To evaluate the microcirculation of retinochoroid capillary between acute and chronic central serous chorioretinopathy with OCTA

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Abstract
To investigate the difference in chorioretinal microcirculation between acute central serous chorioretinopathy (aCSC) and chronic central serous chorioretinopathy (cCSC) using optical coherence tomography angiography.

In total, 65 patients previously diagnosed with central serous chorioretinopathy (33 aCSC and 32 cCSC) were included in our cross-sectional study. All patients underwent complete ophthalmologic assessment including logarithm of the minimum angle of resolution best-corrected visual acuity, fundus fluorescein angiography, and optical coherence topography angiography. Sixty eyes of 60 refractive error and age matched healthy people were selected as control.

The vessel density of inner retina in patients with aCSC were higher than that in patients with cCSC (51.32 ± 2.01 vs 49.15 ± 3.68, P = .004), however, the vessel density of superficial chorioid layer in aCSC were significantly lower than that in cCSC (49.83 ± 6.96 vs 53.42 ± 6.28, P = .033). Further analysis of the data reveals the presence of a distinct choroidal neovascularization (CNV) in 8 patients (25%) with cCSC while there was no evidence of CNV in patients with aCSC.

Our study can contribute to a better understanding of the difference in retinochoroid microcirculation between aCSC and cCSC. The vessel density of inner retina was lower and the vessel density of superficial choroid was higher in cCSC, and patients with cCSC were more susceptible to CNV than patients with aCSC.

Abbreviations: aCSC = acute central serous chorioretinopathy, AMD = age-related macular degeneration, BCVA = best-corrected visual acuity, BRM = Bruch’s membrane, cCSC = chronic central serous chorioretinopathy, CNV = choroidal neovascularization, CSC = central serous chorioretinopathy, FFA = fundus fluorescein angiography, ICGA = indocyanine green angiography, OCTA = optical coherence tomography angiography, RPE = retinal pigment epithelium, SRF = subretinal fluid, VDDR = vessel density of deep retina, VDIR = vessel density of inner retina, VDSO = vessel density of superficial choroid, VDSR = vessel density of superficial retina.

Keywords: central serous chorioretinopathy, choroidal neovascularization, optical coherence tomographic angiography, vessel density

1. Introduction
Central serous chorioretinopathy (CSC) is an idiopathic ophthalmopathy in which the neurosensory retina is often detached in the central macular region due to serous leakage from the choriocapillaris through 1 or more hyperpermeable retinal pigment epithelium (RPE) sites.[1,2] CSC is considered the fourth most common non-surgical retinopathy after neovascular age-related macular degeneration (AMD), diabetic retinopathy, and retinal vein occlusion.[1,3] Although the subretinal fluid (SRF) can resolve spontaneously, many patients have significant clinical complications, including atrophy of the RPE or retina, and patients can also develop more serious sequelae such as subretinal neovascularisation.[4,5] Compared to AMD, diabetic retinopathy, and retinal vein occlusion, which are often seen in the elderly, CSC mostly affects young men of working age, causing a heavy economic burden on families and society.[6]

CSC is one of the most representative diseases in the pachychoroid spectrum.[7,8] However, the pathogenesis of CSC remains poorly understood and there is currently no universally accepted classification system for CSC.[2,9–11] Many authors use a basic distinction between acute central serous chorioretinopathy (aCSC) and chronic central serous chorioretinopathy (cCSC) based on the duration of SRF and the structural changes visible on multimodal imaging examinations.[2] In general, the serous detachment in aCSC usually resolves within 4 months without the need for treatment, the detachment tends to persist in cCSC, and the chronic presence of SRF commonly leads to permanent visual function damages; studies undertaken so far provided certain evidence concerning the worse central vision and microperimetry...
in patients with cCSC.\textsuperscript{[4]} However, there have been no controlled studies which compare differences in retinochoroid microcirculation between aCSC and cCSC by a quantifiable imaging method.

Optical coherence tomography angiography (OCTA) is a new, non-invasive imaging technique that generates volumetric angiography images in a matter of seconds and could provide quantitative statistic data of different layers of retinochoroid capillary.\textsuperscript{[12,13]} It appears to be a promising imaging method that is more convenient and does not involve in any issues with side effects.\textsuperscript{[12]} So, the main aim of this study is to investigate the differences in retinochoroid microcirculation between aCSC and cCSC by using OCTA.

2. Methods

A retrospective, cross-sectional study was performed. Sixty-five eyes of 65 CSC patients from Wuzhou Gongren Hospital and Zibo Central Hospital were included from October 1, 2018, until June 20, 2020. The study was in accordance with the tenets of the Declaration of Helsinki and approved by the Ethics Committee of Wuzhou Gongren Hospital (20200002) and the Ethics Committee of Zibo Central Hospital (202004001). Our ethics committee ruled that written informed consent was not required because our study was retrospective in nature and all the images were fully anonymized.

Patients presenting with visual acuity loss and visual symptoms such as micropsia, metamorphopsia, and central scotomata within 6 months together with serous retinal detachment were defined as aCSC; patients with visual symptoms for more than 6 months or recurrent symptoms together with focal, diffuse, or mottled leakage during angiography were regarded as cCSC.\textsuperscript{[3]} Inclusion criteria were: patients previously diagnosed with CSC and the leakage of fundus fluorescein angiography (FFA) located in macular fovea; patients age ≥ 18 years; best-corrected visual acuity (BCVA) ≤ 1 logarithm of the minimum angle of resolution; and OCTA can be completed successfully. However, patients who had received any previous treatment, such as photodynamic therapy, thermal laser photocoagulation, or intraocular drug injection; patients with any other macular conditions that might compromise image quality and affect the studies, such as AMD, polypoidal choroidal vasculopathy; and patients with pigment epithelial detachment were excluded from the study.

2.1. Ophthalmic examinations

Eligible subjects who matched the selection criteria underwent a detailed evaluation including BCVA measurement, intraocular pressure by non-contact tonometer, and further dilated fundus biomicroscopy. Imaging examinations included FFA (Canon, Japan, in Wuzhou Gongren Hospital and Heidelberg, Germany, in Zibo Central Hospital) and OCTA (Optovue, USA, in both hospital). All examinations were carried out by professional technicians in the morning between 8:00 AM and 12:00 AM, to minimize the effects of time on vessel density of retinochoroid.

2.2. Optical coherence tomography angiography

The 3 × 3 scanning pattern technique centered on the fovea was used to further analyze. Images were displayed at 4 different layers: superficial, deep, outer retinal layers, and superficial choroidal layer. The images of the superficial retina, deep retina layers, and superficial choroidal layers were used for analysis in this study. The superficial retina was defined as the inner limiting membrane to 10 microns above the inner plexiform layer; the deep retina was defined as 10 microns above the inner plexiform layer to 10 microns below the outer plexiform layer, in general, the superficial and deep retina layers were considered as inner retina; the outer retina was defined as 10 microns below the outer plexiform layer to 10 microns above the Bruch’s membrane (BRM), and it was considered as absence of capillaries theoretically; and the superficial choroidal capillary layer was defined as 10 microns above the BRM to 30 microns below the BRM. The vessel density was calculated as the percentage of pixels with a flow signal greater than the threshold.\textsuperscript{[14,15]}

2.3. Statistical analysis

Two different independent and experienced ophthalmologists (Jun Yang and Zuofen Wang) performed all retinochoroid measurements using Optovue (Wuzhou: version 2018.0.0.14; Zibo: version 2017.0.0.164) software. No significant difference was found between the 2 datasets by calculating Pearson correlation (Pearson value ≥ 0.8). All outliers were re-measured by the superior physician (Huawen Lu) before used for further analysis.

All data are presented as mean ± standard deviation. The Shapiro–Wilk test was used to examine the normal distribution of data. Comparisons of visual function and mean vessel density of different layers of retina and choroid between aCSC and cCSC eyes were conducted using independent-sample $t$ test. All analyses were carried out using SPSS, version 19 (IBM, Armonk, New York). A $P$ value of <.05 was considered statistically significant.

3. Results

Thirty-three patients with aCSC and 32 patients with cCSC were enrolled. The patients with CSC include 58 males and 7 females, with a mean age of 46.74 ± 6.12 years (range 34–60 years). Age and refractive error matched control group consists of 60 eyes of 60 healthy people, with a mean age of 45.48 ± 5.53 years (range 34–58 years) and BCVA ≤ 1 logarithm of the minimum angle of resolution. Demographic data are shown in Table 1.

3.1. Visual function

There is a significant difference in BCVA between aCSC and cCSC. An independent-sample $t$ test revealed that patients with aCSC had much better BCVA than that of patients with cCSC ($0.23 \pm 0.12$ vs $0.37 \pm 0.23$, $P = .004$). In addition, the BCVA of
normal control was significantly better than that of patient with CSC ($-0.06 \pm 0.04$ vs $0.30 \pm 0.19$, $P < .001$).

### 3.2. Retinal capillary

A comparison of the 2 results revealed that the retinal vessel density of aCSC was significantly higher than that of cCSC (shown in Fig. 1). The vessel density of inner retina (VDIR) was $51.32 \pm 2.01$ in aCSC eyes and $49.15 \pm 3.68$ in cCSC eyes ($P = .004$). In subgroup, further analysis of the data showed that the vessel density of superficial retina (VDSR) was higher in patients with aCSC than patients with cCSC ($44.42 \pm 2.17$ vs $41.80 \pm 3.08$, $P < .001$), however, there was no significant difference between the groups with respect to the vessel density of deep retina (VDDR). Shown in Table 2 and Figure 2.

### 3.3. Choroidal capillary

The vessel density of superficial choroid (VDSC) layer in aCSC group was statistically lower than that in cCSC ($49.83 \pm 6.96$ vs $53.42 \pm 6.28$, $P = .033$). A further issue that emerged from the data was a special category of cCSC, OCTA in 8 eyes (25%) revealed the presence of a distinct choroidal neovascularization (CNV) in cCSC while there was no evidence of CNV in aCSC. Shown in Table 2 and Figures 1 and 3.

### 3.4. Correlation analysis between vessel density and duration

We found that there is a clear correlation between the VDIR and VDSR and disease duration ($P = .003$, $P < .001$, respectively); however, there was no significant correlation between the VDDR and VDSC and disease duration ($P = .408$, $P = .343$, respectively). Shown in Figure 4.

### 3.5. Comparison with normal eyes

Patients with CSC were similar to the normal control in age and sex distribution. The mean VDIR, VDDR, and VDSC of aCSC and VDIR, VDDR, and VDSC of cCSC was significantly lower compared to normal eyes. Shown in Table 2.

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**Figure 1.** Representative images of acute and chronic central serous chorioretinopathy. A–D: acute CSC; E–H: chronic CSC; I–J: the corresponding color picture of retinal capillary perfusion of acute and chronic CSC. As shown, the retinal blood flow signals are denser in acute patients, and choroid blood signals are denser in chronic patients. BRM = Bruch’s membrane, CSC = central serous chorioretinopathy, ILM = inner limiting membrane, IPL = inner plexiform layer, OPL = outer plexiform layer.
4. Discussion
As mentioned in the literature review, FFA and indocyanine green angiography (ICGA) remain to be the golden standard for diagnosis of CSC currently, but they were limited for being an invasive test that require intravenous administration of dye and imaging up to 20 to 30 minutes.[4,16] Lack of quantification is another limitation of FFA and ICGA.[6] However, OCTA is a non-invasive technique that acquires volumetric angiographic information in 5 seconds, and the observations of vascular microcirculation in different layers are more intuitive.[17,18] OCTA has shown great advantages in diagnosis of retinal and choroidal diseases as well as microcirculation quantification which allow us achieve a new insight in the pathogenesis of diseases.[12,14,19]

Concerning the retinal capillary, a significant difference was found between aCSC and cCSC in VDIR and VDSR, the vessel density of patients with aCSC was higher than that of patients with cCSC. These may be caused by the persistently existing of SRF, which would probably lead to retinal atrophy over a long term. Previous studies have also shown that the impairment in visual function of cCSC patients were more severe than aCSC patients.[20,21] Therefore, early intervention should recommend and may help reduce the risk of structural and functional further impairment in patients with early stage of CSC. Further analysis

| Characteristics | aCSC | cCSC | P (A vs C) | Normal eyes | P (A vs N) | P (C vs N) |
|-----------------|------|------|------------|-------------|------------|------------|
| VDIR (%)        | 51.32±2.01 | 49.15±3.68 | P = 0.004  | 52.85±3.44 | P = 0.021  | P < 0.01   |
| VDSR (%)        | 44.42±2.17  | 41.80±3.08  | P < 0.01   | 44.21±3.13  | P = 0.739  | P = 0.01   |
| VDDR (%)        | 43.45±3.27  | 44.70±3.99  | P = 0.170  | 45.93±3.31  | P = 0.001  | P = 0.119  |
| VDSC (%)        | 49.83±6.96   | 53.42±6.28  | P = 0.033  | 61.58±5.89  | P < 0.01   | P < 0.01   |

Values are showed as means ± SDs.
VDIR, vessel density of inner retina, calculated as the percentage of pixels with a flow signal greater than the threshold (%); VDSR, vessel density of superficial retina; VDDR, vessel density of deep retina; VDSC, vessel density of superficial choroid. A = acute CSC eyes, aCSC = acute central serous chorioretinopathy, C = chronic CSC eyes, cCSC = chronic central serous chorioretinopathy, N = normal eyes.

* P < 0.05 indicates statistically significant difference.

Figure 2. Comparisons of retinochoroid vessel density of acute and chronic central serous chorioretinopathy. VDIR, vessel density of inner retina, calculated as the percentage of pixels with a flow signal greater than the threshold (%); VDSR, vessel density of superficial retina; VDDR, vessel density of deep retina; VDSC, vessel density of superficial choroid. aCSC = acute central serous chorioretinopathy, cCSC = chronic central serous chorioretinopathy.
of the data showed that the VDIR of patients with CSC was significantly lower than that of normal control. A probable explanation of the thinner capillary in patients with CSC is the presence of SRF, which causes morphological changes in the sensory layer of retina.

It is still unclear in terms of the exact pathogenesis of CSC, much of the literature focuses on abnormal choroidal microcirculation.[4,9] Some scholars reported that the ratio of the hyperpermeability in the early phase of ICGA were significantly larger than that of normal eyes, studies also showed abnormality of RPE may be the cause of CSC, but the limitations of these previous studies were lack of quantification evidence.[2,22] Our data showed that the VDSC layer in CSC groups were lower than that in control group. The same conclusion was also reached in subgroup analysis (aCSC vs normal group and cCSC vs normal group) in this study. This phenomenon happened in VDSC suggested that the photoreceptor and RPE were connected with a decreased nutrition supply from choroid. Secondly it indicated that choroid ischemia may present, and thirdly it may cause choroid disfunction in heat conduction. All of these may lead to impairment of RPE cell tight junction and RPE barrier breakdown, followed by RPE or sensory retinal detachment. Atrophy of outer retina such as the external limiting membrane or ellipsoid zone may develop if the pathology last over a long term.

In addition, one of the more significant findings to emerge from this study was that the VDSC of patients with cCSC was higher than that of patients with aCSC. OCTA has considered as a powerful tool in studying the choroidal microcirculation of CSC, choiocapillary hypoperfusion and hyperperfusion often co-exist in the abnormal vascular areas of the leakage point of FFA, and the study by Chan et al[13,23] has shown the hyperperfusion of choriocapillary on OCTA is more common in cCSC. They have proposed hypothesis that the hypoperfusion (a decrease in blood perfusion) with hyperperfusion (an increase in blood perfusion) in the surrounding area on OCTA may cause by the compensatory mechanism of ischemic factors in cCSC, and our research proves this hypothesis quantitatively. Given the possible ischemic compensatory in patients with cCSC, further

Figure 3. Representative images of chronic central serous chorioretinopathy with choroidal neovascularization. A: FFA of the left eye of a 45-year-old female patient with chronic CSC, a hyperfluorescent involving the fovea was visible; B: OCT of the same patient showed a detached sensory retina involving the fovea; C: The superficial retina layer and the corresponding location of 3 x 3 image on OCTA; D: a distinct CNV involving the fovea was visible on the superficial choroid. BRM = Bruch’s membrane, CNV = choroidal neovascularization, CSC = central serous chorioretinopathy, FFA = fundus fluorescein angiography, ILM = inner limiting membrane, IPL = inner plexiform layer, OCT = optical coherence tomography; OCTA = optical coherence tomography angiography.
analysis of the data reveals the presence of a CNV in 8 cCSC patients, however, there was no evidence of CNV in aCSC patients on OCTA.

With regard to the research methods, some limitations need to be acknowledged: first, the sample size included in the observation was small for a cross-sectional study and we only observed at single time point, further expanded sample size was needed and prolonged follow-up can also help to confirm our conclusion. Another source of uncertainty has been the possibility of measurement errors in VDSC, the existence of SRF may be an important factor in the decline of the mean value, but it has rarely been solved in the existing articles.

In conclusion, our study found that the abnormal microcirculation in cCSC was much more complicated than aCSC. The VDIR and VDSR were attenuated significantly in cCSC. This indicated that the microcirculation abnormality may involve the retina as well as choroid in case with longer course of disease. Early intervention might be needed in order to reduce the possibility of developing severe anatomic and functional damage. Furthermore, this study showed that OCTA presented a clearer picture of changes in the different layers of retinal and choroidal capillaries. It may also provide us with valuable quantitative insight in retinal and choroidal microcirculation which may help us in better understanding the microvasculature for many other fundus diseases.

**Author contributions**
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Figure 4. Correlation of retinal and choroidal vessel density and disease duration. A: correlation of VDIR and duration; B: correlation of VDSR and duration; C: correlation of VDDR and duration; D: correlation of VDSC and duration. VDIR, vessel density of inner retina, calculated as the percentage of pixels with a flow signal greater than the threshold (%); VDSR, vessel density of superficial retina; VDDR, vessel density of deep retina; VDSC, vessel density of superficial choroid.
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