• Clinical Research •

Improved thickness measurement method for choroidal hyperpermeability in central serous chorioretinopathy

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Received: 2019-11-21 Accepted: 2020-05-08

Abstract

● **AIM:** To observe choroidal thickness changes in the choroidal hyperpermeability area (CHA) in patients with central serous chorioretinopathy (CSC) after photodynamic therapy (PDT) using indocyanine green angiography (ICGA) combined with optical coherence tomography (OCT).

● **METHODS:** This was a cohort study of 17 eyes (17 patients) with CSC. In all patients, the range of CHA was determined by ICGA. The patients were divided into two groups based on CHA covered the fovea (group A) or not (group B). All patients received half-dose verteporfin PDT over CHA in ICGA. Choroidal thickness was measured by OCT before, 1, and 3mo after treatment. The choroidal thickness values of the fovea and CHAs were obtained for each measurement. Secondary outcomes were changes in the best-corrected visual acuity (BCVA) and amount of subretinal fluid (SRF).

● **RESULTS:** The differences in center choroidal thickness at baseline and at 1 and 3mo post-PDT were statistically significant in group A and all patients (both $P<0.001$). There was no significant difference in group B ($P=0.059$). The differences of thickness of CHA and BCVA at baseline and 1 and 3mo post-PDT were statistically significant in group A, group B, and all patients (all $P<0.01$). All patients showed complete SRF absorption at 3mo post-PDT.

● **CONCLUSION:** Center choroidal thickness does not accurately reflect changes in CHA of patients whose CHA does not covered the fovea center. Using CHA as the observation target can make up for this limitation, expand the scope of application, and reduce bias.

● **KEYWORDS:** central serous chorioretinopathy; choroidal hyperpermeability; choroidal thickness; indocyanine green angiography; optical coherence tomography
DOI:10.18240/ijo.2020.09.10

Citation: Chen XW, Han FY, Su G, Pan L, Cai SJ. Improved thickness measurement method for choroidal hyperpermeability in central serous chorioretinopathy. *Int J Ophthalmol* 2020;13(9):1397-1403

INTRODUCTION

Central serous chorioretinopathy (CSC) is a disease characterized by retinal subepithelial effusion at the posterior pole. Destruction of the retinal pigment epithelium (RPE) results in focal leakage and neuroretinal serous detachment[1]. This condition often occurs in young males. Risk factors for CSC include corticosteroid use, psychological stress during pregnancy, type A personality, and smoking[2-3]. Indocyanine green angiography (ICGA) revealed high choroidal vascular permeability in CSC patients. Optical coherence tomography (OCT) showed increased choroidal thickness in the eyes of CSC patients[4]. Therefore, choroidal circulation dysfunction is related to CSC. Most patients recover spontaneously within 3-4mo. However, persistent or recurrent subretinal effusion occurs in approximately half of the patients, resulting in irreversible vision loss[5]. In these patients, RPE cells and photoreceptor cells are chronically exposed to serum, which can damage cell structure and function, resulting in irreversible vision loss[6].

CSC is thought to be related to choroidal telangiectasia and high choroidal blood perfusion. OCT revealed choroidal thickness in patients with CSC. Half-dose verteporfin photodynamic therapy (PDT) has been used as a new method to treat CSC. The mechanism of PDT in CSC may be PDT-induced choroidal capillary occlusion followed by choroidal vascular remodeling to reduce permeability and leakage[7]. PDT has been used to treat chronic CSC and CSC with subfoveal or parafoveal leaks, and it could reduce subretinal effusion and improve visual sensitivity[8-9]. Most studies monitored macular choroidal thickness in CSC patients

who received PDT[10-18]. All these studies take the subfoveal choroidal thickness (SFCT) as the observation indicator. SFCT was defined as the distance between the outer portion of the RPE and the inner surface of the sclera at the subfoveal. The observation point of SFCT is relatively fixed and easy to measure, but the locations of choroidal hyperpermeability and PDT are not fixed. In a previous cohort study, we retrospectively analyzed the relationship between macular and choroidal hyperpermeability location in 48 eyes of 48 patients. The choroidal hyperpermeability area (CHA) covered part of the fovea in 28 (58.33%) eyes and covered the center of the fovea in 16 (33.33%) eyes. The average distance between the leakage point and fovea center was 1.295±0.94 mm, of which 15 (31.25%) eyes were less than 0.75 mm. The fovea center was covered by CHA in 11 (73.33%) of these 15 eyes. In one eye, the CHA completely covered the fovea. Therefore, macular choroidal thickness measurement cannot fully reflect the CHA in all patients. There is also inevitable bias in the case collection or data measurement process. To avoid this situation, we designed a method to accurately measure the thickness of the CHA through ICGA and OCT. First, ICGA was used to determine the relationship between the hyperpermeability area and the fovea. Then, the center of choroidal hyperperfusion area was scanned accurately and repeatedly on OCT, to measure its choroidal thickness. In this study, we used the above method to focuses on the CHA, which may more intuitively and accurately reflect the therapeutic effect of PDT on the CHA in CSC patients and clarify the relationship between choroidal hyperpermeability and visual acuity.

SUBJECTS AND METHODS

Ethical Approval Written informed consent for study participation was obtained from all patients. This study adhered to the tenets of the Declaration of Helsinki.

Case Collection This was a prospective, exploratory study conducted in the Department of Ophthalmology at the Affiliated Hospital of Zunyi Medical University, Zunyi, China. Patients with acute CSC with a leakage point at the fovea or chronic CSC were recruited from November 2016 to November 2017.

The inclusion criteria were 1) diagnosis of CSC; 2) age ≥18y; 3) best-corrected visual acuity (BCVA) of 1.30 (logMAR) or better; 4) refractive status between -6 and +6 diopters; 5) no previous ocular surgery other than uncomplicated cataract extraction and intraocular lens implantation; 6) no previous CSC therapy. Diagnosis of CSC was established on the basis of the following criteria: 1) subretinal fluid (SRF) and/or pigment epithelium detachment (PED) within the macular area; 2) idiopathic leakage from the RPE during fundus fluorescein angiography (FFA)/ICGA; 3) exclusion of other possible causes of SRF/PED. The exclusion criteria were: 1) history of previous PDT, focal thermal laser photocoagulation or other interventional treatment for CSC; 2) presence of choroidal neovascularization; 3) evidence of polypoidal choroidal vasculopathy, angioid streak, pathological myopia, or other macular degenerative disease; 4) history of other macular abnormalities related to diabetic retinopathy, retinal vein occlusion, uveitis, or other retinal diseases; 5) history of intraocular surgery or intravitreal injection of anti-vascular endothelial growth factor drugs; 6) history of systemic corticosteroid usage within 3mo before clinical symptom onset; or 7) systemic contraindication for PDT.

Routine Examinations of Eyes All patients were tested with the international standard vision chart at a distance of 5 meters and the same brightness. Optometry was performed before each visual acuity test. BCVA was converted to the logMAR for calculation purposes. After pupillary dilation with 0.5% tropicamide, the anterior segment and fundus were detected using the slit-lamp ophthalmoscope.

Indocyanine Green Angiography/Fundus Fluorescein Angiography The allergic history, cardiovascular and cerebrovascular disease history and liver and kidney disease history were asked in detail. Patients were informed of relevant matters to the radiography and signed the informed consent. Skin allergy test: the diluted fluorescein sodium and indocyanine green were subcutaneously injected, and the skin was observed after 15min; no swelling, rash, pruritus, general malaise, *etc.*, indicated the negative. Negative patients received FFA and ICGA; first they underwent the infrared and autofluorescence photography, intravenous injection of mixture of 5 mL 10.0% fluorescein sodium (Guangzhou Baiyunshan Mingxing Pharmaceutical, Guangdong Province, China) and 2 mL 1.25% indocyanine green (Dandong Yichuang Pharmaceutical, Liaoning Province, China), as well as FFA and ICGA synchronously. After the contrast medium injection, the vessels were immediately photographed usually for 30min. All patients received FFA and ICGA before treatment and at 3mo after treatment, and the angiography results were interpreted by experienced experts in fundus disease.

Location of the Hyperpermeability Area All patients were examined with FFA and ICGA. In ICGA images (Figure 1), we delineated the hyperpermeable area of the choroid as line “L” through the center of the fovea “M” and the center of the circle “O”. This generates two intersections: “A” and “B” between line “L” and the circle. During OCT (Figure 2), the scanning line was set to coincide with line “L” and was scanned through the center of the fovea. Points “A”, “B”, and “O” were located according to the distance between the three points and the center of the fovea. Choroidal thicknesses at points “A”, “B”, and “O” were measured, and their mean values were used to represent the mean thickness of CHA.

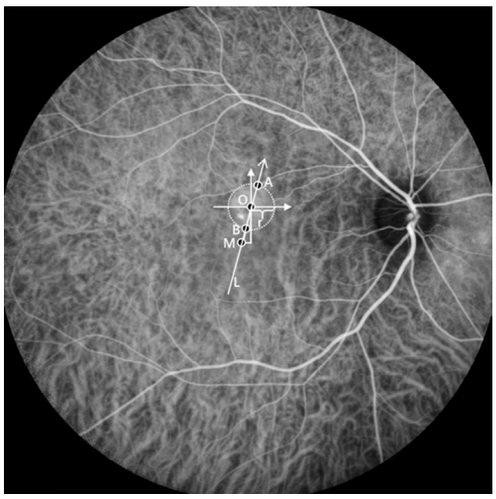

Figure 1 Representative ICGA photograph showing how to locate the hyperpermeable area A circle was drawn around the CHA, the radius of which is "r". A rectangular coordinate system was built with the center of the circle "O" as the coordinate origin. The center of the fovea "M" was the point that coordinates x, y. Line "L" through points "M" and "O." There are two intersections, "A" and "B", between the line "L" and the circle. The distance between "M" and "O" and the values of x and y can be measured by software. We calculated the angle between line "L" and the horizontal line, the lengths of MA and MB. ∠L=arctan(|y|÷|x|); MA=MO+r; MB=MO-r.

According to the relationship between the location of CHA and the center of the fovea, the patients were divided into two groups. In group A, the patients with CHA covered the center of the fovea (point "M" is in circle "O"). In group B, the CHA did not cover the center of the fovea (point "M" is outside circle "O").

Choroidal Thickness Measurement Each examination was performed by an experienced functional room doctor. Each patient underwent an OCT examination before treatment and 1 and 3mo after treatment (Zeiss Model 5000, Oberkochen, Germany). Enhanced depth imaging (EDI) was used to ensure complete choroidal images were obtained. Set the angle value between the scanline and the horizontal line to the value of ∠L. All scans were directed through the center of the fovea. Finally, choroidal thickness was measured at the corresponding distance from the center of the fovea (Figure 2). The center choroidal thickness was measured at the center of the fovea "M".

Half-dose Photodynamic Therapy The half-dose PDT protocol for CSC was performed using half the normal dose (3 mg/m^2) of verteporfin (Visudyne; Novartis AG, Bülach, Switzerland). Verteporfin infusion was performed over a 10-minute period, followed by laser delivery at 15min after the start of infusion as the standard procedure. A laser light at 689 nm was delivered, total light energy of 50 J/cm^2 (*i.e.*, a light power density of 600 mW/cm^2 was used for continuous irradiation for 83s) was used, while other parameters remained the same. Laser irradiation was applied to the area covering the hyperpermeability observed on ICGA. After treatment, protective spectacles were provided, and the patients were instructed to avoid strong light for 3d.

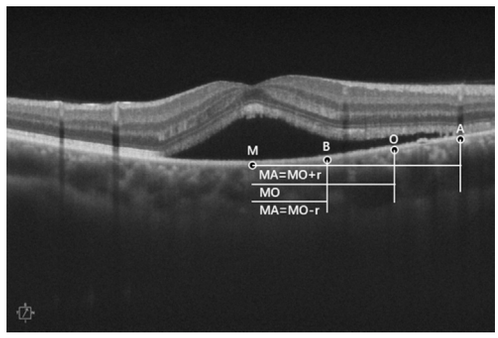

Figure 2 Representative OCT photograph showing how to measure choroidal thickness First, an OCT scan was performed at an angle of ∠L through the center of the fovea, which corresponds to the cross section of the line "L". Points "B", "O", and "A" are located at the corresponding position from point "M". Choroidal thickness was measured at points "B", "O", and "A". The mean choroidal thickness can be regarded as the mean thickness of CHA.

The patients were seen for regular follow-up visits at 1wk before and 1 and 3mo after treatment. A standardized evaluation was performed at each visit, including BCVA at 5 m, OCT, and ophthalmoscopy. FFA and ICGA were performed within 1wk before and at 3mo after treatment. The primary outcome measures were the changes of choroidal thickness, the changes in the mean logMAR of BCVA, and SRF on OCT.

Statistical Analysis Statistical analysis was performed using SPSS software for Windows, version 22.0 (IBM Corp., Armonk, NY, USA). A *P* value of 0.05 was considered statistically significant, and continuous values are expressed as the means±SD. The differences between the observation target before and after treatment were compared by repeated measures analysis of variance.

RESULTS

Baseline Data A total of 17 patients (17 eyes) were included in this study. There were 15 males and 2 females. Patient ages ranged from 32 to 62y, with a mean age of 44±7y. The disease duration ranged from 0.1 to 24mo, with 5 acute and 12 chronic patients. According to the grouping rules, they are divided into group A (11 eyes) and group B (6 eyes). The baseline data of both groups are shown in Table 1.

Choroidal Thickness The choroidal thickness of all patients decreased after PDT (Figure 3). The differences of center choroidal thickness at baseline and 1 and 3mo post-PDT were statistically significant in all patients and group A (both $P<0.001$). There was no significant difference in group B ($P=0.059$). The differences of thickness of CHA at baseline and 1 and 3mo post-PDT were statistically significant in group

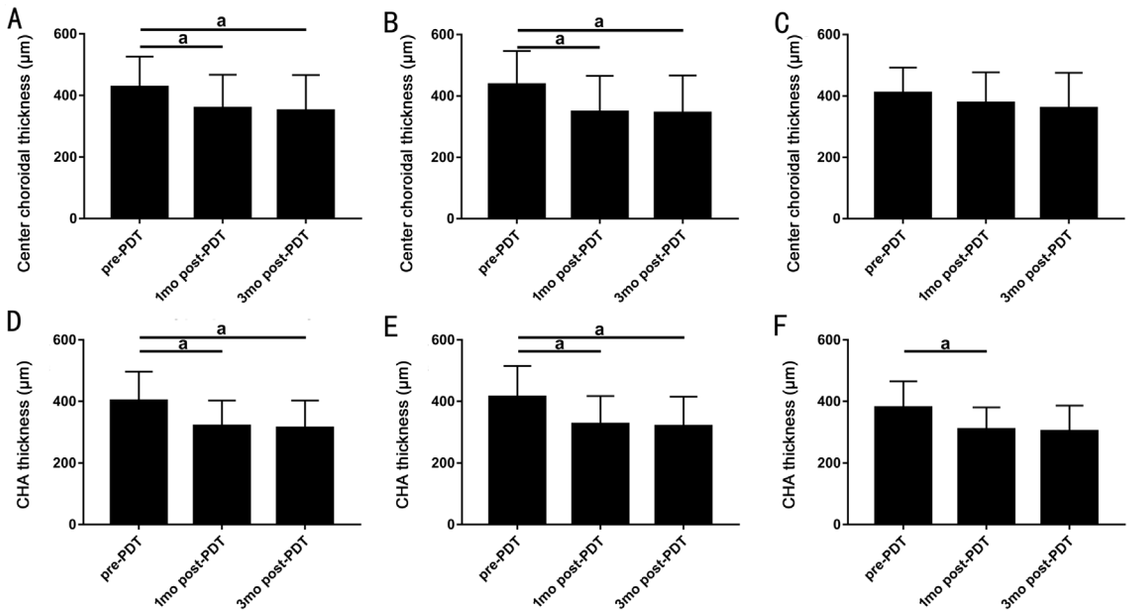

Figure 3 Choroidal thickness changes at baseline and at 1 and 3mo after PDT A: The change of center choroidal thickness after PDT was significant in all patients (P<0.001); B: The change of center choroidal thickness after PDT was significant in group A (P<0.001); C: The change in center choroidal thickness after PDT was not significant in group B (P=0.059); D: The change of thickness in CHA after PDT was significant in all patients (P<0.001); E: The change of thickness in CHA after PDT was significant in group A (P<0.001); F: The change of thickness in CHA after PDT was significant in group B (P=0.005). [a]Statistically significant difference at the two time points in the same group.

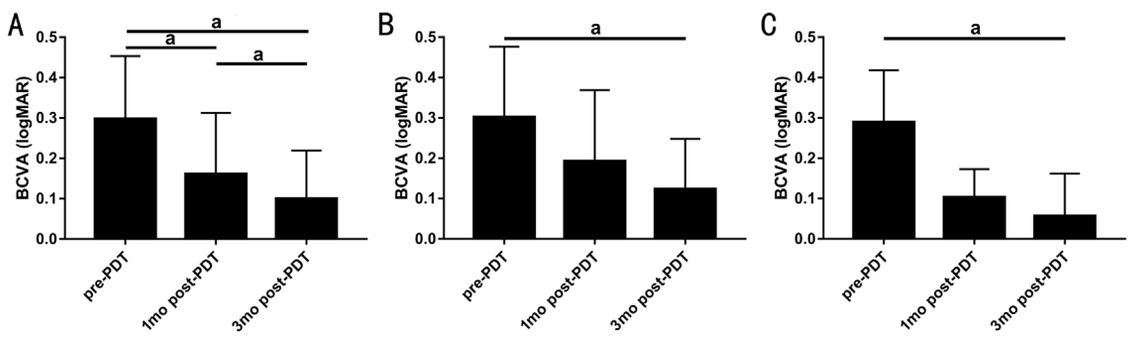

Figure 4 BCVA changes at baseline and 1 and 3mo after PDT A: There was a significant change in BCVA after PDT in all patients (P<0.001); B: The change in BCVA after PDT was significant in group A (P=0.001); C: The change in BCVA after PDT was significant in group B (P=0.001). [a]Statistically significant difference in BCVA at the two time points in the same group.

Table 1 Baseline demographics

Groups	Age (y)	Gender (male/female)	Disease duration (acute/chronic)	BCVA (logMAR)	Center choroidal thickness (μm)	Thickness of CHA (μm)
All patients (n=17)	44±7	15/2	5/12	0.30±0.16	427.35±99.01	402.35±94.91
Group A (n=11)	45±8	9/2	2/9	0.30±0.18	437.09±109.21	414.76±101.16
Group B (n=6)	42±4	6/0	3/3	0.29±0.13	409.50±83.22	379.61±86.03
P	0.491	0.266	0.169	0.869	0.599	0.483

BCVA: Best-corrected visual acuity; CHA: Choroidal hyperpermeability area.

A, group B and all patients (P<0.001, P=0.005, and P<0.001).

Changes in Best-corrected Visual Acuity The BCVA values measured at baseline and 1 and 3mo after PDT are is shown in Figure 4. There were significant differences in the BCVA at baseline and post-PDT at both time points in all patients and in group A and group B (P<0.001, P=0.001, and P=0.001). The results showed that BCVA significantly improved after treatment, with no effect of group.

Subretinal Fluid on Optical Coherence Tomography Among the 17 patients, 15 (88.24%) showed complete absorption 1mo after treatment, and the remaining 2 were completely absorbed 3mo after treatment.

Improvement of Choroidal Hyperpermeability ICGA showed significant improvement of choroidal hyperpermeability in all 17 patients 3mo after treatment. A representative case depicting the effect of PDT on ICGA and OCT is shown in Figure 5.

Complications No patient experienced any systemic or ocular complications during the study period.

DISCUSSION

With the development of technology to image the eye, our understanding of CSC has gradually deepened. Abnormal catecholamine and glucocorticoid levels in human blood are a fundamental cause of CSC[19]. The direct cause is high choroidal vascular permeability, which leads to excessive hydrostatic pressure in choroidal tissue, followed by local RPE detachment, mechanical destruction of the RPE barrier, and fluid leakage into the retina, ultimately leading to retinal neuroepithelial detachment. Traditional treatments such as laser photocoagulation cannot improve the dilatation and leakage of choroidal capillaries, so many patients experience recurrence after treatment. In addition, laser treatment is obviously not suitable for patients with subfoveal or macular vascularity leaks, and this treatment may cause paracentral scotoma and even damage the Bruch membrane, leading to choroidal neovascularization[20-21]. Lai *et al*[22] used PDT to treat chronic CSC, which is a treatment for choroidal neovascularization. Zhao *et al*[23] subsequently made improvements in PDT, and this treatment achieved good results for CSC and was gradually accepted by doctors and patients.

Many researchers have reported effects of PDT on tissue function and structure. Commonly used outcomes are BCVA, fluorescein leakage on FFA, and SRF absorption. The specific targets for PDT were choroidal permeability (ICGA), choroidal thickness, and central retinal thickness. ICGA can reflect choroidal permeability; however, there are many limitations to this invasive test. Choroidal thickness can also indirectly reflect choroidal permeability and can be noninvasively assessed with OCT. Compared with ICGA, OCT is more acceptable to patients and can dynamically assess choroidal thickness changes. Most studies on PDT for CSC measure choroidal thickness. Because choroidal hyperpermeability lesions in CSC are mostly located at the posterior pole of the eye, these studies used the center of the fovea[10-16,18] or the center and a nearby area[17] as fixed choroidal thickness observation targets. However, the relationship between the CHA and the center of the fovea is not fixed. As we previously observed, the center of the fovea was covered by CHA in about 58.33% of patients. Although the macular center choroidal thickness of these patients can reflect the condition of the choroid in the hyperpermeable area, the relationship between the center of the fovea and the hyperpermeability area is not fixed, and the anomaly can be located in the center or at the edge of the area.

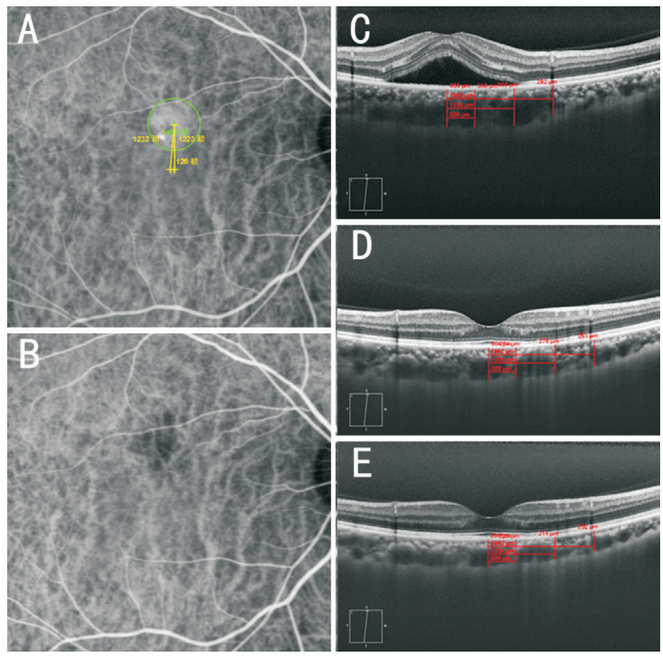

Figure 5 Half-dose PDT in a 42-year-old male patient with chronic CSC of the right eye A, B: ICGA at baseline and at 3mo after PDT, respectively; C-E: OCT at baseline and at 1 and 3mo after PDT, respectively. ICGA showed that perfusion of the CHA was lower after treatment. OCT showed that choroidal thickness decreased and SRF completely absorbed after treatment.

Only in 2.08% of patients can correctly reflect the condition of the CHA through the average choroidal thickness of the subfoveal.

In this study, 35% (6 eyes) of patients had a CHA that did not cover the center of the fovea. When we measured center choroidal thickness in all patients, the results were no different from those of other studies. The same observation method yielded the same results in group A, but the results in group B were very different. This suggests that center choroidal thickness measurement is only applicable to patients with a CHA covering the center of the fovea. When this method was used to observe all patients, the credibility of the results was questionable. When the CHA was used as the observation target, the results were the same in each group. Therefore, the research method using the fovea as an observation target does not always reflect the hyperpermeability area of the choroid. First, a fixed observation area may not cover the hyperpermeability area of all patients, and the measured data may not accurately reflect the hyperpermeability area. With this approach, only patients with hyperpermeability areas located in the center of the fovea are considered. This consideration ensures the credibility of the data, but the objective of study is not comprehensive, and the findings are bound to produce bias that does not fully reflect patient response to PDT.

For this reason, we deviated from traditional research methods focused on the center of the fovea. First, the hyperpermeability

area was displayed by ICGA, and the location relationship between the area and the center of the fovea was calculated. Then, the choroid thickness of the fixed points in the hyperpermeable area was measured on OCT. The measuring points of this method are fixed relative to the hyperpermeability area of the choroid, and the position requirement of the hyperpermeability area of the choroid is greatly reduced. This method improves the credibility of the data and ensures a smaller bias.

The results of this study show that half-dose PDT for CSC can reduce choroidal hyperpermeability, promote SRF absorption, and improve visual acuity. These findings are similar to previous studies[11-14,17-18] and reflect the feasibility and credibility of the research method. We observed a significant correlation between CHA thickness and permeability state. The thickness of the CHA could indirectly reflect its permeability status.

However, there are some limitations in this study. First, the sample size was small, and the observation time was short. Second, there is no available software to automatically measure choroidal thickness. We manually measured choroidal thickness, which may lead to poor subjective repeatability. Additionally, we did not include a control group. Future studies with larger sample sizes, longer follow-up periods, and control groups are expected to confirm that this method can be used to monitor CSC patients after PDT.

In conclusion, center choroidal thickness does not accurately reflect changes in the hyperpermeability area of patients in which the hyperpermeability area does not covered the fovea center. Using the hyperpermeability area as the observation target can make up for this limitation, expand the scope of application, and reduce bias. This study again indicate that half dose of verteporfin PDT can improve and stabilize the vision, stop or reduce the choroidal vasodilatation and leakage, accelerate the absorption of serous SRF.

ACKNOWLEDGEMENTS

Foundations: Supported by the National Natural Science Foundation of China (No.81760174; No.31871261); the Zunyi Science and Technology Project (No.2018-166); the Research Initiation Fund for Masters in Affiliated Hospital of Zunyi Medical College (No.2016-43).

Conflicts of Interest: Chen XW, None; **Han FY,** None; **Su G,** None; **Pan L,** None; **Cai SJ,** None.

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