Comparison of Choriocapillary Flow Density Between Fellow eyes of Polypoidal Choroidal Vasculopathy and Neovascular Age-Related Macular Degeneration

CURRENT STATUS: ACCEPTED

BMC Ophthalmology  BMC Series

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DOI: 10.21203/rs.2.21264/v2

SUBJECT AREAS  Ophthalmology

KEYWORDS  polypoidal choroidal vasculopathy, age-related macular degeneration, optical coherence tomography angiography, contralateral eye, choriocapillary flow density
Abstract
Purpose: To compare the choriocapillary flow density (CFD) among the fellow eyes of polypoidal choroidal vasculopathy (PCV), neovascular age-related macular degeneration (nAMD) and healthy controls with spectral-domain optical coherence angiography tomography (SD-OCTA).
Methods: This is a cross-sectional study, including the fellow eyes of 38 patients with unilateral PCV, 36 patients with unilateral nAMD, and 36 eyes from 36 healthy volunteers. PCV group was further classified into polypoidal CNV (P-CNV) and typical PCV (T-PCV) for subgroup analysis. Age, subfoveal choroidal thickness (SFCT), Age-Related Eye Disease Study (AREDS) classification and fellow eye diagnosis were acquired. All subjects underwent 6.0 mm scan pattern of SD-OCTA. Circles with radius of 1.00, 1.50 and 3.00 mm were manually selected in choriocapillaris (CC) slab, and CFD was calculated as the percentage of flow area to the whole selected area as CFD-1.00, 1.50, 3.00 respectively. Univariate and multivariate analysis were performed to study correlation between aforementioned factors with CFD,
Results: Mean CFD-1.00, 1.50, 3.00 of nAMD group were 61.51, 63.18 and 66.20, significantly lower than PCV group (65.90, 66.89, 67.94, P<0.001 , <0.001, and 0.010, respectively) and control (66.28, 66.96, 68.42, P<0.001 , <0.001, and 0.001, respectively), while no difference were detected between PCV group and control or between PCV subtypes. AREDS classification and fellow eye diagnosis were correlated with CFD in univariate analysis, but only fellow eye diagnosis remained significantly correlated after multiple linear regression.
Conclusions: CFD of nAMD fellow eyes were significantly lower than that of PCV and control eyes, while no difference was detected between PCV and control group, indicating different role of CC loss in early pathogenesis of nAMD and PCV.
Background
Polypoidal choroidal vasculopathy (PCV) is characterized by orange-red nodules in fundus examinations, polypoidal lesions during indocyanine green angiography (ICGA) and tremendous bleeding of posterior pole. It has raised many controversies since first described by Yannuzzi in 1980s[1], especially its pathogenesis and whether it is a subtype of neovascular age-related macular
degeneration (nAMD), or a distinct disease within pachychoroid disease spectrum[2], due to obvious heterogeneity that lies in their clinical, pathophysiological and epidemiological features and treatment responses to anti-vascular endothelium growth factor (VEGF) agents[3].

The pathogenesis and nature of PCV remains to be elucidated, so is its characteristic lesions, namely polyps and branching vascular network (BVN). In recent years, multimodal imaging technologies allows more precise view of polypoidal lesions and PCV choroid. Specifically, with optical coherence tomography angiography (OCTA), a novel imaging modality reflecting choroid flow with higher accuracy and resolution compared to traditional dye-based ophthalmic angiography[4], emerging evidence suggests the classical polypoidal lesions manifest as tangled vessels at the edge of BVN[5].

This finding further complicates our knowledge that whether there is actual difference between PCV and nAMD, since the characteristic lesions of PCV and choroidal neovascularization (CNV) in nAMD are essentially both vascularization in nature and there might be actually no “polyps” or “aneurysmal vessels”[6].

Despite various rates of bilateral presentation[3], substantial studies identified asymptomatic lesions in fellow eyes of both PCV and nAMD patients. For example, non-exudative neovascularization of the fellow eye was found associated with pachychoroid pigment epitheliopathy in PCV and nAMD patients[7], and an increased trend of choriocapillaris (CC) nonperfusion was detected in the fellow eyes of nAMD using OCTA[8]. Additionally, retinal pigmented epithelium (RPE) and outer retinal abnormalities were observed in 84% of a cohort of unilateral PCV patients, and CNV formation was observed more if these abnormalities were accompanied with pachyvessels [9]. These studies, among other fellow eye studies, may shed light on the pathogenesis, especially in the early phases. It remains to be clarified whether there is a direct causal effect between pachychoroid and the pathogenesis of PCV, yet RPE alterations seems a secondary downstream event occurring in later stage of the disease. This differs from nAMD, in which the interplay between RPE and CC[10, 11] plays a central role in the early phase, and finally elevated VEGF gives rise to CNV.

CC flow deficits (CFD) detected with OCTA has emerged as a potential metrics to evaluate inner choroid vasculature with fast non-invasive imaging, which has been extensively utilized in various
retinal diseases [12-15]. However, there has not been a comparison between PCV and nAMD in their fellow eyes with OCTA. This study aimed to compare the fellow eyes of PCV and AMD in terms of CFD at an early stage without signs of neovascularization.

Methods
This is a cross-sectional, observational study of unilateral PCV and nAMD patients recruited from June 2017 to July 2019 at Peking Union Medical College Hospital. Healthy controls were also included. The study was approved by the institutional review board (S-K631) and was conducted in accordance with the tenets of the Declaration of Helsinki. Written informed consent was waived because of the study’s retrospective design.

PCV and nAMD were diagnosed according to published criteria[1, 16]. Two masked ophthalmologists (M.L. and M.Y.) reviewed the early to late phases of the angiography images, verified the diagnosis and classified PCV cases into polypoidal CNV (P-CNV) or typical PCV (T-PCV)[17]. A third retinal consultant (Y.C.) arbitrated in case of any discrepancy. The inclusion criteria for patients were unilateral PCV or nAMD cases with complete medical records. Patients and controls were excluded if (1) any signs of neovascularization in the included eyes, namely exudation in FFA or ICGA for patients, and BVN or blood flow signal between RPE and Bruch’s membrane in OCTA for all; (2) comorbid with other ophthalmic diseases except for myopia less than -3.0D and mild cataract; (3) cloudy refractory media impedes examination of the posterior pole (4) OCTA scan quality was lower than 7.

All patients received comprehensive ophthalmologic examinations, including Snellen best-corrected visual acuity (BCVA), and SD-OCTA (RTVue XR Avanti AngioVue; Optovue, Inc., Fremont, CA, USA) and simultaneous fluorescein angiography ICGA and enhanced depth imaging (EDI) SD-OCT (Heidelberg Retina Angiography 2, HRA2, Heidelberg Engineering, Heidelberg, Germany). For statistical analysis, the Snellen BCVA was converted to a logarithm of the minimal angle of resolution (logMAR).

All included eyes were stratified according to Age-Related Eye Disease Study (AREDS) classification[18] into: (1) No apparent aging changes or normal aging changes; (2) Early AMD; (3) Intermediate AMD; and (4) Late AMD, according to drusen size and pigmentary abnormalities (AREDS category 1-4, respectively). Subfoveal choroidal thickness (SFCT) was measured using EDI-OCT.
horizontal B-scans as the distance between the Bruch membrane and choroid-scleral border. HD Angio Retina 6.0 mm scan pattern of each subject was acquired and used for further analysis. Motion correction technology and 3D projection artifact reduction was automatically employed. Circles centered at the fovea with radius of 1.00, 1.50 and 3.00 mm were manually adjusted in CC slab using built-in software, and CFD was calculated as the percentage of flow area to the whole selected area, which were generated automatically, as CFD-1.00, 1.50, and 3.00 respectively.

Statistical analysis
Statistical analyses were performed using SPSS 22 (IBM, Inc, Chicago, IL). Normally distributed continuous data were presented in mean and standard deviation (SD), otherwise in median and interquartile range (IQR). A $P$ value less than 0.05 was considered significant in all aforementioned analysis. Categorical and continuous variables were assessed using chi-square test and one-way analysis of variance (ANOVA) respectively with post-hoc Bonferroni correction. Bivariate relationships were assessed with Spearman correlation coefficient analysis to evaluate potential correlating factors of CFD. Multivariate linear regression analysis was performed with age, SFCT and other factors with significance from univariate analysis as dependent factors.

Results
The fellow eyes of 38 patients with unilateral PCV (mean age: 63.8±8.8 years), 36 patients with unilateral nAMD (mean age: 67.1±8.4 years), and 36 eyes from 36 healthy volunteers (mean age: 63.4±7.1 years) were included. Subjects were matched in terms of age, gender, BCVA, smoking status, hypertension, and diabetes mellitus (DM) among the groups. Basic demographic and clinical characteristics of the subjects are summarized in Table1. AREDS category of AMD group were more advanced, compared to PCV and control group ($P=0.012$ and 0.001, respectively), with 7 and 8 subjects classified as AREDS category 2 and 3, respectively. SFCT of PCV group was significantly greater than that of AMD and control group (242.97±53.59 vs 196.61±45.58 and 209.94±46.22 μm, $P<0.001$ and $=0.013$, respectively). Mean CFD-1.00, 1.50, 3.00 (SDs) of nAMD group were 61.51, 63.18 and 66.20, significantly lower than PCV group (65.90, 66.89, 67.94, $P<0.001$, <0.001, and 0.010, respectively) and control (66.28, 66.96, 68.42, $P<0.001$, <0.001,
and 0.001, respectively), while no difference was detected between PCV group and control.

Univariate analysis (Table 2) indicated that CFD-1.00, CFD-1.50 and CFD-3.00 were all correlated with AREDS classification ($P=0.001$, 0.006 and 0.049, respectively) and fellow eye diagnosis ($P<0.001$, <0.001 and =0.001, respectively). Multiple linear regression (Table 3) revealed that in this study cohort, fellow eye diagnosis was the only factor strongly correlated with CFD ($P<0.001$, <0.001 and =0.001, respectively).

There were 13 P-CNV and 25 T-PCV patients in PCV group. SFCT of T-PCV group was significantly greater than P-CNV, wAMD and control group (265.08±43.68 μm vs 200.46±45.44μm, 196.61±45.58μm and 209.94 46.22μm, all $P<0.001$). CFD-1.00 and CFD-1.50 of P-CNV and T-PCV were significantly higher than that of wAMD, but not significantly different from control (Supplementary files, Table 4). CFD-3.00 of wAMD group was significantly lower than T-PCV and control, but not P-CNV. All CFD values were not significantly different between PCV subtypes (Supplementary files, Table 4). Univariate analysis and multiple linear regression results were similar.

(Supplementary files, Table 5-6)

Discussion
In this study, we evaluated the CFD of fellow eyes of nAMD and PCV with OCTA, and found fellow eyes of nAMD had significantly lower CFD compared with PCV and control group, while the difference was not statistically significant between PCV group and control or between PCV subtypes. Although CFD was found negatively correlates with aging[19], it is unlikely that aging itself can account for the difference, since PCV, AMD and control group were age-matched. Another important factor is the existence of drusen, which is considered a hallmark of dry AMD. In this study, all included eyes were stratified according AREDS classification, and more subjects with advanced category were observed in nAMD group. But this index was not statistically significant in multivariate linear regression analysis. Although there is a myriad of overlap between PCV and nAMD, the difference of CFD in their fellow eyes may serve as a proof of their heterogeneity.

The interplay of RPE and CC loss has always been a hotspot in the pathogenesis of AMD[20-23], although the sequential order remains controversial. Indeed, PCV is a well-recognized disease within
pachychoroid disease spectrum, characterized by dilation of Haller layer and attenuation of choriocapillaries and Sattler layer. Engorgement of vortex vein is often observed in PCV, with correlating choroidal hyperpermeability[24], also confirmed by the pathology showing atherosclerotic change of choroid vessel wall, massive exudation of fibrin and blood plasma at polypoidal lesion[25, 26]. Apoptosis of smooth muscle cells and choroidal endothelial cells were also observed[25]. Chen et al induced polyp-like structures by ligating vortex veins in cynomolgus monkeys[27] These findings above suggest a role of choroidal hemodynamics in PCV pathogenesis[28]. While the CFD of fellow eyes of PCV was not significantly different from control, indicating RPE-Bruch’s membrane-CC complex may not be involved in the preclinical stage of PCV and may be a downstream effect secondary to primary pathology. Specifically, near normal CFD of fellow eyes of PCV is not a contradiction to the vital role of CC flow deficit and RPE changes in pachychoroid pathogenesis, which may be a downstream event secondary to dilation of Haller layer. Thus, in the relatively healthy contralateral eyes of PCV, CFD may be near normal, possibly accompanied with some pachychoroid features. Alternatively, this might be associated with lower bilaterality of PCV eyes. Further studies regarding PCV laterality and sequential order of choroidal changes in PCV are necessary for elaboration.

A plethora of studies investigated the difference of choroidal morphology between PCV and nAMD. SFCT is often used as an index, but it fluctuates with circadian rhythm and correlates with age and refractive errors[29]. Bakthavatsalam et al. [29] found that choroidal vascular index (CVI) of nAMD was lower than that in PCV (64.94 vs 62.54), but the difference was not statistically significant (P=0.10). Pachyvessels especially diffuse pattern were observed more commonly in thick-choroid PCV[30], and vascular area of typical PCV was significantly larger than nAMD[31]. All aforementioned results indicate the two diseases are heterogeneous in terms of choroidal morphology.

Our study had the limitations that are inherent as a retrospective cross-sectional study. Besides, the sample size is relatively small. Lastly, DM, hypertension and smoking status was collected from patients’ past medical records which were recorded in a self-report manner, thus not accurate enough to be included into multivariate analysis. Nevertheless, to the best of our knowledge, this is the first
study that provided quantitative analysis of CC among the fellow eyes of PCV, nAMD, and healthy eyes. Our study may provide evidence for the heterogeneity of nAMD and PCV.

Conclusions
In conclusion, our findings suggest that CFD of nAMD fellow eyes were significantly lower than that of PCV and control eyes, while no difference was detected between PCV and control group or between PCV subgroups, indicating a different role CC loss plays in the early pathogenesis of nAMD and PCV.

Abbreviations
polypoidal choroidal vasculopathy, PCV
indocyanine green angiography, ICGA
neovascular age-related macular degeneration, nAMD
vascular endothelium growth factor, VEGF
branching vascular network, BVN
optical coherence tomography angiography, OCTA
choroidal neovascularization, CNV
choriocapillaris, CC
retinal pigmented epithelium, RPE
CC flow deficits, CFD
polypoidal CNV, P-CNV
typical PCV, T-PCV
best-corrected visual acuity, BCVA
enhanced depth imaging, EDI
logarithm of the minimal angle of resolution, logMAR
Age-Related Eye Disease Study, AREDS
standard deviation, SD
interquartile range, IQR
analysis of variance, ANOVA
diabetes mellitus, DM
Declarations
**Ethics approval and consent to participate**

The study was approved by the institutional review board (S-K631) and was conducted in accordance with the tenets of the Declaration of Helsinki. Written informed consent was waived because of the study’s retrospective design.

**Consent to publish**

Not applicable.

**Availability of data and materials**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

**Funding**

This work was supported by The Non-profit Central Research Institute Fund of Chinese Academy of Medical Sciences (2018PT32029).

**Authors’ contributions**

**ML:** collection of medical records, image evaluation, statistical analysis, drafting the manuscript and manuscript revision. **XZ:** modification of study design, data collection and manuscript revision. **NZ:** statistical analysis. **MY and JY:** data collection. **RD:** manuscript revision. **YC:** conceived of the study, coordinated and participated in the entire process of drafting and revised the manuscript. All authors read and approved the final manuscript.

**Acknowledgements**

Not applicable.

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Table 1. Baseline Demographics and Clinical Characteristics of Subjects

|                          | PCV (N = 38) | nAMD (N = 36) | Control (N = 36) |
|--------------------------|--------------|---------------|------------------|
| Age, y mean (SD)         | 63.8 (8.8)   | 67.1 (8.4)    | 63.4 (7.1)       |
| Gender, female (N) (%)   | 20 (52.6)    | 12 (33.3)     | 22 (61.1)        |
| BCVA (logMAR) (IQR)      | 0.09 (0.00-0.10) | 0.12 (0.00-0.22) | 0.08 (0.00-0.10) |
| Smoker/non-smoker        | 4/34         | 5/31          | 3/33             |
| Hypertension (%)         | 4 (10.5)     | 9 (25.0)      | 5 (13.9%)        |
| DM (%)                   | 4 (10.5)     | 4 (11.1)      | 1 (2.8)          |
| AREDS Category           | 34/3/1/0     | 21/7/8/0      | 36/0/0/0         |
| SFCT (μm)                | 242.97 (53.59) | 196.61 (45.58) | 209.94 (46.22)   |
| CFD-1.00 (%)             | 65.90 (3.47) | 61.51 (3.90)  | 66.28 (3.39)     |
| CFD-1.50 (%)             | 66.89 (3.30) | 63.18 (3.42)  | 66.96 (2.96)     |
| CFD-3.00 (%)             | 67.94 (2.52) | 66.02 (3.10)  | 68.42 (2.59)     |

SD: standard deviation; BCVA: best-corrected visual acuity; logMAR, logarithm of the minimal angle of resolution; IQR: interquartile range; DM: diabetes mellitus; AREDS: Age-Related Eye Disease Study; SFCT: subfoveal choroidal thickness; CFD: choriocapillaris flow deficit; PCV: polypoidal choroidal vasculopathy; nAMD: neovascular age-related macular degeneration.

*Statistically significant P value. a Post-hoc Tambane correction. b Fischer’s exact test.

Table 2. Univariate Analysis of Potential Correlation Factors (Age, gender, BCVA, smoking status, hypertension, DM, AREDS classification, and SFCT) With CFD-1.00, CFD-1.50, and CFD-3.00 as dependent variable.
| Characteristic          | Correlation Coefficient | $P$ value $^a$ | Correlation Coefficient |
|------------------------|-------------------------|---------------|-------------------------|
| Age                    | -0.06                   | 0.537         | 0.01                    |
| Gender                 | -0.07                   | 0.483         | -0.06                   |
| BCVA                   | -0.01                   | 0.902         | 0.03                    |
| Smoking status         | -0.08                   | 0.388         | -0.07                   |
| Hypertension           | -0.07                   | 0.453         | -0.063                  |
| DM                     | -0.08                   | 0.428         | -0.06                   |
| AREDS classification   | -0.30                   | 0.001*        | -0.26                   |
| SFCT                   | 0.11                    | 0.244         | 0.10                    |
| Fellow eye diagnosis   | -0.46                   | <0.001*       | -0.42                   |

DM: diabetes mellitus; AREDS: Age-Related Eye Disease Study; SFCT: subfoveal choroidal thickness; CFD: choriocapillaris flow deficit.

*Statistically significant $P$ value. $^a$ Spearman correlation analysis.

Table 3. Multiple linear regression analysis of Correlation Factors with CFD-1.00, CFD-1.50 and CFD-3.00 as Dependent Variables

|                        | CFD-1.00 | $P$ value | CFD-1.50 |
|------------------------|----------|-----------|----------|
| Fellow eye diagnosis   | -0.443   | <0.001*   | -0.437   |
| AREDS Classification   | -0.166   | 0.082     | -0.399   |
| Age                    | 0.059    | 0.518     | 0.109    |
| SFCT                   | -0.038   | 0.671     | -0.037   |

AREDS: Age-Related Eye Disease Study; SFCT: subfoveal choroidal thickness; CFD: choriocapillaris flow deficit.

*Statistically significant $P$ value.

Supplementary Files

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