Special Focus, Retina, Original Article

Choriocapillaris flow deficits in polypoidal choroidal vasculopathy using swept source optical coherence tomography angiography

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Purpose: To evaluate the choriocapillaris flow deficits (CCFD) on swept-source optical coherence tomography angiography (SS-OCTA) in eyes with unilateral polypoidal choroidal vasculopathy (PCV), fellow unaffected eyes, and to compare them with age-matched healthy controls. **Methods:** This study was a cross-sectional study which included treatment-naïve eyes with unilateral PCV (group 1), fellow unaffected eyes of patients with PCV (group 2), and normal eyes (group 3). Using the SS-OCTA, the Choriocapillaris (CC) slab was segmented from the structural optical coherence tomography (OCT) and the corresponding flow map was multiplied after signal compensation. The resultant image was evaluated for CCFD in equidistant squares measuring 1 × 1 mm, 1.5 × 1.5 mm, 2 × 2 mm, 2.5 × 2.5 mm, 3 × 3 mm, and 6 × 6 mm centered on the fovea. **Results:** The percentage of flow deficits were significantly increased (one-way ANOVA, $P = 0.003$ and $P = 0.049$) in the eyes with PCV as compared to the fellow eyes, and age-matched healthy controls. In the multiple pairwise comparison using post hoc Bonferroni, CCFD of 1 mm in group 1 and 2 ($P = 0.019$), group 1 and 3 ($P = 0.003$), and CCFD of 1.5 mm in group 1 and 3 ($P = 0.044$) were statistically significant. Correlation analysis showed no significant correlation between CCFD, age, Best corrected visual acuity (BCVA), foveal thickness (FT), and subfoveal choroidal thickness (SFCT) in our study. Linear regression analysis showed that the CCFD was negatively correlated with the distance from the foveal center in group 1 ($\beta = -0.613$, $P = 0.046$). **Conclusion:** Eyes with PCV demonstrated a significant flow impairment in the choriocapillaris layer as compared to the fellow unaffected eyes and age-matched healthy eyes.

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Polypoidal choroidal vasculopathy (PCV) is characterized by serosanguineous maculopathy and polypoidal choroidal vascular lesions.[1,2] It is considered by many as a subtype of type 1 neovascularization and a variant of age-related macular degeneration (AMD).[3–5] Indocyanine green angiography (ICGA) is considered the gold standard to detect the characteristic lesions of PCV.[1,2] However, the need for dye injection, the absence of depth-resolved analysis, and obscuration of the underlying structures because of leakage are some of the disadvantages of ICGA that don't allow its regular use in a busy clinical practice.

Swept-source optical coherence tomography angiography (SS-OCTA), with greater penetration and resolution, allows the visualization of the choriocapillaris (CC) layer and analysis.[6] The relatively low flow signals in the granular structure of CC layer, seen as dark regions in the CC slab, are called flow deficits.[7] The CC blood flow is known to decrease with age and this decrease is further enhanced in disease conditions like AMD.[5,8] Many investigators have reported increased choriocapillaris flow deficits (CCFD) in AMD,[9] diabetic retinopathy,[10] central serous chorioretinopathy,[11] and geographic atrophy.[12] Furthermore, alterations in CC flow have also been implicated in the onset of the pachychoroid spectrum of diseases, especially pachychoroid pigment epitheliopathy.[13] Also, recent studies have analysed the CCFD in the fellow eyes of patients with unilateral PCV and AMD.[14] This suggests that an increase in CCFD may be a potential biomarker of disease onset and activity in pachychoroid diseases.[14] Therefore, it becomes imperative to understand the changes taking place in the CC layer in diseases like PCV. Recognition of these changes may allow early diagnosis and a more effective therapy. Hence, this study aimed to understand the CCFD changes using SS-OCTA in eyes with PCV and fellow unaffected eyes in the Indian population.

Methods

This cross-sectional study was conducted at a tertiary eye care center in South India and was approved by the Institutional Review Board. It was conducted in accordance with the tenets

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of the Declaration of Helsinki. Patients with treatment-naïve eyes with PCV, unaffected fellow eyes with unilateral PCV, and normal eyes of healthy individuals between January 2019 and March 2021 were enrolled in the study. Either of the two eyes of normal healthy individuals was selected as control for the study.

Selection criteria

Patients above 50 years of age with clinical signs of PCV, i.e., presence of orange-red, sub-retinal nodules with a serosanguineous detachment of the retina, and subretinal/sub macular hemorrhage, subretinal fluid, subretinal exudates, edema involving the macula and/or peripapillary retina were included.[2] The diagnosis was confirmed based on OCT criteria[1] and ICGA wherever available. The OCT criteria were sharp-peaked or multilobular PED, sub-RPE ring-like lesion, double layer sign, thick choroid with dilated Haller's vessels and retinal pigment epithelium (RPE) elevation[1] whereas the ICGA criteria were the presence of early sub-retinal focal hyperfluorescence on ICGA (within the first 6 mins), and at least one of the following criteria: nodular appearance of the polyps on stereoscopic examination, hypofluorescent halo around the nodules, presence of a branched vascular network (BVN), pulsatile filling of the polyps and massive submacular hemorrhage.[1] The fellow unaffected eyes of patients with unilateral PCV were categorized as group 2 for comparison. Subjects above 50 years of age with no ocular or systemic diseases (group 3) were included as healthy control group.

All eyes with refractive error greater than of ± 6 diopters (D) spherical equivalent, glaucoma, intraocular inflammation, any previous history of intraocular surgery or intravitreal anti–vascular endothelial growth factor (anti -VEGF), laser photocoagulation, presence of any media opacities, and those patients who did not consent for the study were excluded. Also, eyes with PCV with large PED (pigment epithelial detachment) or subretinal hemorrhage that did not allow good imaging of the CC were excluded; eyes with scans of signal intensity less than 7 were also excluded. Systemic diseases that could affect the choroid like hypertension, diabetes mellitus, and pregnancy were also excluded.

All patients underwent a comprehensive eye examination including Snellen BCVA (best-corrected visual acuity), dilated fundus examination using a binocular indirect ophthalmoscope, slit-lamp biomicroscopy, and SS-OCTA.

Image acquisition

All the subjects underwent SS-OCTA imaging using PLEX Elite 9000 device (Carl Zeiss Meditec, Dublin, California, USA). It uses a swept laser source with a central wavelength of 1050 nm (1000–1100 nm full bandwidth); operates at 100,000 A-scans per second with an axial resolution of 2 microns. A 6 × 6 mm scan was taken, centered on the fovea, with each A-scan having 500 × 500 A-scans. A validated, semiautomated retinal layer segmentation algorithm was used to identify the CC layer of 10-µm thickness, starting from 31-µm below the RPE reference.[15] Manual correction of segmentation slabs was done as necessary.

For quantification of CCFD, both *en face* structural and flow images were exported and image analysis was done using the technique described by Algorie *et al*.[16]

Image pre-processing

The CC slab was segmented from the structural OCT scan, and the corresponding flow map was identified from the OCT angiogram. In eyes with signs of PCV, the CC slab was adjusted manually for segmentation to accurately follow the RPE elevations overlying lesions of the BVN, polypoidal lesions (PL), and sub-RPE hemorrhage. Using inverse transformation to the *en face* structural image, the attenuated signal was enhanced and the speckle noise was reduced via a Gaussian smoothing filter (3 × 3 pixels kernel). Signal compensation was done by multiplying the *en face* CC flow image and inverted, smoothened CC structural image to overcome signal attenuation. The resultant image, i.e., the compensated CC *en face* image was used for image analysis[16] [Fig. 1].

Image analysis

The image thus obtained was exported and analyzed for CCFD using ImageJ software version 1.50 (National Institutes of Health, Bethesda, Maryland, USA; available at http://rsb.info.nih.gov/ij/index.html). The computation of CCFD was done in progressively enlarging squares centered on the fovea to assess the topographic changes over the macular region. A 1 × 1 mm square was selected initially, centered on the fovea. Subsequent squares of increasing size were generated. This was done using the "Edit-Selection-Enlarge" function in ImageJ. Each square was evaluated for CCFD in all three study groups.

The compensated CC *en face* images were then binarized for quantitative measurement of the signal deficits employing the Phansalkar method, using a window radius of 17.6 mm (3 pixels in a 6 × 6 mm image).[17] The black pixels seen in these post-analysis images of CC are termed as "flow deficits". The flow deficits were calculated as the percentage of these black pixel areas using the "Analyse particles" command in all the six square regions [Fig. 2].

Statistical analysis

Statistical analysis was performed using SPSS version 20.0 (IBM Corporation, Armonk, New York, USA). All the descriptive data were reported as mean ± standard deviation (SD). The normality of data was assessed using the Shapiro–Wilk test. The data was normally distributed and thus, we proceeded with parametric analysis. ANOVA with post-hoc Bonferroni correction for pairwise comparison was performed to compare CCFD in six regions between three groups. Pearson correlation was used to assess the correlation between the percentage of flow deficits and age, foveal thickness, subfoveal choroidal thickness, and visual acuity. Linear regression analysis was performed to test the association between distance from the fovea and the CCFD in all three groups. A P value less than 0.05 was considered as a statistically significant difference. Based on the enrolled sample size, the study had the power of 99%, which was performed using post-hoc power analysis in G-power 3.1.

Results

Demographics and clinical characteristics

The study cohort consisted of 15 treatment naïve eyes with unilateral PCV (group 1), 27 fellow unaffected eyes of unilateral PCV patients (group 2), and 31 age-matched healthy controls (group 3). The mean age was: 62.2 ± 8.36 (50–74 years)

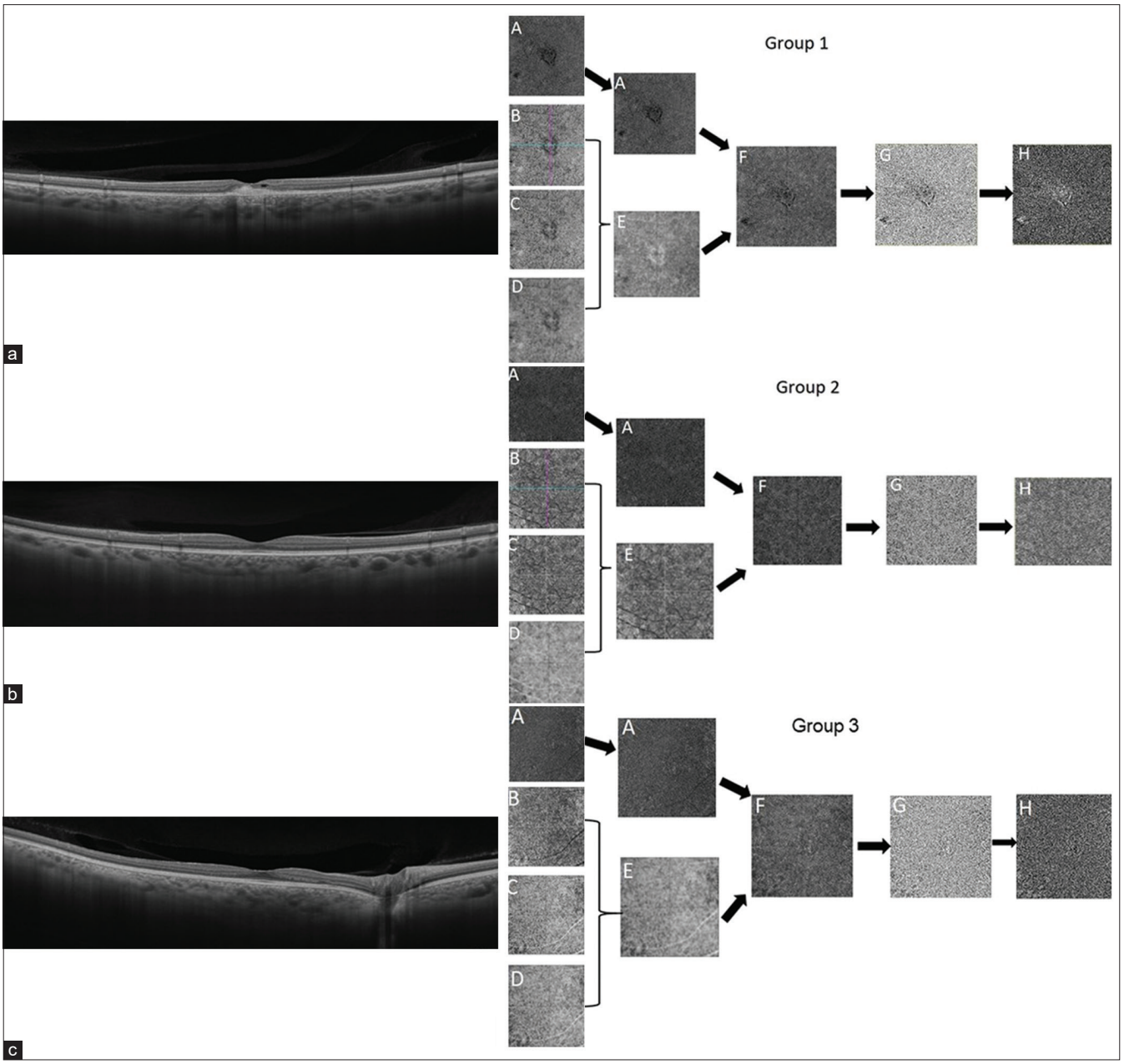

Figure 1: (a) Derivation of the resultant compensated angiogram image in group 1. CC slab angio Image (A). For each acquisition, a 10-μm thick slab, starting 31 μm below the RPE reference band was segmented to extract the *en face* image of the CC from the angiogram (B). After being inverted (C) and blurred (D), The resultant image (E) was multiplied with the angiogram (A) to compensate the angiogram for regions of signal loss. The resultant compensated angiogram image (F) was thresholded (G) and inverted (H) to calculate the flow deficits (%). (b) Derivation of the resultant compensated angiogram image in group 2. CC slab angio image (A). For each acquisition, a 10-μm thick slab, starting 31 μm below the RPE reference band was segmented to extract the *en face* image of the CC from the angiogram (B). After being inverted (C) and blurred (D), the resultant image was multiplied with the angiogram (A) to compensate the angiogram for regions of signal loss. The resultant compensated angiogram image (F) was thresholded (G) and inverted (H) to calculate the flow deficits (%). (c) Derivation of the resultant compensated angiogram image in group 3. CC slab angio image (A). For each acquisition, a 10-μm thick slab, starting 31 μm below the RPE reference band was segmented to extract the *en face* image of the CC from the angiogram (B). After being inverted (C) and blurred (D), the resultant image was multiplied with the angiogram (A) to compensate the angiogram for regions of signal loss. The resultant compensated angiogram image (F) was thresholded (G) and inverted (H) to calculate the flow deficits (%)

for group 1, 62.56 ± 10.53 (50–86 years) for group 2, and 60.35 ± 4.99 (54–73 years) for group 3. Table 1 summarizes the demographic details and the clinical variables of the study population. Among the patients with unilateral PCV, all the 15 subjects had BVN, 9 had polyps and 11 had pigment epithelial detachment.

Quantitative analysis of choriocapillaris

In the subgroup analysis, the CCFD in the first two squares was significantly increased (one-way ANOVA, $P = 0.003$ and $P = 0.049$) among the three groups. In the multiple pairwise comparison using post hoc Bonferroni, CCFD of 1 mm in groups 1 and 2 (45.36 ± 5.28% vs 41.04 ± 5.15%, $P = 0.019$),

Table 1: Baseline demographics and clinical characteristics of the study cohorts

	Group 1 (*n*=15 eyes)	Group 2 (*n*=27 eyes)	Group 3 (*n*=31 eyes)	*P* (group 1 vs group 2)	*P* (group 2 vs group 3)	*P* (group 3 vs group 1)
Age (Mean±SD)	62.2±8.36	62.56±10.53	60.35±4.99	0.73	0.14	0.35
Gender (Male *n*, %)	10 (66%)	15 (55%)	20 (65%)	0.49	0.56	0.83
BCVA (Mean±SD)	0.43±0.37	0.01±0.03	0.00±0.00	<0.0001*	0.28	<0.0001*
SE (Mean±SD)	0.96±1.73	0.25±1.93	0.37±0.96	0.18	0.41	0.21
FT (Mean±SD)	225.6±76.95	180.52±14.31	179.06±17.89	<0.0001*	0.74	<0.0001*
SFCT (Mean±SD)	353.73±96.00	305.85±77.11	300.81±50.28	0.033*	0.76	<0.0001*

SD: Standard deviation, BCVA: Best-corrected visual acuity, FT: Foveal thickness, SFCT: Subfoveal choroidal thickness, SE: Spherical equivalent, *statistically significant

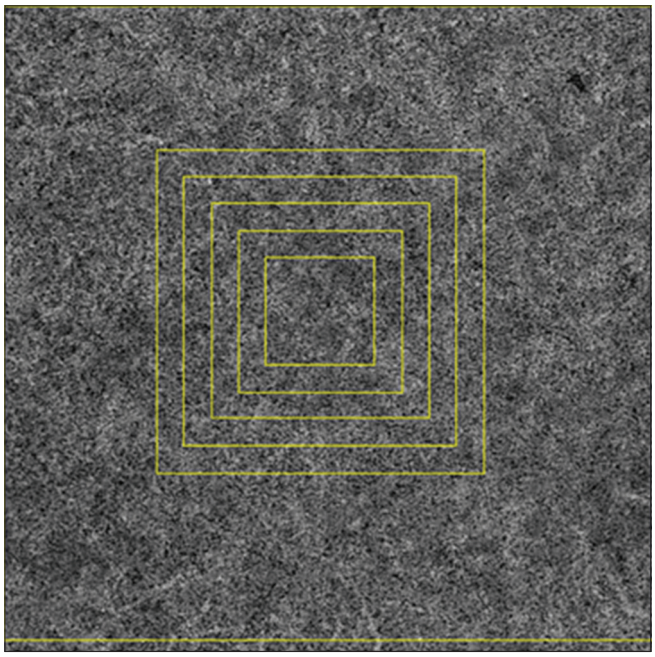

Figure 2: Areas of interest as squares of increasing sizes starting from 1 × 1 mm, centered at the fovea. CCFD was calculated in these squares, in all the three groups

groups 1 and 3 (45.36 ± 5.28% vs 40.22 ± 4.13%, P = 0.003), and CCFD of 1.5 mm in groups 1 and 3 (44.08 ± 4.35% vs 40.46 ± 4.35%, P = 0.044) were statistically significant. CCFD in other squares in group 1 were increased as compared with those of groups 2 and 3, though the increase was not statistically significant [Fig. 3].

Univariate linear regression analysis of distance from the fovea and the CCFD, showed a significant association in group 1 (β = −0.613, P = 0.046), whereas the other two groups were not significant (β = −0.131, P = 0.571; β = −0.246, P = 0.188).

Discussion

Choriocapillaris is a layer of dense meshwork of capillaries, which is vital for the blood supply and nourishment to the outer retina including the RPE. Damaged CC would result in an ischemic insult to the RPE and outer retina, triggering the onset of diseases like AMD.[16] SS-OCTA has the additional advantage of depth-resolved visualization of the retinal vascular plexus and allows us to inspect the CC *in vivo*.[7] Flow deficits are seen as relative areas of decreased local flow signal in the CC slab. These flow deficits can be a part of the pathological changes that are seen in diseased eyes and have been analyzed in different posterior segment diseases such as diabetic retinopathy,[10] Biette's crystalline dystrophy,[18] geographic atrophy,[12] central serous chorioretinopathy,[11] choroidal neovascular membrane,[16] AMD[19] and pachychoroid diseases.[13] It is useful for researchers and clinicians to evaluate the earliest changes taking place in CC flow to assess for disease activity and progression.[20,21] With a high prevalence of PCV in Asians, analyzing such changes in CC becomes extremely important to understand and treat the disease effectively.

In this study, we examined the presence and topographic distribution of CC flow deficits over a 6 × 6 mm scan area centered on fovea among treatment-naïve unilateral eyes with PCV, fellow unaffected eyes of unilateral PCV, and age-matched healthy eyes. Signal compensation method was used to compensate the signal attenuation, thereby improving the image quality.[16] Also, multiple areas centered at the fovea were compared between age-matched healthy and PCV eyes to account for any physiological changes that may be seen in CCFD with age as well as topographical changes in CCFD that may be seen in healthy eyes.

The results showed that on average, the CCFD was highest in eyes with PCV (group 1), followed by fellow unaffected eyes (group 2) and lowest in normal (group 3), although the significant difference was noted only in 1 mm area (groups 1 and 2, and groups 1 and 3), and 1.5 mm area (groups 1 and 3). A study by Baek *et al*. showed that the changes in CC may be the earliest event in the pathogenesis of the pachychoroid spectrum of diseases.[22] They also suggested that the flow impairment in the CC layer may precede the changes taking place in RPE and the outer retina. Our results are consistent with their hypothesis, as the eyes with active treatment-naïve PCV lesions had greater CCFD as compared to the fellow eyes of PCV patients with no lesions, and the lowest values were seen in healthy controls. These results possibly indicate increase in CCFD in PCV eyes with appearance of signs of PCV.

The topographical analysis in our study showed that the CCFD values decreased from the foveal center towards the periphery of the 6 × 6 mm scan area. This was significant in eyes with PCV. In other groups, the difference was non-significant. This was contrary to the results of the study by Nassisi *et al*.[23] who showed that the flow deficits tend to decrease from fovea towards the periphery in healthy eyes. This difference in flow deficits from the fovea towards the periphery in healthy eyes has been hypothesized to be due to the thickening of Bruch's

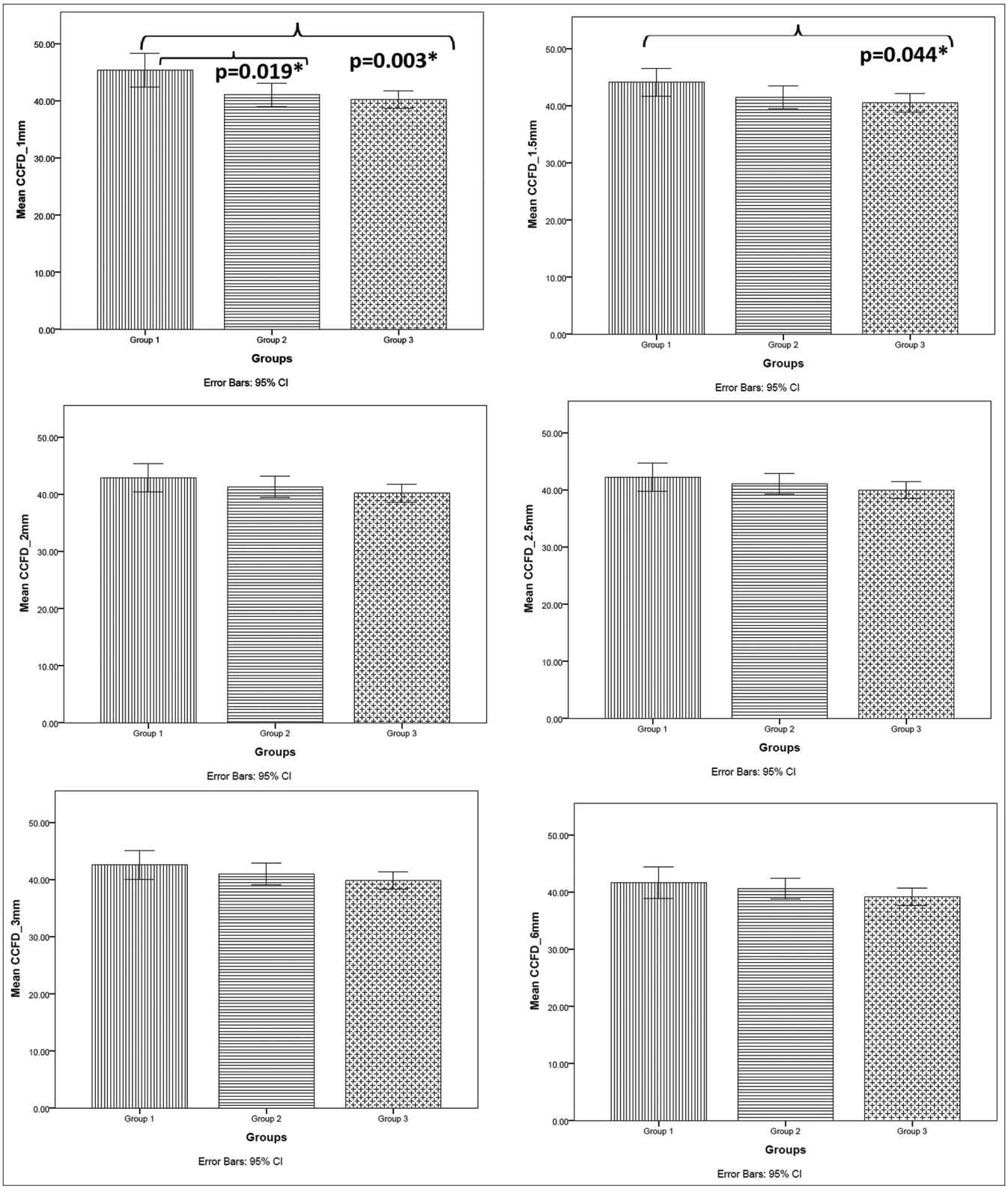

Figure 3: Bar graphs showing the CCFD in three groups in six regions. Error bars showing the 95% confidence interval. * Statistically significant

membrane under the fovea and the higher level of stress on CC under the fovea due to recycling of the metabolites.[19] This higher level of stress could be toxic, thereby leading to an increased CC flow impairment under the fovea.[23] As our study included a narrower age range and a lesser number of subjects from a single ethnicity, the topographic variations in the study cohort might have been obscured.

Correlation analysis in our study showed that there was no significant correlation between CCFD, foveal thickness,

subfoveal choroidal thickness, and visual acuity. Thus, the CCFD was not possibly influenced by these physiological factors, indicating that CCFD maybe a robust index of choroidal vascularity. However, further studies with larger samples will be required to establish this.

To the best of our knowledge, this study is the first to quantitatively assess CC flow deficits in eyes with PCV as well as fellow unaffected eyes in the Indian population. With the existing knowledge of known ethnic variations in the CC flow[24] and increased prevalence of AMD as well as PCV in the Asian population, the importance of such a study cannot be underestimated.

The study is limited by the small sample size and cross-sectional nature. Larger longitudinal studies with longer follow-up periods in various ethnic groups are essential to assess the actual choroidal pathological changes in eyes with PCV as well as to determine the effect of physiological factors on CCFD. Also, eyes with large hemorrhagic retinal pigment epithelial detachment were excluded, as the potential hypodense area below these lesions in the *enface* CC slab might have altered results. Therefore, more pathological phenotypes could not be included, limiting our results further.

Conclusion

In summary, our study confirms the presence of significant CC flow impairment in eyes with PCV lesions. Larger longitudinal studies are warranted to unravel the pathophysiological significance of our findings.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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