMvD was significantly associated with VF MD (coefficient of determination, $R^2 = 0.29$). In multivariate model 2 (Table 2), which included pretreatment IOP and average RNFL thickness as independent variables, CMvD was significantly associated with both RNFL thickness and pretreatment IOP ($R^2 = 0.28$). In multivariate model 3 (Table 2), which included pretreatment IOP and average peripapillary vessel density as independent variables, CMvD was significantly associated with both peripapillary vessel density and pretreatment IOP ($R^2 = 0.40$).

Table 3 shows the factors associated with the presence of CMvD in PACG eyes. On univariate analysis, VF MD was the only factor significantly associated with the presence of CMvD ($R^2 = 0.11$).

Factors associated with the presence of CMvD in the entire cohort of glaucoma patients ($n = 64$ eyes) were also evaluated. Type of glaucoma and the measures of glaucoma severity were associated with CMvD in univariate analysis. Table 4 shows the results of multivariate logistic regression analysis performed subsequently. The odds of CMvD were statistically significantly higher in POAG compared to PACG after accounting for the glaucoma severity.

Table 5 shows the association between the type of VF defect and CMvD separately in POAG and PACG eyes. CMvD was more frequently seen in eyes with IPFS than IND ($P < .001$), in both POAG and PACG groups. CMvD was also more frequently seen in eyes with combined ND and PFS than IND ($P < .001$). There was no difference in the frequency of CMvD between eyes showing IPFS and combined ND and PFS types ($P > .05$) in both the glaucoma groups.

Although the mean VF MD was similar between the POAG and PACG groups, 1-to-1 matching of POAG and PACG eyes by severity was not performed in the main analysis. Therefore, a separate analysis was run by choosing 1 POAG eye matched to within 1 dB of MD for every PACG eye (26 POAG eyes, mean MD: -9.2 ± 6.3 dB vs 26 PACG eyes, mean MD: -9.0 ± 6.8 dB). This matching was performed by a person masked to all details of the patients (including the CMvD details) except the type of glaucoma and the VF MD values. CMvD was seen in 18 POAG (69.2%) and 8 PACG (30.8%) eyes ($P = .006$). All other results were similar to that seen in

TABLE 1. Clinical Features, Visual Field Parameters, Retinal Nerve Fiber Layer Thickness, Vessel Density, and Choroidal Microvascular Dropout Measurements of Study Participants

	POAG Group (36 Eyes, 36 Subjects)	PACG Group (28 Eyes, 28 Subjects)	*P*
Age (y), mean ± standard deviation	64.4 ± 11.1	62.8 ± 8.5	.53
Sex (male:female)	23:13	19:9	.74
Sphere (D)	0 (0, 1.5)	0 (0, 0.75)	.39
Cylinder (D)	−0.75 (−1.25, −0.5)	−0.5 (−0.75, 0)	.01
Pseudophakia, n (%)	8 (22.2%)	5 (17.9%)	.67
IOP at the scanning visit (mm Hg)	14 (12, 18)	15 (12, 21)	.35
Pretreatment IOP (mm Hg)	21 (15, 25)	26 (24, 30)	<.001
Hypertension (yes:no)	21:15	8:20	.02
Diabetes mellitus, n (yes:no)	11:25	8:20	.94
Disc hemorrhage, n (%)	4 (11.1%)	2 (7.1%)	.59
Mean deviation (dB)	−7.6 (−13.1, −4.3)	−7.8 (−13.7, −4.0)	.97
Pattern standard deviation (dB)	8.4 (3.7, 11.9)	6.9 (3.3, 8.7)	.16
Visual field index (%)	78 (67, 93)	82 (61, 93)	.98
Type of visual field defect, n (%)			
Initial nasal defect	13 (36.1%)	10 (35.7%)	
Initial parafoveal scotoma	7 (19.4%)	2 (7.1%)	.33
Combined nasal and parafoveal defect	16 (44.5%)	16 (57.2%)	
SSI (OCT ONH scan), mean ± standard deviation	55.0 ± 7.0	48.3 ± 8.9	.002
Peripapillary RNFL thickness (μm), mean ± standard deviation	77 ± 13	73 ± 12	.23
SSI (OCTA ONH scan), mean ± standard deviation	52.8 ± 4.4	50.6 ± 4.2	.08
Average peripapillary vd (%), mean ± standard deviation	53.7 ± 7.0	51.4 ± 7.0	.24
Choroidal slab measurements			
Optic disc area (mm^2)	1.91 (1.63, 2.10)	2.28 (1.81, 2.54)	.003
Parapapillary atrophy area (mm^2)	1.34 (1.00, 1.84)	1.31 (1.07, 1.48)	.53
Presence of CMvD, n (%)	21 (58.3%)	10 (35.7%)	.07
CMvD area (mm^2)	0.09 (0.06, 0.15)	0.07 (0.04, 0.11)	.31
Angular extent of CMvD (degrees)	43 (29, 59)	48 (25, 63)	.61

CMvD = choroidal microvascular dropout; D = diopter; IOP = intraocular pressure; OCTA = optical coherence tomography angiography; ONH = optic nerve head; PACG = primary angle closure glaucoma; POAG = primary open-angle glaucoma; RNFL = retinal nerve fiber layer; SSI = signal strength index; vd = vessel density.

All values represent median and interquartile range unless specified.

the main analysis. When analyzed in the entire cohort (52 eyes), the odds of CMvD were significantly higher in POAG than PACG (odds ratio = 6.4, P = .006), after accounting for the severity of glaucoma.

DISCUSSION

PERIPAPILLARY CHOROIDAL CIRCULATION IS OF PARTICular interest in glaucoma as it may be a surrogate marker for the perfusion of the deep ONH structures. Abnormality in the peripapillary choroidal microvasculature, recently noted as CMvD on OCTA, has been shown to be a true perfusion defect using indocyanine green angiography.[27] Recently, Lee and associates have argued that CMvD is likely to precede glaucomatous ONH damage.[22]

Unlike previous studies, which identified CMvD in only POAG eyes, the current study included POAG and PACG eyes and found that the prevalence of CMvD in PACG eyes was lower than in POAG eyes. CMvD was detected in 35.7% of PACG eyes as opposed to 58.3% of POAG eyes. The prevalence of CMvD in POAG eyes found in the current study was similar to that reported in previous studies. In a study by Suh and associates[17] on patients of predominantly European descent, CMvD was detected in 52.1% of POAG eyes, and in another study by Lee and associates[19] on patients of Korean descent, CMvD was observed in 53.9% of POAG eyes. The lower prevalence of CMvD in PACG as compared to POAG possibly implies

TABLE 2. Factors Associated With the Presence of Choroidal Microvascular Dropout in Eyes With Primary Open-Angle Glaucoma

	Univariate Analysis		Multivariate Analysis 1		Multivariate Analysis 2		Multivariate Analysis 3	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Age	1.02 (0.96-1.09)	.45						
Male sex	2.12 (0.55-8.76)	.27						
Spherical refraction	1.29 (0.75-2.21)	.36						
Hypertension	0.89 (0.23-3.42)	.86						
Diabetes mellitus	0.47 (0.11-1.98)	.30						
Pretreatment IOP	0.91 (0.83-1.00)	.06	0.92 (0.82-1.02)	.10	0.86 (0.75-0.99)	.04	0.82 (0.67-1.00)	.05
Disc hemorrhage	0.20 (0.02-2.15)	.18						
Disc area	0.50 (0.07-3.36)	.48						
Area of PPA	2.71 (0.66-11.1)	.17						
VF MD	0.75 (0.61-0.93)	.007	0.76 (0.62-0.94)	.01				
Average RNFLT	0.92 (0.86-0.98)	.02			0.90 (0.82-0.98)	.02		
Peripapillary vd	0.80 (0.68-0.95)	.01					0.73 (0.57-0.93)	.01

CI = confidence interval; IOP = intraocular pressure; MD = mean deviation; OR = odds ratio; PPA = parapapillary atrophy; RNFLT = retinal nerve fiber layer thickness; vd = vessel density; VF = visual field.

TABLE 3. Factors Associated With the Presence of Choroidal Microvascular Dropout in Eyes With Primary Angle Closure Glaucoma

	Univariate Analysis	
	Odds Ratio (95% CI)	*P* Value
Age	0.93 (0.84-1.03)	.20
Male sex	0.58 (0.11-2.95)	.51
Spherical refraction	0.90 (0.54-1.51)	.69
Hypertension	0.50 (0.08-3.13)	.46
Diabetes mellitus	0.20 (0.02-1.93)	.12
Pretreatment IOP	1.01 (0.91-1.12)	.86
Disc hemorrhage[a]	-	
Disc area	2.06 (0.58-7.32)	.26
Area of PPA	0.39 (0.05-2.83)	.35
VF MD	0.90 (0.80-1.00)	.05
Average RNFLT	0.99 (0.93-1.06)	.79
Peripapillary vd	0.94 (0.83-1.06)	.32

CI = confidence interval; IOP = intraocular pressure; MD = mean deviation; PPA = parapapillary atrophy; RNFLT = retinal nerve fiber layer thickness; vd = vessel density; VF = visual field.

[a]Analysis not done as both eyes with disc hemorrhage showed choroidal microvascular dropout.

that the pathogenesis of these 2 glaucoma subtypes is different, with non-IOP-related (vascular) factors playing a less important role in the pathogenesis of PACG.

CMvD, both in POAG and in PACG, was associated with greater severity of glaucomatous damage. Similar findings have been reported in previous studies in POAG eyes.[17,19,20] While a significant association was seen between CMvD and both the structural (RNFL thickness, peripapillary vessel density) and functional (VF MD) measures of glaucoma severity in POAG, CMvD in PACG was associated only with functional measures of severity but not with structural measures. This possibly suggests that CMvD is a marker of glaucoma severity in both POAG and PACG. CMvD was more strongly associated with VF MD ($R^2 = 0.25$) and peripapillary vessel density ($R^2 = 0.25$) in the univariate analysis than with RNFL thickness ($R^2 = 0.15$) in POAG eyes. One of the possible reasons for this weaker association of RNFL thickness with CMvD may be the floor effect seen with RNFL thickness.[28] A previous study has demonstrated that the floor effect with the peripapillary vessel density occurs later than the RNFL thickness measurements in the spectrum of glaucoma severity.[29] Another possible reason could be a direct relationship between the choroidal circulation (which is responsible for CMvD) and retinal circulation (which is responsible for reduced peripapillary vessel density) in POAG eyes.[17] To better understand the associations of CMvD, further studies are required that will evaluate not only the global measures of glaucoma severity, but also sectoral measures.

Another interesting finding in the current study was that CMvD was more common in POAG eyes with lower pretreatment IOP. In a previous study, pretreatment IOP was found to be similar in POAG eyes with and without CMvD.[19] The mean pretreatment IOP in this previous study performed on a Korean population (18.1 mm Hg)[19] was less than that in the current study (21.2 mm Hg). Since the number of POAG patients having pretreatment IOP > 20 mm Hg was small, the previous study may not have had the power to detect an association between pretreatment IOP and CMvD. CMvD in the current study was not associated with pretreatment (preiridotomy) IOP in PACG eyes. Pretreatment IOP is known to be less informative in

TABLE 4. Association Between the Presence of Choroidal Microvascular Dropout and the Type of Glaucoma After Adjusting for Disease Severity

	Multivariate Analysis 1		Multivariate Analysis 2		Multivariate Analysis 3	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Type of glaucoma (reference: PACG)	3.49 (1.07-11.39)	.04	4.28 (1.33-13.82)	.01	4.71 (1.37-16.20)	.01
VF MD	0.85 (0.77-0.94)	.002				
Average RNFLT			0.95 (0.91-0.99)	.04		
Peripapillary vd					0.88 (0.80-0.96)	.005

CI = confidence interval; MD = mean deviation; OR = odds ratio; PACG = primary angle closure glaucoma; RNFLT = retinal nerve fiber layer thickness; vd = vessel density; VF = visual field.

TABLE 5. Association Between the Type of Visual Field Defect and the Presence of Choroidal Microvascular Dropout in Primary Open-Angle and Angle Closure Glaucoma Eyes

	Primary Open Angle Glaucoma		Primary Angle Closure Glaucoma	
Type of VF Defect	CMvD−	CMvD+	CMvD−	CMvD+
IND	12 (92%)	1 (8%)	10 (100%)	0 (0%)
IPFS	1 (14%)	6 (86%)	1 (50%)	1 (50%)
Combined ND and PFS	2 (12%)	14 (88%)	7 (44%)	9 (56%)
	$P < .001$		$P = .01$	

CMvD = choroidal microvascular dropout; IND = initial nasal defect; IPFS = initial parafoveal scotoma; ND = nasal defect; VF = visual field. *P* values represent the overall difference in the type of VF defect between eyes with and without CMvD.

PACG, especially in the Indian population, as PACG is known to have intermittent IOP spikes that are not necessarily detected during office hours.[30] Future studies should validate this association between the pretreatment IOP and CMvD.

The current study also found a positive association between CMvD and IPFS on VF examination in both POAG and PACG eyes. Six of 7 POAG eyes with IPFS showed CMvD. One of 2 PACG eyes with IPFS showed CMvD. In contrast, only 1 of 13 POAG eyes and none of 10 PACG eyes with an IND showed CMvD. A similar association between CMvD and IPFS has been reported in POAG eyes by Lee and associates[22] and Kwon and associates.[31] IPFS is known to develop when the papillomacular bundle gets affected. The inferior region of the papillomacular bundle, which is more commonly affected and leads to a superior PFS, has been referred to as the macular vulnerability zone.[32] CMvD was seen close to this zone (inferior and inferotemporal peripapillary region) in most of the POAG and PACG eyes in the current study, as well as in previous studies,[22,31] and possibly leads to a PFS. A study by Nouri-Mahdavi and associates compared the patterns of VF damage in POAG and PACG eyes and found that the VF damage in PACG eyes was less likely to involve the paracentral points.[33] The number of eyes with IPFS in the current study was less in the PACG group (7%) compared to the POAG group (19%), although this difference was not statistically significant. It is, therefore, possible that the lower prevalence of IPFS in PACG eyes, despite comparable VF global indices, is a reason for lower prevalence of CMvD in PACG eyes. A significant number of eyes in the current study showed a combined ND and PFS. As it is not possible to determine the type of initial VF defect in these eyes, these were categorized separately into combined ND and PFS group. CMvD, in both POAG and PACG eyes, was more frequently associated with combined ND and PFS than an IND. In this context, it is important to know if the CMvD develops before or after an IPFS. The current study, like the previous 2 studies,[22,31] had a cross-sectional design and is therefore unable to answer this question, and future longitudinal studies are required to evaluate the temporal sequence of CMvD and IPFS.

Although the current study found a lower prevalence of CMvD in PACG compared to POAG, the clinical implications of this finding is unknown. Although the importance of CMvD itself, either in the pathogenesis of glaucoma or in its progression, has not been determined yet, Lee and associates have argued that CMvD is likely to precede glaucomatous ONH damage.[22] Longitudinal studies are therefore required to determine the clinical implication of CMvD in glaucoma and the lower prevalence of CMvD in PACG as seen in the current study.

There are a few limitations that should be considered while interpreting the results of the current study. First is the limitation in the OCTA technology for visualizing choroidal vasculature. Projection artifacts,[24] which are signals from the superficial retinal vessels projecting onto the choroidal slab, can affect the detection of CMvD. This may have caused an underdetection of CMvD in the current study. Second, the microstructure of PPA was not studied. Previous studies have reported differences in the characteristics of CMvD in POAG eyes with β- and γ-zones of PPA.[18,34] Future studies should evaluate the microstructure of PPA and also the association between various PPA zones and CMvD in PACG eyes. Third, systemic blood pressure (BP) was not measured in the current study. Previous study by Suh and associates found an association between lower diastolic BP and CMvD in POAG eyes.[17] Future studies should evaluate the association between BP and CMvD in PACG eyes. Lastly, the sample size of the current study was small. Although the sample size was adequate to detect a significant difference in the prevalence of CMvD between the 2 glaucoma groups and the significant associations of a few factors with CMvD in each glaucoma group, it may have been inadequate to detect other differences and associations with significant but smaller effects.

In conclusion, the prevalence of CMvD was significantly lower in PACG compared to POAG eyes. Like in POAG eyes, CMvD in PACG eyes was associated with more advanced glaucomatous VF damage. CMvD was less likely to be seen in PACG eyes with initial nasal defects on VF compared to initial parafoveal defects.

FUNDING: SUPPORTED IN PART BY R01 EY029058 (R.N.W.) FOR THE NATIONAL EYE INSTITUTE AND AN UNRESTRICTED GRANT from Research to Prevent Blindness (New York, New York, USA). Financial Disclosures: Harsha L. Rao: Allergan (Consultant [C]); Robert N. Weinreb: Optovue (Research Support [S]), Meditec-Zeiss (S), Heidelberg Engineering (S), Genentech (S), Allergan (C), Alcon (C), Eyenovia (C), Bausch & Lomb (C), Sensimed (C), Unity (C); Kaweh Mansouri: Santen (C), Sensimed (C), Topcon (S), Alcon (S); Carroll A.B. Webers: Alcon (S), Allergan (C), Pfizer (C), Santen (C). The following authors have no financial disclosures: Shruthi Sreenivasaiah, Mohammed Riyazuddin, Srilakshmi Dasari, Shivani Dixit, Jayasree P. Venugopal, Zia S. Pradhan, Narendra K. Puttaiah, and Sathi Devi. All authors attest that they meet the current ICMJE criteria for authorship.

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