

Changes in Retinal and Choroidal Vasculature in Eyes with Acute Central Serous Chorioretinopathy Using Optical Coherence Tomography Angiography

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Research article

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Abstract

Background To compare the vascular changes of superficial capillary layer (SCP) and deep capillary layer (DCP) in retina and choriocapillary layer in eyes with acute central serous chorioretinopathy (CSC) by optical coherence tomography angiography (OCTA) between at baseline and 3 months. **Methods** Prospective case series; Twelve patients (12 eyes) with acute CSC at the baseline and 3 months were included. All patients underwent comprehensive ophthalmic examinations. Subfoveal choroidal thickness (SFCT) and central macular thickness (CMT) were evaluated by spectral domain optical coherence tomography (SD-OCT). The foveal avascular zone (FAZ), the microvascular morphology and density of SCP and DCP, and the choriocapillary morphology were assessed by OCTA or Image J software. All data in this study were presented as mean and standard deviations (SD) **Results** The mean \pm SD CMT ($p=0.018$), the mean \pm SD SFCT ($p=0.013$), the mean \pm SD microvascular density of DCP ($p\leq 0.001$) and choriocapillary layer ($p\leq 0.001$) at baseline were different from the ones at 3 months. The density of DCP was increased and choriocapillaris flow signal void was recovered at 3 months in the process of self-resolve. Two eyes exhibited vascularized flat pigment epithelial detachment (FIPED) by OCTA. The en-face OCT can illustrate the area of the elongation of ellipsoid zone (EZ). **Conclusions** OCTA enables the visualization of microvascular features of the DCP and choriocapillary in eyes with acute CSC in the process of self-resolve to help elucidate the pathophysiology. Vascularized FIPED could be obtained in acute CSC eyes by OCTA. OCTA imaging seems to be a useful tool in the identification of acute CSC.

Background

Acute central serous chorioretinopathy (CSC) is a chorioretinopathy disorder characterized by limited serous detachments of the neurosensory retina and usually combined with focal pigment epithelial detachments (PED) on account of choroidal hyperpermeability, dilated choroidal vessels and retinal pigment epithelial (RPE) barrier breakdown.¹ Color photograph presents oval lesions in the macula.² Spectral domain optical coherence tomography (SD-OCT) is the primary imaging modality for the diagnosis of CSC;³ Enhanced-depth imaging (EDI) have supplied full-depth visualization of the choroid, enhancing the morphological analysis of the vessels in choriocapillary, Sattler's and Haller's layers.³ Fundus autofluorescence (FAF) could reflect RPE functions and allow a detection of alterations at different phases and types of CSC.^{4,5} Fluorescein fundus angiography (FFA) indicates the origin of leakage of acute CSC.⁶ In spite of not compulsiveness for the diagnosis of CSC, but FFA is helpful to confirm the diagnosis and provides a guide for possible photodynamic therapy.⁷ Indocyanine green angiography (ICGA) has become the gold standard of the visualization of the choroidal vasculature and CNV complicating CSC.⁸ However, FFA and ICG were not only both invasive examinations and a spectrum of contraindication, but also not suitable for observation of microvascular changes of retina and choriocapillary during follow-up time.

Optical coherence tomography angiography (OCTA) is a new- noninvasive imaging modality that allows the visualization of blood flow of retina and choriocapillary, applying to evaluate retinal vascular disease.⁹⁻

¹¹ Signal strength is positively correlated with blood perfusion.¹² Recently, several studies applied OCTA to assess the presence of CNV in CSC patients with variable and noncomparable results.^{13,14} However, less research focus on the microvascular changes of retina and choriocapillary in eyes with acute CSC.¹⁵ Because serous retinal detachments resolve spontaneously within three months in most acute CSC episodes,¹ the ideal timing for interventions still remains to be determined. Moreover, it can further supply more morphological informations for exploring the mechanisms of acute CSC.

On account of the previous research about the structure changes of retina and choroid by OCT, the aim of our study is to further explore the microvascular changes of retina and choriocapillary in eyes with acute CSC by OCTA during the process of self-resolve.

Methods

This was a prospective case series study. 12 consecutive patients with acute CSC were enrolled from September 2016 to December 2017 at the outpatient clinic of the Eye & ENT Hospital of Fudan University, Shanghai, China. Informed consent was obtained from all patients. All procedures were performed according to the principles of the Declaration of Helsinki.

Comprehensive ocular examinations were performed for all patients in both eyes, involving slit-lamp biomicroscopic ophthalmoscopic, best-corrected visual acuity (BCVA), dilated funduscopy, fundus photography (Topcon TRC50LX; Topcon, Tokyo, Japan), intraocular pressure (IOP), SD-OCT (Heidelberg Engineering, Heidelberg, Germany) and OCTA (Optovue RTVue XR 100 Avanti, Fremont, CA, USA). All patients in this study were included without any ocular treatment previously.

Acute CSC was defined by the presence of serous retinal detachment within 3 months. The clinical criteria for diagnosing acute CSC were confirmed by OCT and OCTA, including the following: (1) the onset of visual symptoms (vision impairment, metamorphopsia, micropsia, dyschromatopsia or central scotoma) within 3 months, (2) the contralateral eyes without any anterior and posterior disorders, (3) SD-OCT detection of serous retinal detachment involving the fovea, increased choroidal thickness and dilated choroidal vessels, (4) OCTA detection of focal high-intensity lesions indicating abnormal choroidal vessels and flow void lesion at the choriocapillaris layer and (5) The signal strength index of all images by OCTA was greater than 60 without disordered layers.(6) the symptom improved and subretinal fluid resolved at 3 months. Exclusion criteria were patients with spherical error superior to 2D, bilateral CSC, amblyopia or anisometropia, cataracts, combined with history of other ophthalmic diseases and ocular trauma, the history of laser and surgery and drug therapy, and corticosteroid and sildenafil therapy that could affect ocular circulation. The follow-up scheme for this observational study included repeated monthly clinical evaluation for 3 months.

A 6-mm-line vertical and horizon scans across the center of fovea and a 19-line scan covered (5.8×4.3 mm) area on the fevea were obtained by SD-OCT. The CMT was measured using Spectralis software.¹⁶ The subfoveal choroidal thickness (SFCT) was measured using enhanced-depth imaging scans as the

axial distance from the RPE to the sclera interface. All images were obtained by two independent well-trained operators.

Observers assessed the OCTA data using the best-quality 3 × 3-mm scan and controlled the corrected segmentation for the 12 patients before reporting the data. Vascular retinal layers were divided into the SCP, DCP, outer retina and choriocapillary layers (CC) by OCTA. The FAZ and vascular density of the macula were assessed using flow density map software Angio-Analytics (Optovue RTVue XR 100 Avanti). The RTVue XR with 70,000 A-scans per second and a split-spectrum amplitude decorrelation algorithm can produce 3-dimensional microvascular volume maps. Whole-image data were used to measure the microvascular densities in the SCP and DCP layers. The density of choriocapillary was assessed by Image J software.

Statistical Analysis

Visual acuity were incorporation into logarithm of the minimum angle of resolution (logMAR) for statistical analysis. Quantitative data (mean BCVA, CMT, vascular density of SCP, DCP and choriocapillary layer, FAZ areas of the SCP) were compared between at baseline and 3 months by the Mann–Whitney test using IBM SPSS Statistics 19.0 (SPSS Inc., Chicago, IL, USA). Significance was defined as $P < 0.05$. All data were presented as mean and standard deviations.

Results

A total of 12 eyes in 12 patients (8 men and 4 women) were included in the study. The demographic characteristics of the patients are listed in Table 1. The mean \pm SD age were 45.50 ± 9.69 years (range, 25–63 years). The BCVA values (mean \pm SD) in the eyes with acute CSC at baseline (logMAR) were (0.27 ± 0.23) (range, 20/25 to 20/100), and at 3 months (0.08 ± 0.15) (range, 20/20 to 20/50), respectively ($p=0.03$). The CMT values (mean \pm SD) in the eyes with acute CSC at baseline and 3 months were (420.33 ± 123.43) μm , (296.42 ± 114.01) μm ($p=0.018$), respectively (Table 1). The SFCT values (mean \pm SD) in the eyes with acute CSC at baseline and 3 months were (376.42 ± 72.66) μm , (280.08 ± 100.61) μm ($p=0.013$).

The FAZ areas of the SCP were (0.33 ± 0.11) mm^2 at baseline and (0.32 ± 0.92) mm^2 at 3 months ($p=0.915$) in acute CSC eyes using OCTA software. The mean vessel density value of SCP, DCP and CC in acute CSC eyes (shown in Table 2) and fellow eyes (shown in Table 2) were evaluated by OCTA and Image J software respectively. The morphology of SCP, DCP and CC was presented by OCTA, comparing the microvascular changes, and the extent and range of angiectasis at baseline and 3 months. (shown in Figure 1) The range of subretinal fluid and the areas of the elongation of photoreceptor outer segment were evaluated by en-face imaging. (shown in Figure 2). Two eyes exhibited vascularized flat PED by OCTA, demonstrating the formation of vascular between RPE and Bruch's membrane. (shown in Figure 3)

The microvascular density of DCP corresponding to the high signal in the CC layer was recovered at 3 months. (shown in Figure 4)

Discussion

In acute CSC, OCTA could be a potentially useful imaging modality for providing a real-time direct visualization of the blood flow in the SCP, DCP and CC in the process of self-resolve, contributing to provide theoretical basis for the mechanism of acute CSC. In a previous study, based on dye angiography combined with SD-OCT, we were only able to identify subretinal fluid and leakage of RPE. However, in the present study, OCTA can enhance to detect the microvascular morphology and density of SCP, DCP and CC at baseline and 3 months. Although the key mechanisms of acute CSC are choroidal hyperpermeability and congestion, the choroidal circulation is not only for the choroid, but also for the RPE and as far as the lateral part of the retinal inner layer (ie, the deep capillary region).^{17,18} Birol et al. confirmed in an animal model that the deep capillary bed is conducive to the oxygen requirements of the photoreceptor layer.¹⁸ In their study, the primary oxygen supply to photoreceptor layers was derived from the choroidal circulation, but 10%–15% was derived from the retinal circulation.¹⁹ As oxygenation of the fovea is somewhat different from that of the perifoveal retina, it would be useful to discuss this and any other potentially relevant correlations regarding the foveal and perifoveal areas.¹⁸ From these results, the microvascular changes of DCP and choriocapillary could contribute to prognosis for acute CSC patients. In our study, the density of DCP and choriocapillary increased at 3 months, which proved the recovery of acute CSC.

Chan et al²⁰ retrospectively reported 12 CSC eyes with foci high signal in choriocapillary layer by OCTA, demonstrating the dilated choriocapillary. It is concluded that OCTA can be used as an auxiliary tool to diagnose CSCR. In contrast, we observed changes of the choriocapillary dilatation during the recovery of acute CSC patients, which was the increasing density of CC at three months compared with the ones at baseline. Although the subretinal fluid was completely absorbed detected by OCT, choriocapillary with high signal can still be remained by OCTA. This phenomenon, related stimuli, such as smoking, alcoholism, staying up late and so on, explains why many patients with acute CSC are prone to recurrence. Therefore, with the advantage of OCTA in the follow-up process, it is possible to extend the follow-up treatment time after the complete recovery of choriocapillaries, which indicates that OCTA provides an effective reference for clinical follow-up treatment. Teussink et al²¹ compared 18 patients with chronic CSC with 6 normal controls who underwent FFA, ICGA and OCTA, illustrating the same presentation of choriocapillary by OCTA as the ones by ICGA. Referred to the aboved research, the main diagnosis were: less than 3 months of onset, subretinal fluid accumulation by OCT, and squamous high signal in choriocapillary layer presented by OCTA in our study.

The changes of microvascular density in different layers are diverse not only among various retinal diseases, but also the progress or efficacy of disease.²²⁻²⁵ For example, the extend of photoreceptor damage is related to the blood flow density of DCP in diabetic retinopathy.^{24,25} Moreover, Battaglia et al

showed reduced microvascular density of SCP and the increased density of DCP in adult-onset foveomacular vitelliform dystrophy.²³ At present, rare study is focus on the microvascular density in SCP, DCP and CC in acute CSC episodes without treatment. Nelis et al²⁶ compared 16 eyes with acute CSC with contralateral eyes and normal eye, resulting in the much more density of SCP and much smaller of FAZ in eyes with acute CSC than the contralateral and normal eyes. However, the higher density of DCP in 12 eyes with acute CSC at 3 months compared with eyes at initial visit, but no significant difference in density and FAZ of SCP between at baseline and at 3months. At the same time, in spite of completely absorption of subretinal fluid, the photoreceptor layer need longer time to recovery. We could identify the elongation of EZ by en -face imaging, which is related with the visual acuity.

Elevation of RPE by OCT was found in 19-68% in acute CSC patients,³ but few studies focus on the vascular changes caused by flat PED in eyes with acute CSC. In our study, two eyes with acute CSC exhibited vascularized flat PED by OCTA demonstrated the formation of vascular between RPE and Bruch' membrane.

Several improvements are needed: the larger sample size; OCTA underwent contemporaneously with FFA/ICGA in order to determine more accurately the relative sensitivities of each of these modalities; Longitudinal studies are needed to describe the microvascular changes of retina and choroid.

Conclusions

OCTA can be used as an important aid in the diagnosis and follow-up of acute CSC. Through observation during self-resolved period, the increasing microvascular density of DCP and CC in patients with acute CSC was showed after subretinal fluid improved or resolved. The elongation of EZ can be initially determined by en-face OCT , which is helpful for providing a good basis for visual observation during follow-up.

Abbreviations

BCVA: best-corrected visual acuity; CC: choroicapillary layers; CSCR: central serous chorioretinopathy; DCP: deep capillary layer; EDI: enhanced-depth imaging; FAF: fundus autofluorescence; FFA: fluorescein fundus angiography; ICGA: indocyanine green angiography; OCTA: optical coherence tomography angiography; PED: pigment epithelial detachments; RPE:retinal pigment epithelial; SCP: superficial capillary layer; SD-OCT: swept domain optical coherence tomography; SFCT: subfoveal choroidal thickness;

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of the Eye and ENT Hospital of Fudan University, Shanghai, China. All procedures were approved by the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants or their guardians

Availability of data and materials

Transcripts from this study are available for sharing upon request; however, all identifying and confidential information of the participants will be removed.

Consent for publication

Not Applicable

Competing interests

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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Author contributions

JLG: data analysis and manuscript preparation; XYD: analysis and interpretation of data; HXW: concept and design, data acquisition, critical revision for important intellectual content; GZX: concept and design, critical revision for important intellectual content; YJZ: concept and design.

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Tables

Table 1 Demographics and Clinical Data of Patients with acute CSC at baseline

Case	Sex	BCVA	Eye	Age, Ranges	Time onset, days	FIPED
1	M	20/25	OD	41-50	7	(-)
2	M	20/80	OD	51-60	36	(-)
3	M	20/25	OS	41-50	14	(-)
4	F	20/25	OD	31-40	6	(-)
5	F	20/32	OS	61-60	16	(-)
6	M	20/25	OD	41-50	10	(-)
7	F	20/125	OD	51-60	30	(-)
8	F	20/32	OS	51-60	14	(-)
9	M	20/25	OD	31-40	5	(+)
10	M	20/32	OS	41-50	30	(+)
11	M	20/40	OS	21-30	15	(-)
12	M	20/50	OD	31-40	30	(-)

BCVA: best-corrected visual acuity; FIPED: flat irregular pigment epithelial detachment;

Time: Time from symptoms onset to first visit

Table 2 OCT and OCTA-derived characteristics of patients with acute CSC at baseline and 3 months

		At baseline	At 3 months	<i>p</i> value
CMT	μm	420.33±123.43	296.42±114.01	0.018
SFCT	μm	376.42±72.66	280.08±100.61	0.013
SCP	FAZ(mm2)	0.33±0.11	0.32±0.92	0.915
	Density(%)	49.15±2.54	49.87±2.01	0.450
DCP	Density(%)	53.31±2.58	56.68±1.47	0.001
SCP'	Density(%)	0.37±0.09	0.38±0.04	0.560
DCP'	Density(%)	0.38±0.03	0.43±0.01	0.001
CC'	Density(%)	0.33±0.05	0.47±0.04	0.001

CC: choriocapillary layer; CMT: central macular thickness; CSC: central serous chorioretinopathy; DCP: deep capillary layer; OCT: optical coherence tomography; OCTA: optical coherence tomography angiography; SCP: superficial capillary layer; SFCT: subfoveal choroidal thickness; SCP, DCP and CC presented the density measured by OCTA software; SCP', DCP' and CC' showed the density measured by Image J software.

Table 3 OCTA-derived characteristics of fellow eyes with acute CSC at baseline and 3 months

		At baseline	At 3 months	<i>p</i> value
SCP	Density(%)	50.13±1.92	50.87±2.01	0.892
DCP	Density(%)	53.31±2.23	53.89±2.32	0.951
CC'	Density(%)	0.45±0.04	0.46±0.05	0.942

CC: choriocapillary layer; CSC: central serous chorioretinopathy; DCP: deep capillary layer; SCP: superficial capillary layer;

Figures

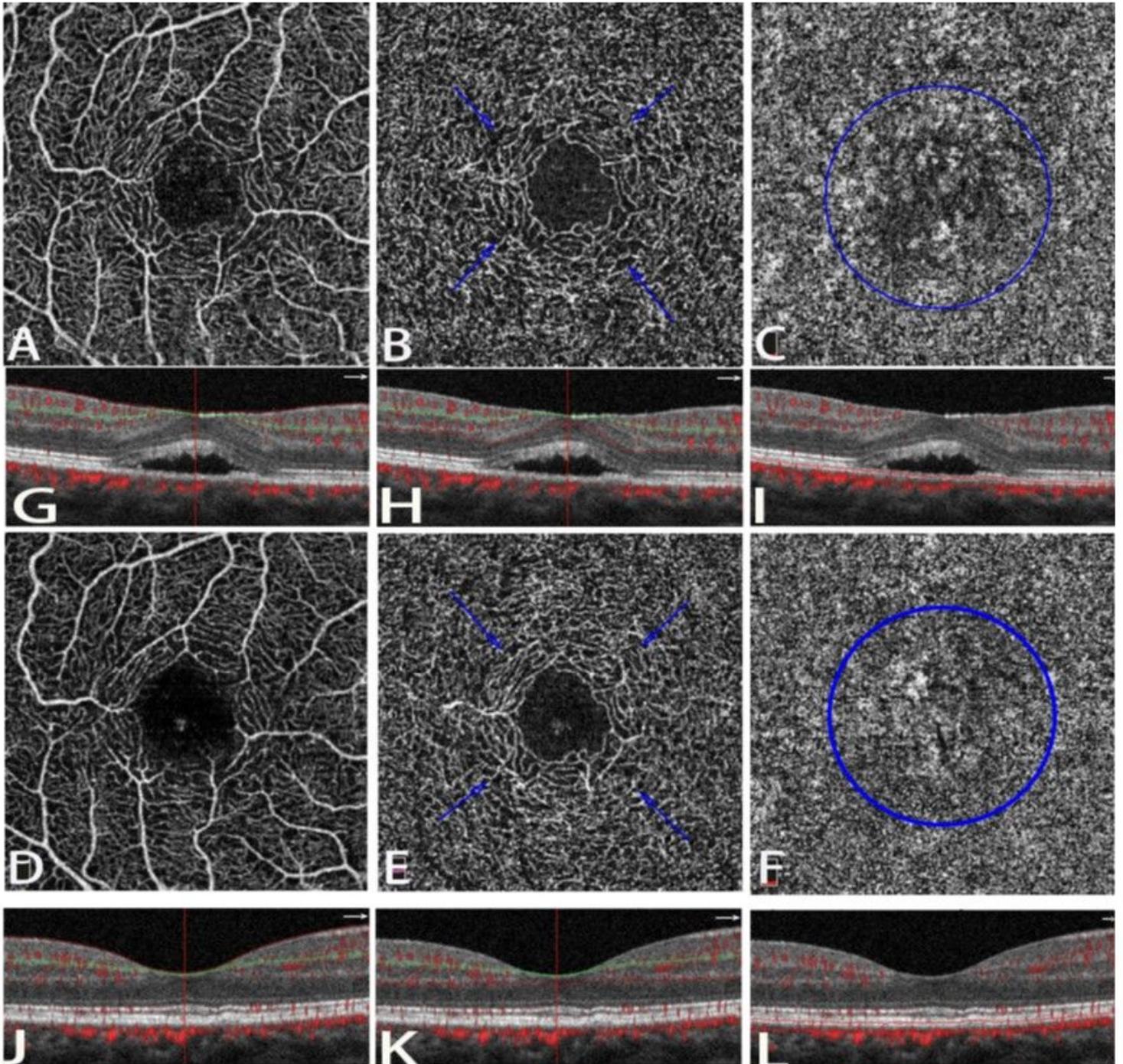


Figure 1

The manifestation of microvascular in superficial capillary layer (SCP), deep capillary layer (DCP) and choriocapillary layer (CC) layer at baseline and 3 months. (A): the morphology of SCP at baseline, corresponding to the structure of OCT (G); (B): the morphology of DCP at baseline,, corresponding to the structure of OCT (H); (C): the morphology of CC at baseline, corresponding to the structure of OCT (I); (D): the morphology of SCP at 3months, corresponding to the structure of OCT (J); (E): the morphology of DCP at 3 months,, corresponding to the structure of OCT (K); (F): the morphology of CC at 3 months, corresponding to the structure of OCT (L); (Blue arrow)the microvascular density of DCP layer at 3

months (E) were increased compared with the one at baseline (B). (Blue circle) the density of CC layer were increased at 3 months compared with the one at baseline.

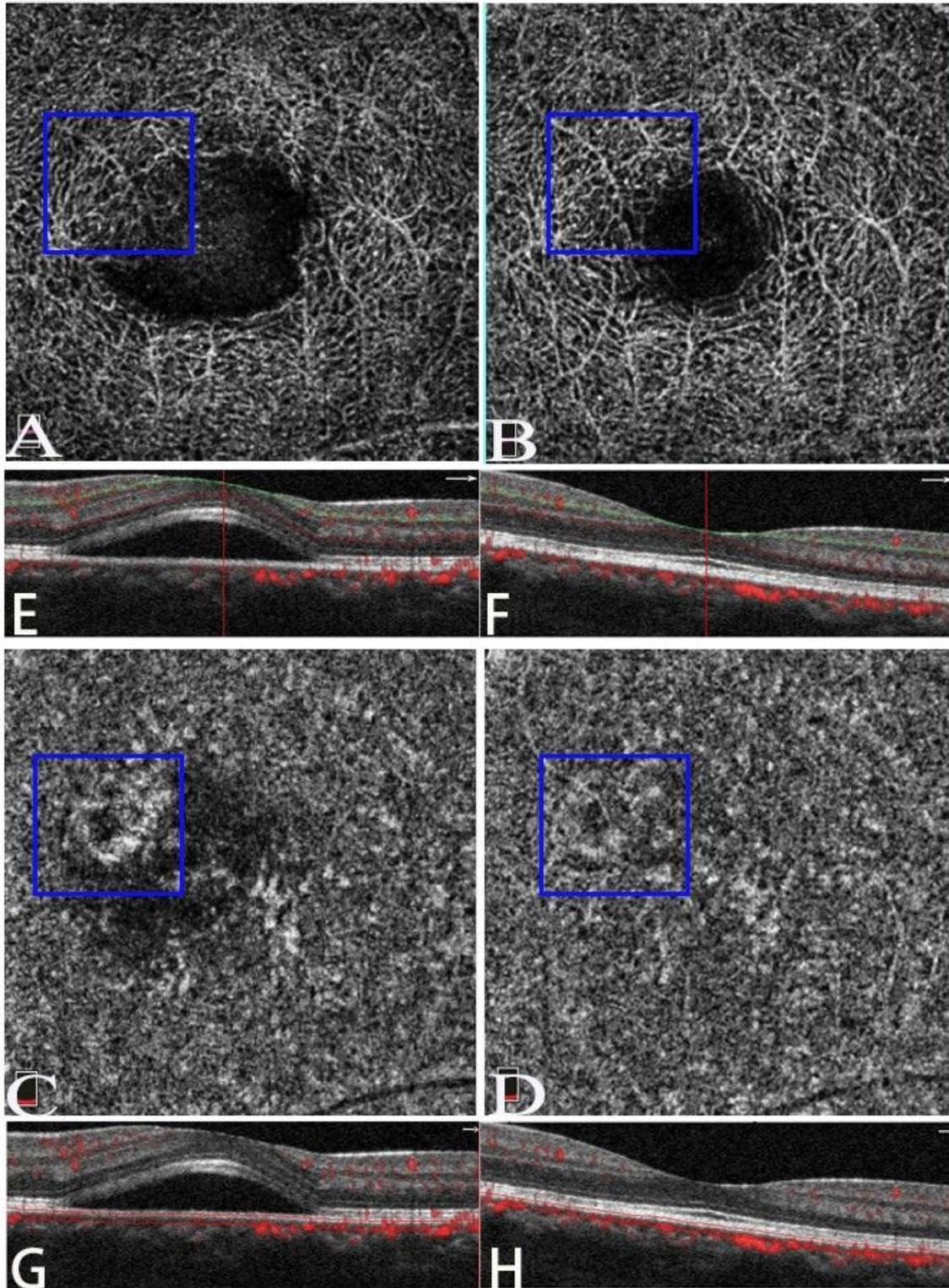


Figure 2

En-face OCT imaging of outer layer in a man at the age of thirty-six by the model of 3mm×3mm OCTA. A and B showed the en-face of outer layer at baseline and at 3 months. C and D showed the structure of OCT from OCTA at the first of follow-up time and at three months. A stands for the range of

photoreceptor disruption in blue circle corresponding the range of fluid accumulation at the picture of C. The range of photoreceptor disruption at picture A was larger than the one of it at picture C.

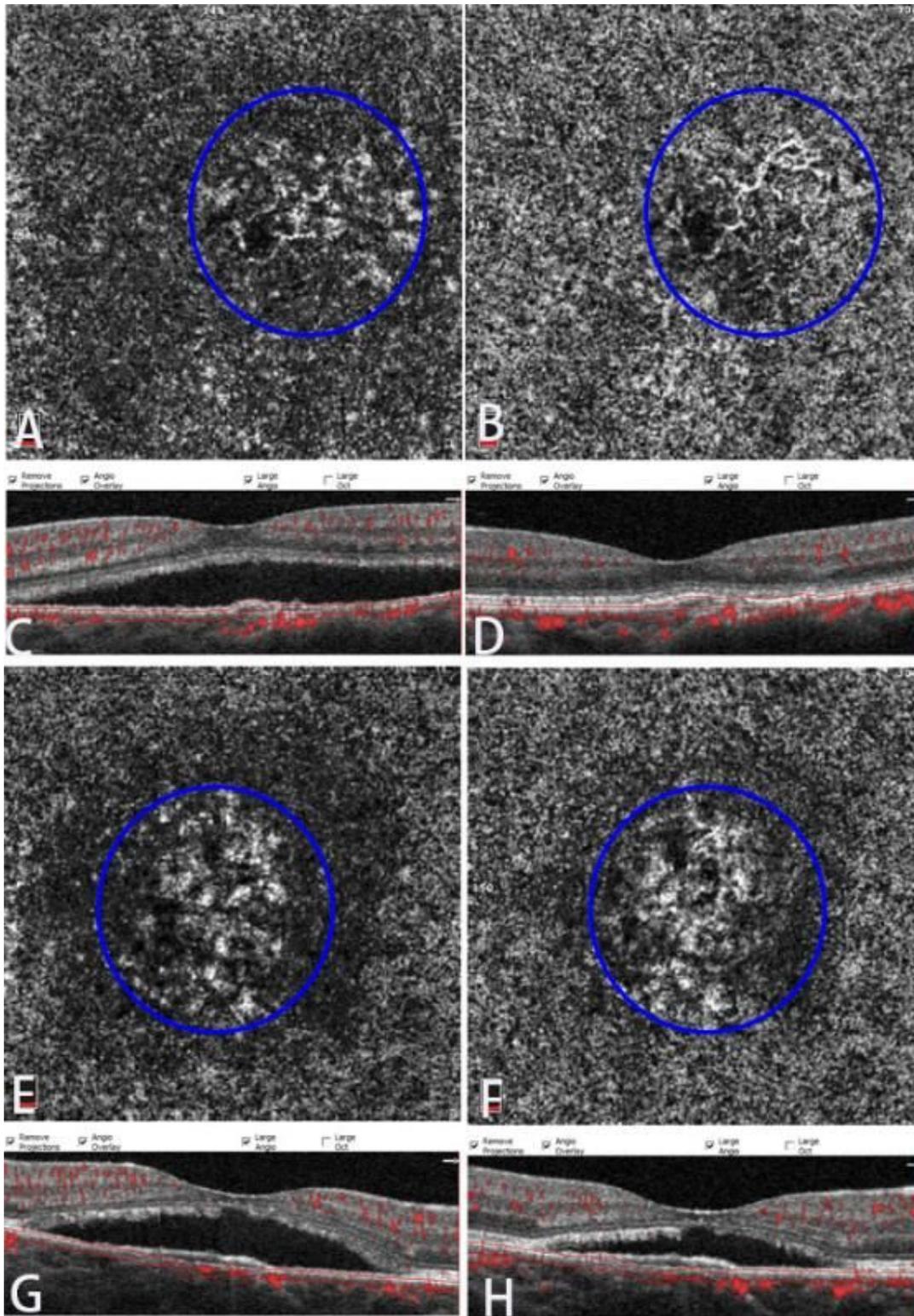


Figure 3

OCT and OCTA imaging of flat PED in 2 females by the model of 3mm×3mm OCTA. A and E presented locally high signal and peripheral low signal of choriocapillary layer at baseline. B showed remodeling

choroidal neovascularization at 3 months. F manifested much high signal and less low signal at 3 month than at baseline.

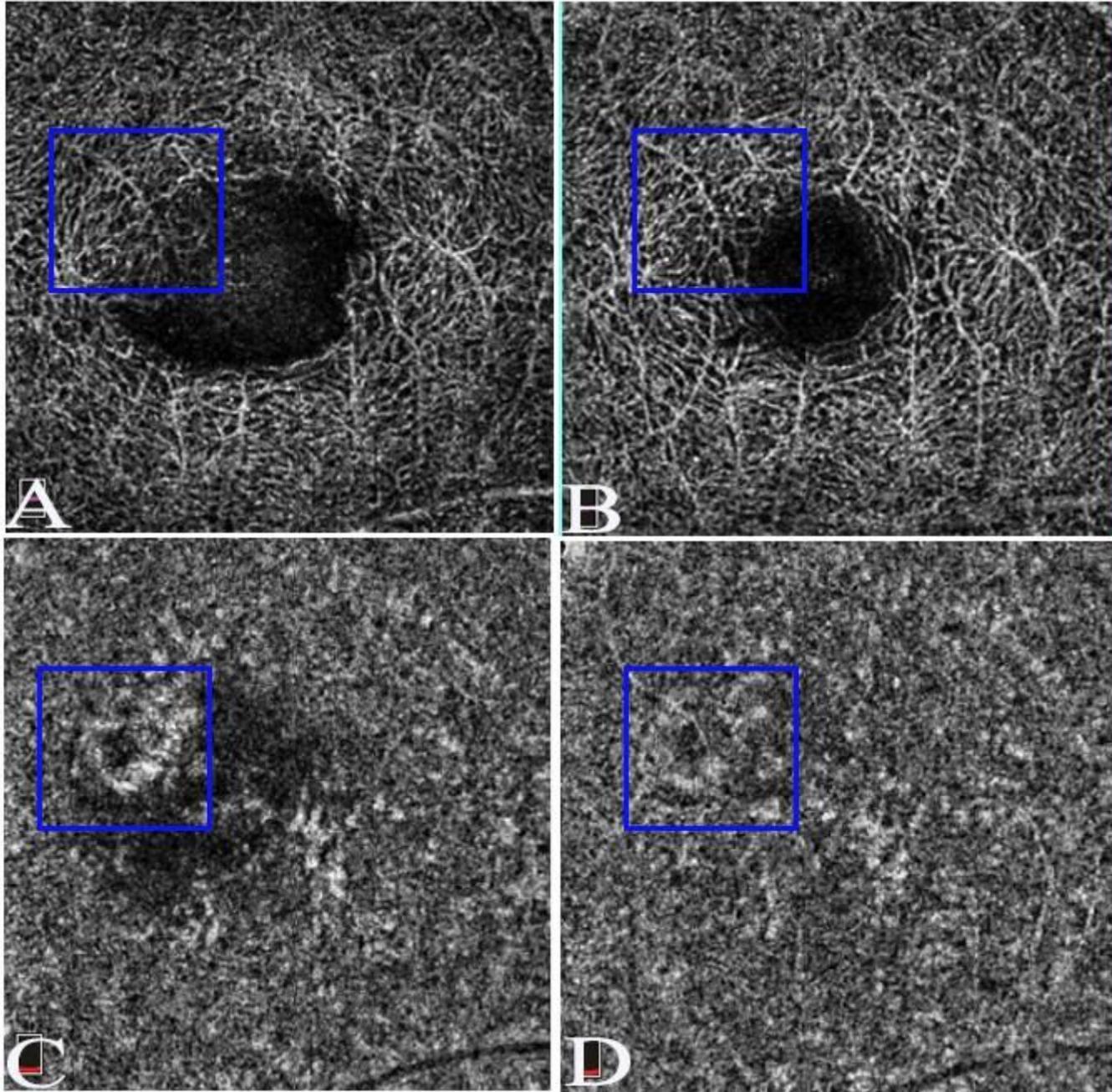


Figure 4

The vascular morphology of deep layer and choroidal capillary layer in a man at the age of thirty. A and B showed the vascular density of DCP at baseline and at three months, respectively. C and D showed correspondingly angiectasis in choroidal capillary layer at baseline and at three months, respectively. The increased density of deep layer at three months(B) compared with the one of DCP at baseline(A) indicated the recovery of choroidal capillary layer(D) compared with the angiectasis at choroidal capillary layer(C) correspondingly. The corresponding structure of OCT(E,F,G and H) was shown in every SCP and CC layer. The region of blue circle stands for the similar position.