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RETINAL DISORDERS

# Hyper- and hypo-perfusion of choriocapillaris in the eyes with pachychoroid pigment epitheliopathy

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## Abstract

**Purpose** To evaluate the changes in choriocapillaris vessel density (VD) in eyes with pachychoroid pigment epitheliopathy (PPE) using swept-source optical coherence tomography (OCT) angiography (OCTA).

**Methods** This study included 83 eyes with PPE and 42 control eyes. We collected OCT and OCTA parameters, including central point thickness, subfoveal choroidal thickness (SFChT), and choriocapillaris VD of the fovea (CC fovea) and parafovea. The parafoveal area was divided into superior, nasal, inferior, and temporal choriocapillaris areas. Maximum (CC max) and minimum (CC min) choriocapillaris VD were defined as the highest and lowest values among the four parafoveal subfield VDs, respectively. We analyzed the average choriocapillaris VD, CC max, CC min, CC fovea, and the difference between CC max and CC min (CC delta) individually and compared all the parameters between PPE and control eyes.

**Results** CC max (56.0% ± 1.7%) was significantly higher and CC min (50.9% ± 2.0%) significantly lower in eyes with PPE than in control eyes (CC max, 55.3% ± 1.0%, $P = 0.006$; CC min, 51.5% ± 1.3%, $P = 0.046$). The CC delta value (5.0% ± 2.1%) and SFChT (389.9 ± 129.9 μm) were also significantly higher in eyes with PPE than in the control group (3.7% ± 1.5%, $P < 0.001$; 268.2 ± 102.2 μm, $P < 0.001$; respectively).

**Conclusions** Choriocapillaris VD showed higher variability (hyperperfusion and hypoperfusion) in eyes with PPE than in control eyes. Choriocapillaris hypoperfusion may precede the development of PPE; however, choriocapillaris hyperperfusion is associated with projection artifacts.

**Keywords** Choriocapillaris · Vessel density · Hyperperfusion · Hypoperfusion · Flow void area · Pachychoroid epitheliopathy

**Key messages**

- Choriocapillaris variability was shown in eyes with pachychoroid pigment epitheliopathy.
- Choriocapillaris hypoperfusion may precede the development of pachychoroid pigment epitheliopathy and choriocapillaris hyperperfusion may be associated with projection artifacts.

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## Introduction

Central serous chorioretinopathy (CSC) is a common retinal disease characterized by serous macular detachment of the neurosensory retina [1]. The involvement of the choroid in CSC has been demonstrated in several studies. Previous studies, using indocyanine green angiography (ICGA), showed multifocal choroidal vascular hyperpermeability [2], and recent studies using multimodal imaging suggested that the choroid and retinal pigment epithelium (RPE) are the key structures presumed to play a primary role in CSC development [3, 4]. Although the exact pathogenesis is unknown, some studies

have suggested that the pathophysiology of CSC might be associated with choroid thickening, dilated pachyvessels, and abnormalities of the overlying RPE in the unaffected contralateral eye, as well as in the eye with CSC [1, 5, 6].

Warrow et al. introduced the new concept of "pachychoroid pigment epitheliopathy (PPE)" as a forme fruste of CSC [6]. They described a spectrum of RPE abnormalities, including drusen-like changes of RPE, and suggested that both PPE and CSC share similar structural abnormalities with the exception of clinically detected subretinal fluid [6]. Spaide renamed the drusenoid changes of RPE in the eyes with pachychoroid as pachydrusen [7]. Recent optical coherence tomography (OCT) angiography (OCTA) studies demonstrated the insufficiency of choriocapillaris flow in eyes with CSC or PPE [8–10]. Sakurada et al. showed that reduced choriocapillaris flow density, increased choroidal thickness, and choroidal vascular hyperpermeability were simultaneously observed in eyes with PPE [10]. However, a few OCTA studies have described localized hyperperfusion or mixed irregular flow pattern of choriocapillaris in eyes with pachychoroid disease, especially chronic CSC or resolved CSC [11–13].

Thus, the purpose of this study was to quantitatively investigate the changes in the choriocapillaris in eyes with PPE and compare them with those in control eyes.

## Methods

### Patients

This was a retrospective cross-sectional study and was conducted as per the tenets of the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of Chung-Ang University Hospital. Informed consent was waived because of the retrospective nature of the study. We included the eyes of patients diagnosed with unilateral CSC between January 2016 and September 2020. PPE was defined as eyes with drusenoid RPE changes and/or RPE detachment directly overlying the pachyvessel with no history of subretinal fluid retention. The eyes with PPE were included and their images were registered at the initial diagnosis. For age- and sex-matched controls, normal contralateral eyes with unilateral epiretinal membrane (ERM) were included from the same period. Comprehensive ocular examinations, including OCT and OCTA (same day), were performed on the patients and age-matched controls. Age, sex, best-corrected visual acuity (BCVA), intraocular pressure, refractive error, OCT, and OCTA parameters were recorded.

The exclusion criteria were as follows: bilateral history of CSC; other retinal diseases such as age-related macular degeneration, retinal vessel occlusion, and diabetic retinopathy; history of any intraocular surgery other than cataract surgery. If the OCTA image quality was less than 60, due to motion artifacts or segmentation errors, the OCTA images were excluded or follow-up images of the patients were used. Eyes with definite projection artifacts on the choriocapillaris slab were excluded.

### Swept-source optical coherence tomography (SS-OCT)

OCT images were acquired using a swept-source OCT (DRI Triton OCT, IMAGEnet 6 Version 1.21, Topcon Corp., Tokyo, Japan). The central point thickness (CPT) was obtained on the central fovea of the provided 5-line images using built-in software. We also manually obtained the subfoveal choroidal thickness (SFChT) assessment from Bruch's membrane to the chorioretinal interface below the fovea center on 5-line images. Pachyvessels were defined as prominently thick vessels of the Haller's layer with choriocapillaris attenuation under pigment epitheliopathy within $3.0 \times 3.0$ mm macular area. The two authors judged the pachyvessels and measured their diameter using built-in software. The cases in which the two authors disagreed were excluded. Mean values of the measurement were used for statistical analysis. All thicknesses were measured vertically to Bruch's membrane at 1:1 pixel scale.

### SS-OCT angiography (SS-OCTA)

We analyzed the choriocapillaris slab images of $3.0 \times 3.0$ mm macular scans, which were automatically set from the basement membrane (BM) to 10.4 μm below the BM (Figs. 1A, F, and 2A, F). The built-in software provided a color-coded perfusion density map with a modified 2.5-mm early treatment diabetic retinopathy study (ETDRS) grid (Figs. 1B, G, and 2B, G). The choriocapillaris slab images were divided into five subfield zones (foveal subfield, superior, inferior, nasal, and temporal parafoveal subfields) using built-in grid software. The perfused vessel density (VD) of each subfield was automatically measured using grid software. Manual adjustment was performed for foveal centering if required.

Foveal VD was defined as the central subfield perfused VD (1 mm in diameter), and parafoveal VD was defined as the paracentral subfield perfused VD of the corresponding

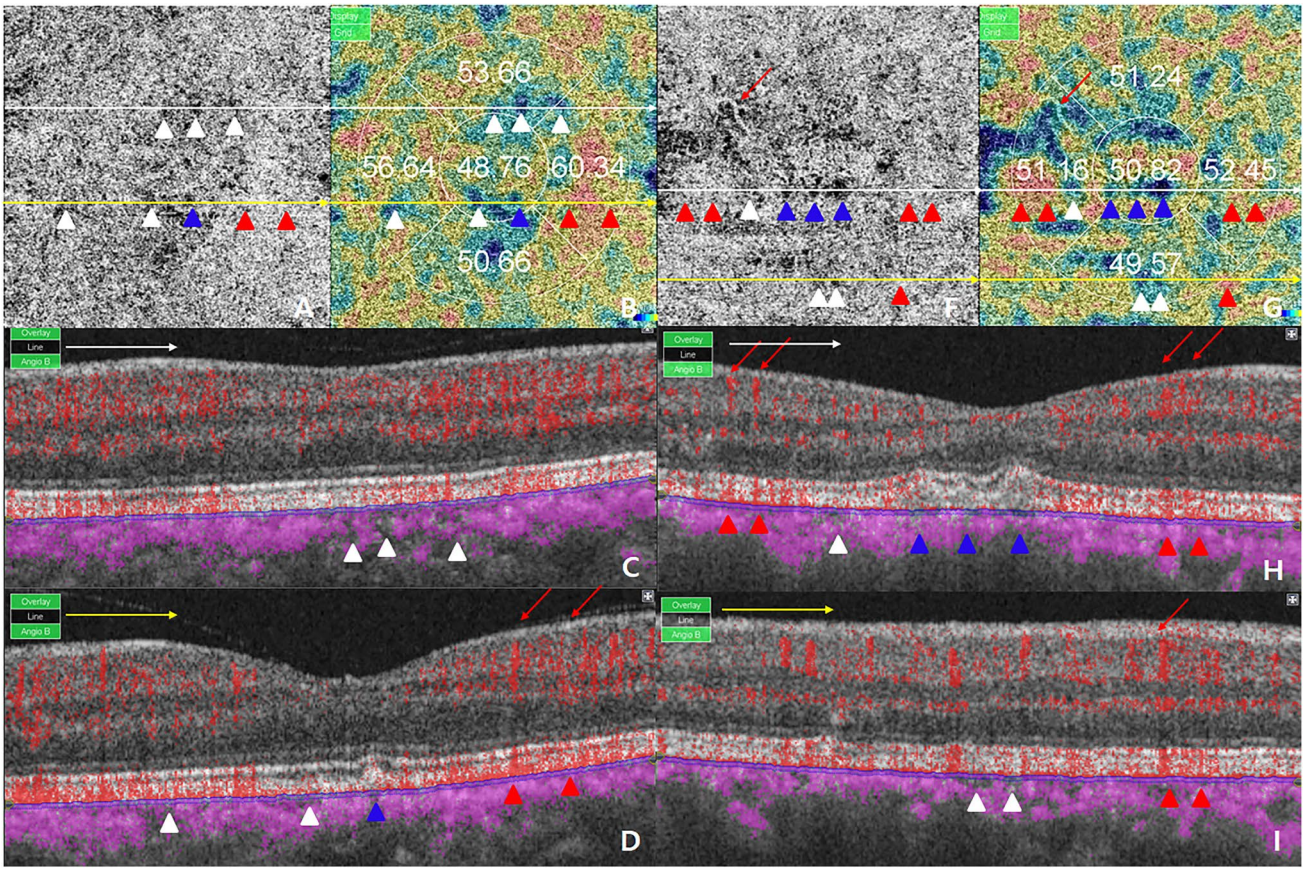


**Fig. 1** Representative choriocapillaris images of two eyes with pachychoroid pigment epitheliopathy (PPE). Choriocapillaris slab images (**A**, **F**), color-coded choriocapillaris images with modified early treatment diabetic retinopathy study grid (**B**, **G**), and B-scan images with flow overlay (**C**, **D**, **H**, **I**). The choriocapillaris slab shows a flow void area with (blue arrowhead) and without (white arrowhead) PPE. The color-coded area in red represents hyperperfusion of the choriocapillaris (red arrowhead). However, B-scan images with flow overlay indicated prominent projection artifacts (red arrowhead) from the superficial capillary plexus (red arrow)

area (1–2.5 mm). The average choriocapillaris VD was defined as the mean value of the five subfield VD. The maximum and minimum values of the choriocapillaris VD were defined as the highest and lowest values among the parafoveal subfield VD, respectively. The delta value of the choriocapillaris VD was defined as the difference between the maximum and minimum values of the parafoveal subfield VD.

### Statistical analysis

Baseline characteristics of eyes with PPE were compared with that of the control eyes using the independent *t*-test and chi-square test. OCT and OCTA parameters were compared using an independent *t*-test. Univariate regression analysis was performed for multiple variables. For subgroup analysis, the Mann–Whitney test and Fisher's exact test were used. SPSS software (version 20.0; IBM Corporation, Armonk, NY, USA) was used for statistical analyses. *P* values of $<0.05$ were considered statistically significant.

## Results

A total of 149 eyes of patients with unilateral CSC were analyzed. From them, 44 eyes without PPE were excluded, and 105 eyes with PPE were evaluated. After applying the exclusion criteria, a total of 83 eyes from 83 patients with PPE and 42 age- and sex-matched controls were included. All eyes with PPE were the contralateral eyes of patients with unilateral CSC. The mean age of patients with PPE was $53.3 \pm 11.7$ years, and the mean LogMAR BCVA was $0.02 \pm 0.04$ (Snellen, 20/20.9). There were no differences in age, sex, BCVA, intraocular pressure, or spherical equivalent between the two groups. The baseline characteristics of the patients are shown in Table 1.

Among OCT and OCTA parameters, SFChT was significantly higher in eyes of patients with PPE than in the control group eyes ($389.9 \pm 129.9$ µm vs $268.2 \pm 102.2$ µm, $P<0.001$). CPT and choriocapillaris VD in the foveal, superior, nasal, inferior, and temporal parafoveal areas were not significantly different between the two groups.

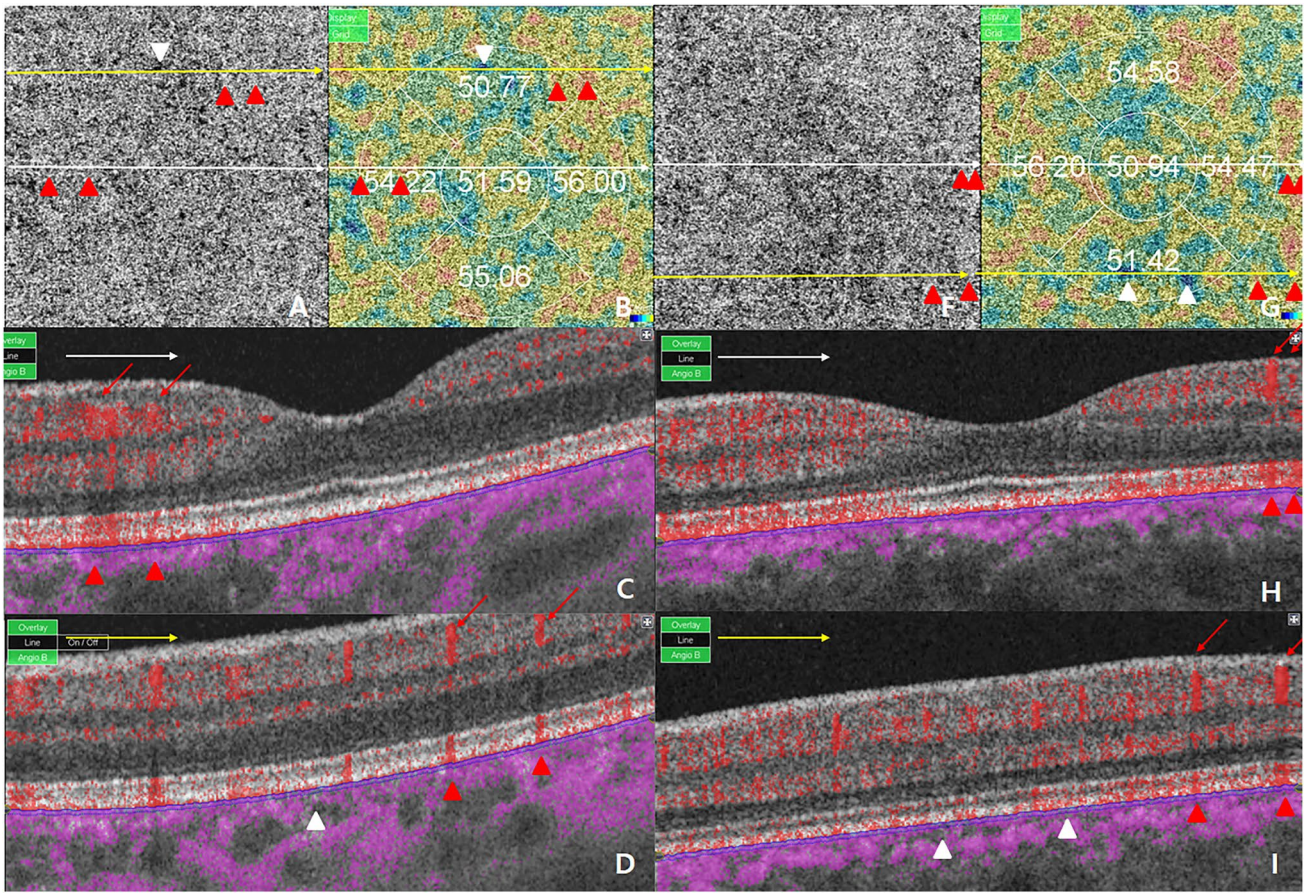


**Fig. 2** Representative choriocapillaris images in two control eyes. The choriocapillaris slab images (**A**, **F**), color-coded choriocapillaris image with modified early treatment diabetic retinopathy study grid (**B**, **G**), and B-scan images with flow overlay in the control eyes (**C**, **D**, **H**, **I**). The choriocapillaris images had a lesser flow void area (white arrowhead) and projection artifact area (red arrowhead) compared with eyes with PPE

**Table 1** Baseline characteristics

| | Eyes with PPE | Control eyes | *P*-value |
|---|---|---|---|
| No. of patients | 83 | 42 | |
| Age, years | 53.3 ± 11.7 | 54.4 ± 9.1 | 0.279* |
| Sex, M:F (%male) | 58:25 (69.9%) | 26:16 (61.9%) | 0.370† |
| BCVA, Log MAR (Snellen) | 0.02 ± 0.04 (20/20.9) | 0.01 ± 0.03 (20/20.6) | 0.388* |
| IOP, mmHg | 15.4 ± 2.9 | 14.7 ± 2.5 | 0.139* |
| Spherical equivalent, diopter | − 0.63 ± 1.5 | − 1.18 ± 3.0 | 0.084* |

*Independent *t*-test; †chi-square test

Values are presented as number (%) or mean ± SD deviation unless otherwise indicated

*BCVA*, best-corrected visual acuity; *IOP*, intraocular pressure; *PPE*, pachychoroid pigment epitheliopathy

To investigate the variability of the choriocapillaris VD, we analyzed the maximum and minimum values among the four parafoveal areas. The choriocapillaris maximum value (56.0% ± 1.7%) was significantly higher in eyes with PPE than in the control group (55.3% ± 1.0%; $P = 0.006$). The choriocapillaris minimum value (50.9% ± 2.0%) was significantly lower in eyes with PPE than in the control group (51.5% ± 1.3%; $P = 0.046$). The choriocapillaris delta value in eyes with PPE (5.0% ± 2.1%) was significantly higher than that in the control group (3.7% ± 1.5%; $P < 0.001$). The OCT and OCTA parameters of the two groups are summarized in Table 2. Two representative

**Table 2** Comparison of retinal and choroidal thickness and choriocapillaris between eyes with pachychoroid pigment epitheliopathy and age-matched normal controls

| | Eyes with PPE | Control eyes | *P*-value* |
|---|---|---|---|
| CPT, μm | 184.4 ± 18.9 | 190.3 ± 21.7 | 0.135 |
| SFChT, μm | 389.9 ± 129.9 | 268.2 ± 102.2 | < 0.001 |
| CC fovea | 51.5 ± 4.0 | 50.6 ± 3.0 | 0.150 |
| CC superior | 53.4 ± 2.4 | 53.3 ± 1.6 | 0.809 |
| CC nasal | 53.7 ± 2.6 | 53.9 ± 1.5 | 0.587 |
| CC inferior | 52.9 ± 2.5 | 53.1 ± 1.8 | 0.721 |
| CC temporal | 54.1 ± 2.4 | 53.5 ± 1.9 | 0.138 |
| CC average | 53.1 ± 1.2 | 52.9 ± 0.8 | 0.185 |
| CC maximum | 56.0 ± 1.7 | 55.3 ± 1.0 | 0.006 |
| CC minimum | 50.9 ± 2.0 | 51.5 ± 1.3 | 0.046 |
| CC delta | 5.0 ± 2.1 | 3.7 ± 1.5 | < 0.001 |

*Independent *t*-test

Values are presented as number (%) or mean ± SD deviation unless otherwise indicated

*CPT*, central point thickness; *SFChT*, subfoveal choroidal thickness; *CC*, choriocapillaris density

CC average = (CC fovea + CC superior + CC nasal + CC inferior + CC temporal)/5

CC maximum = maximum of (CC superior + CC nasal + CC inferior + CC temporal)

CC minimum = minimum of (CC superior + CC nasal + CC inferior + CC temporal)

CC delta = CC maximum − CC minimum

**Table 3** Comparison between subgroups

| | Group A (SFChT ≥ 268μm) | Group B (SFChT < 268μm) | *P*-value |
|---|---|---|---|
| No. of patients | 70 | 13 | |
| Age, years | 51.7 ± 10.3 | 61.7 ± 15.3 | 0.003* |
| Sex (M:F) | 52:18 | 6:7 | 0.199† |
| BCVA, Log MAR | 0.01 ± 0.04 | 0.02 ± 0.04 | 0.298** |
| IOP, mmHg | 15.6 ± 2.8 | 14.3 ± 3.0 | 0.117* |
| Spherical equivalent, D | −0.46 ± 1.33 | −1.50 ± 2.2 | 0.143* |
| SFChT, μm | 422.5 ± 113.3 | 214.1 ± 41.5 | < 0.001* |
| Pachyvessel, μm | 328.4 ± 88.3 | 221.8 ± 52.9 | 0.001* |
| CPT, μm | 183.5 ± 18.2 | 189.4 ± 22.8 | 0.325* |
| CC average, % | 53.19 ± 1.19 | 53.04 ± 1.72 | 0.693* |
| CC maximum, % | 56.12 ± 1.79 | 55.47 ± 1.55 | 0.185* |
| CC minimum, % | 51.01 ± 1.94 | 50.79 ± 2.51 | 0.912* |
| CC delta, % | 5.11 ± 2.19 | 4.67 ± 1.7 | 0.770* |

*Independent *t*-test; **Mann–Whitney test; †Fisher's exact test

Values are presented as number (%) or mean ± SD deviation unless otherwise indicated

*BCVA*, best-corrected visual acuity; *CPT*, central point thickness; *IOP*, intraocular pressure; *PPE*, pachychoroid pigment epitheliopathy; *SFChT*, subfoveal choroidal thickness; *CC*, choriocapillaris density;

CC average = (CC fovea + CC superior + CC nasal + CC inferior + CC temporal)/5

CC maximum = maximum of (CC superior + CC nasal + CC inferior + CC temporal)

CC minimum = minimum of (CC superior + CC nasal + CC inferior + CC temporal)

CC delta = CC maximum − CC minimum

cases of eyes with PPE and control eyes are shown in Figs. 1 and 2, respectively.

We divided the eyes with PPE into two groups according to the mean SFChT value in the control group (268 μm as the cut-off value). The diameter of the pachyvessel (328.4 ± 88.3 μm and 221.8 ± 52.9 μm, $P = 0.001$) and age (51.7 ± 10.3 and 61.7 ± 15.3) were significantly different between the two subgroups. The parameters of the two groups are listed in Table 3.

## Discussion

In this study, we investigated the differences in the choriocapillaris and choroidal thickness between eyes with PPE and age-matched controls. Eyes with PPE showed variability in the choriocapillaris density, and the choriocapillaris slab showed hyperperfusion and hypoperfusion compared with age-matched controls.

To quantitatively analyze the variability in choriocapillaris, we used the built-in software of the modified ETDRS grid. The grid was composed of the following five zones: central subfields of 1-mm diameter and four parafoveal subfields between 1- and 2.5-mm diameter. We analyzed the maximum and minimum values among the four parafoveal subfields and compared the parameters with those of age-matched controls. The eyes with PPE showed a higher maximum value and lower minimum value compared with those of the age-matched controls. The lower minimum value in eyes with PPE reflects the flow impairment of the choriocapillaris.

The control eyes also had flow void areas, as shown in Fig. 2 (white arrowhead), which is consistent with previous findings [14]. However, the eyes with PPE had a greater flow void area than the normal control eyes. This finding is also consistent with the previous studies that showed flow impairment of the choriocapillaris in eyes with pachychoroid disease [8, 15, 16]. Baek et al. described choriocapillaris flow impairments in the early stages of pachychoroid disease [15]. Yun et al. reported that the flow void area was more frequently found in eyes with CSC or PPE than in controls

[8]. Sakurada et al. described a reduced choriocapillaris flow density in the area of choroidal vascular hyperpermeability, observed using ICGA, in eyes with PPE [10]. The choriocapillaris flow deficit tends to increase with aging in normal eyes [17]. The choriocapillaris flow damage has been hypothesized to result from mechanical compression from the underlying pachyvessel in eyes with pachychoroid disease [8, 16]. Thick choroid might cause a choriocapillaris flow void area, assuming focal ischemia or direct barotrauma on the microvasculature of the choriocapillaris-RPE complex [18, 19]. Similarly, in our study, the minimum choriocapillaris density was significantly decreased in eyes with PPE, representing the flow void area.

Another finding was that the eyes with PPE had several flow void areas not only in the area with epitheliopathy (Fig. 1A, B, F, G; blue arrowhead) but also in the areas without epitheliopathy (Fig. 1A, B, F, G; white arrowhead). Although the pathogenesis of pachychoroid disease is associated with pachyvessels, the relationship between epitheliopathy and flow void areas has not been clearly investigated until now. The representative cases suggest that choriocapillaris flow impairment precedes the development of epitheliopathy, despite the lack of longitudinal or quantitative data.

This study also showed a higher maximum value of the choriocapillaris in eyes with PPE than in normal controls. This finding might be associated with hyperperfusion or engorgement of the choriocapillaris in the eyes with PPE. Although the choriocapillaris has highly fenestrated structures, the choriocapillaris around the flow void area may be dilated or hyperpermeable to compensate for the flow impairment. This redistribution would result in increased variability of choriocapillaris densities. A few OCTA studies have reported irregular choriocapillary flow patterns in pachychoroid eyes. Teussink et al. described choriocapillary hypoperfusion with hyperperfusion in the surrounding area in chronic CSC [11]. Seo et al. also reported hyper- and hypo-flow signal and hyperperfusion signals in the choriocapillaris level in eyes with active and resolved CSC [12]. Cakir et al. described increased choriocapillaris OCTA signal in eyes with pachychoroid disease [13]. However, Cakir et al. concluded that areas of increased choriocapillaris signal co-localize with the area of RPE atrophy [13]. The authors have explained the inward displacement of the high-flow deeper choroid layer in the CC slab through thinning and/or atrophy of CC.

Increased choriocapillaris density should be interpreted carefully because it could be affected by the projection or shadowing effects of the overlying retinal vessels. It is important to review B-scan images with flow overlay along with choriocapillaris images in order to check for possible errors [20]. The analysis of flow-overlaid B-scans should be used to evaluate the projection artifacts or segmentation errors [20]. Thus, to confirm whether the hyperperfusion of the choriocapillaris slab reflected true choriocapillaris changes, we analyzed the flow-overlaid B-scans. However, the images showed projection artifacts (red arrowhead) from the superficial capillary plexus (red arrow) at the location where the choriocapillaris scan showed hyperperfusion signals in eyes with PPE (Fig. 1D, H, I) as well as in normal control eyes (Fig. 2C, D, H, I). It is not clear why the eyes with PPE have more projection artifacts than the normal control eyes. Considering that the choriocapillaris slab of the segmentation algorithm ranges from the BM of the RPE to 10.4 μm below the BM, we believe that the increased reflectivity of the RPE layer in eyes with PPE may contribute to more prominent projection artifacts than in normal controls [20, 21]. In part, the increased choriocapillaris density might reflect the real redistribution of choriocapillaris or segmentation errors associated with RPE and CC atrophy might lead to hyperperfusion signals [13]. Further studies using detailed flow-overlaid B-scan images are required to address this issue clearly.

Additionally, we hypothesized that eyes with thicker choroid and pachyvessels have more choriocapillaris flow deficit areas. Thus, we further divided the eyes into two subgroups according to the SFChT of the control eyes (268 μm). In the larger SFChT group, pachyvessel diameter (328.4 ± 88.3 μm) was significantly larger, as expected, than that of the smaller SFChT group (221.8 ± 52.9 μm), but no significant difference was found in any choriocapillaris indices. Although a thicker choroid and pachyvessel might affect the choriocapillaris flow pattern and lead to pigment epitheliopathy, we believe that other factors also contribute to the pathologic status. Further studies on these findings should be conducted.

This study had several limitations. First, this was a retrospective cross-sectional study. Thus, this study could not show the cause-and-effect relationships of the pathogenesis, as well as the percentage of eyes progressing to CSC. Although we suggest that the flow void area precedes the development of PPE, a longitudinal study with a large sample size is required to explain this relationship. Moreover, the eyes with PPE were not followed-up regularly because the patients were followed-up for the subretinal fluid in eyes with CSC. Less than 30% eyes (21 eyes) with PPE had a follow-up examination after 3 years. Among them, subretinal fluid developed in 3 eyes during the 3 years. However, we could not conclude that 14.2% (3/21 eyes) was the progression rate. Second, we analyzed only the 3 × 3 mm foveal zone. A recent imaging protocol provided a wider scan area. Thus, investigations of larger scan areas will help understand the relationship between PPE and the choroid. Third, choriocapillaris images could

be distorted by various artifacts; media opacities, motion artifacts, and blink artifacts could result in less clear images [22]. We included only choriocapillaris images with a quality better than 60% (ranging from 0 to 100%) to minimize confounding artifacts. Furthermore, we manually adjusted the choriocapillaris images in case of segmentation errors. Finally, we used contralateral eyes with unilateral ERM as a control group. This cannot be called a pure control group. However, we required age-matched control eyes without any ocular and systemic commodities as a control group. Therefore, we believe that the chosen eyes could be used as control.

In conclusion, eyes with PPE have choriocapillaris flow abnormalities, including hyperperfusion and hypoperfusion. Choriocapillaris flow impairment may precede the development of PPE and hyperperfusion of the choriocapillaris may be associated with projection artifacts.

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## Declarations

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the Chung-Ang University Hospital, Seoul, South Korea, and with the 1964 Helsinki declaration.

**Informed consent** The need for informed consent was waived owing to the retrospective study design.

**Conflict of interest** The authors declare no competing interests.

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