·技术研究·

应用光学相干断层扫描血管成像技术评价中心性浆液性脉络膜视网膜病变视网膜及脉络膜的微循环变化

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摘　要：【目的】应用光学相干断层扫描血管成像(OCTA)技术定量分析中心性浆液性脉络膜视网膜病变(CSC)视网膜脉络膜的微循环变化。【方法】经常规眼科临床检查，眼底荧光血管造影(FFA)、吲哚菁绿血管造影(ICGA)等方法确诊 CSC 患者 61 例 67 眼。选取年龄、屈光匹配的正常人 15 名、30 眼作为正常对照组。对 OCTA 检测结果进行比较，分析 CSC 患者视网膜脉络膜微循环的特点。【结果】CSC 患眼视网膜表层血流密度(VDSR)和视网膜深层血流密度(VDDR)均低于正常眼，但差异无显著性意义($P = 0.325$，$P = 0.056$)。CSC 患眼脉络膜浅层血流密度(VDSC)明显低于正常对照组，差异有显著性意义($P < 0.001$)。经亚组分析，慢性 CSC 组中 VDSR、VDDR 均显著低于正常对照组($P = 0.042$，$P = 0.037$)，而急性 CSC 组中 VDSR、VDDR 与正常对照组无显著性差异。【结论】本研究发现 CSC 患眼存在眼底微循环异常，脉络膜浅层血流密度低于正常眼，并首次发现了慢性 CSC 视网膜表层和深层毛细血管血流密度低于正常眼，提示病史较长的患眼微循环异常不仅累及脉络膜血管而且累及视网膜血管。

关键词：中心性浆液性脉络膜视网膜病变；光学相干断层扫描血管成像；视网膜脉络膜；血流密度
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Evaluation of the Microcirculation Changes in Retina and Choroid of Central Serous Chorioretinopathy by Using Optical Coherence Tomography Angiography

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Abstract: 【Objective】To evaluate the microcirculation changes in retina and choroid of central serous chorioretinopathy (CSC) by using optical coherence tomography angiography (OCTA).【Methods】A retrospective study was performed in 67 eyes of 61 patients with CSC diagnosed by conventional eye examination, fundus fluorescein angiography (FFA) and indocyanine green angiography (ICGA), 30 eyes of 15 age matched healthy people were selected as normal control group. OCTA was performed to study the microcirculation within the chorioretinal layers.【Results】The vessel density of superficial retina (VDSR) and deep retina (VDDR) layers in CSC eyes were lower than that in normal eyes, but the difference was no statistical significance ($P = 0.325$, $P = 0.056$). The vessel density of superficial choroid (VDSC) layer in CSC eyes was significantly lower than control group. In subgroup analysis, the value of VDSR, VDDR in chronic group were lower than that of the control group, and the difference was statistically significant ($P = 0.042$, $P =$

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0.037); While there was no statistical differences in VDSR, VDDR between acute group and control group.【Conclusion】Our study found that the abnormal microcirculation in CSC was existed. The VDSC in CSC was decreased. Furthermore, to our knowledge, the VDSR and VDDR were firstly observed to be attenuated in chronic CSC. This indicated that the microcirculation abnormality may involve the retina as well as superficial choroid in case with longer course of disease.

Key words: central serous chorioretinopathy; optical coherence tomographic angiography; retinochoroid; vessel density

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Central serous chorioretinopathy (CSC) is characterized by serous retinal detachment (SRD) with or without pigment epithelial detachment (PED) in the central macular region due to abnormalities in the choroid circulation, leading to a disruption of the retinal pigment epithelium (RPE)[1-4]. CSC can be divided into acute and chronic conditions according to the course of disease: typically, acute CSC has been defined as the presence of visual symptoms and SRD of less than six months duration with focal RPE leakage on fundus fluorescein angiography (FFA), chronic CSC is a more severe and characterized by persistent or recurrent SRD more than six months[5-7]. FFA and indocyanine green angiography (ICGA) remain the gold standard for diagnosing CSC[8-9]. However, the risk of adverse reactions of FFA and ICGA such as nausea and allergic reactions may still occur after the injection of contrast agent, retinal and choroidal capillary structure could be obscured by the leakage in late phase of FFA and ICGA, and localization of the depth of the capillary lesions can be difficult due to dye leakage and poor stereopsis[9-10]. 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 objective statistic data of different layers of retinochoroid, it appears to be a promising imaging method that is more convenient and does not involve in any issues with side effects[9, 11]. The aim of our study is to quantify the microcirculation of the retina and choroid in CSC imaged by OCTA and to evaluate the findings of retinochoroid vascular density in order to further understand its pathogenesis.

1 Materials and Methods

1.1 CSC patients

A retrospective, cross-sectional, single-center study was performed. 67 eyes of 61 CSC patients from Zhongshan Ophthalmic Center were included from October 1, 2016, until April 30, 2017. Patients presenting with visual acuity loss and visual symptoms such as micropsia, metamorphopsia and central scotomata within six months together with SRD and angiographic focal leakage were defined as acute CSC. Patients with visual symptoms for more than six months or recurrent symptoms together with focal, diffuse or mottled leakage during angiography were regarded as chronic recurrent CSC[3-4].

The criteria for inclusion in this study included CSC diagnosed by FFA and ICGA with active leakage located in macular fovea and SRF confirmed by B-scan of OCTA; Patient age ≥18 years; best corrected visual acuity (BCVA) ≥35 letters on early treatment diabetic retinopathy study (ETDRS) charts; OCTA can be completed successfully.

Patients who had received any previous treatment, such as PDT, photocoagulation or intraocular drug injection; Patients with any other macular conditions that might compromise image quality and affect the studies, such as age-related macular degeneration (AMD), polypoidal choroidal vasculopathy (PCV); Patients with PED which the average diameter (transverse diameter and vertical diameter) are more than 400 microns; Patients with refractive errors, defined as spherical equivalent < -6.0 diopters, or an axial length >26.5 mm were

excluded from the study.

1.2 Ophthalmic examinations

Each patient underwent a baseline assessment including BCVA measurement, intraocular pressure by non-contact tonometer, and dilated fundus biomicroscopy. Image examinations included FFA (Heidelberg Spectralis, Heidelberg, Germany), ICGA (Heidelberg spectralis, Heidelberg, Germany) and OCTA (RTVue XR Avanti with AngioVue; Optovue Inc., Fremont, CA, USA). All the examinations were conducted in the morning between 9:00 AM and 11:00 AM, to minimize the effects of time on vessel density of retinochoroid.

1.3 Optical Coherence tomography Angiography

Optical coherence tomography angiography (OCTA) is a new non-invasive imaging technique that employs motion contrast imaging to high-resolution volumetric blood flow information generating angiographic images in a matter of seconds[9]. OCTA compares the decorrelation signal (differences in the backscattered OCT signal intensity or amplitude) between sequential OCT b-scans taken at precisely the same cross-section in order to construct a map of perfusion[10,11]. Axial bulk motion from patient movement is eliminated so sites of motion between repeated OCT b-scans represent strictly erythrocyte movement in retinal blood vessels[12]. We incorporated the images obtained from the 3 × 3 scanning pattern of OCTA into our study. The images were displayed at 4 different layers: superficial, deep, outer retina layers, and superficial choroid layer. The images of the superficial retina, deep retina layers and superficial choroid layers were used for analysis in this study. The superficial retina was defined as 3 microns below the inner limiting membrane (ILM) to 15 microns below the inner plexiform layer (IPL). Deep retina was defined as 15-70 microns below the IPL. The outer retina was defined as 70 microns below the IPL to 30 microns below the RPE. Less emphasis was placed on the outer retina, as a result of absence of capillaries theoretically. The superficial choroidal capillary layer was defined as 30-60 microns below the RPE. The vessel density was calculated as the percentage of pixels with a flow signal greater than the threshold[13-14].

1.4 Statistical analysis

Quantitative data data are presented as median (P_{25}~P_{75}, Q) or mean ± standard deviation (SD). The Shapiro-Wilk test was used to examine the normal distribution of data. Comparisons of mean vessel density of different layers of retina and choroid between CSC eyes and normal eyes were conducted using nonparametric test for two independent samples. Statistical analysis were carried out with SPSS version 19 software (IBM, Armonk, New York, USA). A P-value of <0.05 was considered statistically significant.

2 Results

2.1 Baseline demographic data

Among total of 67 eyes of 61 CSC patients, 32 eye of 32 patients were classified as acute CSC and 35 eyes of 29 patients classified as chronic CSC based on the previously described criteria. The control group consists of 30 eyes of 15 healthy people, including 4 females, with a mean age of (42.5 ± 8.6) years. No refractive error and BCVA equal to or better than 80 letters on ETDRS charts. Demographic data are shown in Table 1.

Table 1 Baseline demographic data of the patients and normal control

Characteristics	Acute CSC	Chronic CSC	Control group
No of Patients/eyes	32/32	29//35	15/30
Sex (male/female)	26/6	25/5	11/4
Age/years	42.2 ± 6.7	46.5 ± 7.4	42.5 ± 8.6
Duration of symptom /months	3.0 ± 1.7	13.9 ± 10.8	0
BCVA (letters, ETDRS)	68.8 ± 9.3	67.0 ± 13.1	⩾ 80
No of Patients with bilateral CSC (n)	0	6	0

Values are shown as means ± SD, SD, standard deviation; CSC, central serous chorioretinopathy; ETDRS, early treatment diabetic retinopathy study.

2.2 Comparisons of different layers capillaries of retinochoroid

The vessel density of superficial retina (VDSR) and deep retina (VDDR) layers [48.0 (45.9~49.7, 3.8), 53.7 (51.6~55.0, 3.4), respectively] in CSC eyes were lower than that [48.4 (46.9~49.8, 2.9), 54.5 (52.6~56.2, 3.6), respectively] in normal eyes, but the difference was no statistical significance (P = 0.325, P = 0.056). In subgroup analysis, the value of VDSR, VDDR in chronic group [47.6 (44.2~49.3, 5.1), 52.9 (50.2~54.9, 4.7), respectively] were lower than that of the control group, and the difference was statistically significant (P = 0.042, P = 0.037); While there was no statistical differences in VDSR, VDDR between acute group and control group (P = 0.778, P = 0.334; Table 2-4, Fig 1-3).

The vessel density of superficial choroid (VDSC) layer [62.6 (61.7 ± 64.0, 2.4)] in CSC group was lower than that [58.0 (55.9~61.1, 5.3)] in control group. Which was statistically significant (P < 0.001). And the result showed the same in subgroup analysis when compared acute/chronic CSC with normal control (Table 2-4, Fig 1-3).

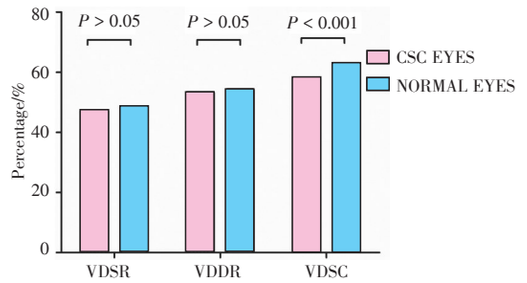


Fig.1 Comparisons of vessel density in different layers of retinochoroid

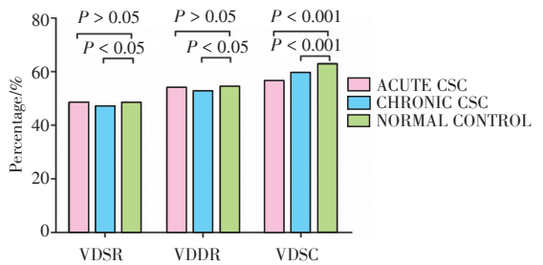


Fig.2 Comparisons of vessel density in subgroup analysis

Table 2 Layer-by-layer comparison analyses of retinochoroid microcirculation of affect eyes and normal eyes

[$M(P_{25}$~$P_{75}, Q)$]

Characteristics	Affect eyes	Normal eyes	Z value	P value
VDSR	48.0(45.9 ~ 49.7, 3.8)	48.4(46.9 ~ 49.8, 2.9)	−0.984	0.325
VDDR	53.7(51.6 ~ 55.0, 3.4)	54.5(52.6 ~ 56.2, 3.6)	−1.874	0.056
VDSC	58.0(55.9 ~ 61.1, 5.3)	62.6(61.7 ~ 64.0, 2.4)	−5.787	< 0.001[1)]

VDSR: vessel density of superficial retina; VDDR: vessel density of deep retina; VDSC: vessel density of superficial choroid. 1)P < 0.05 indicates statistically significant difference.

Table 3 Subgroup analysis of retinochoroid microcirculation of acute CSC eyes and normal eyes [$M(P_{25}$~$P_{75}, Q)$]

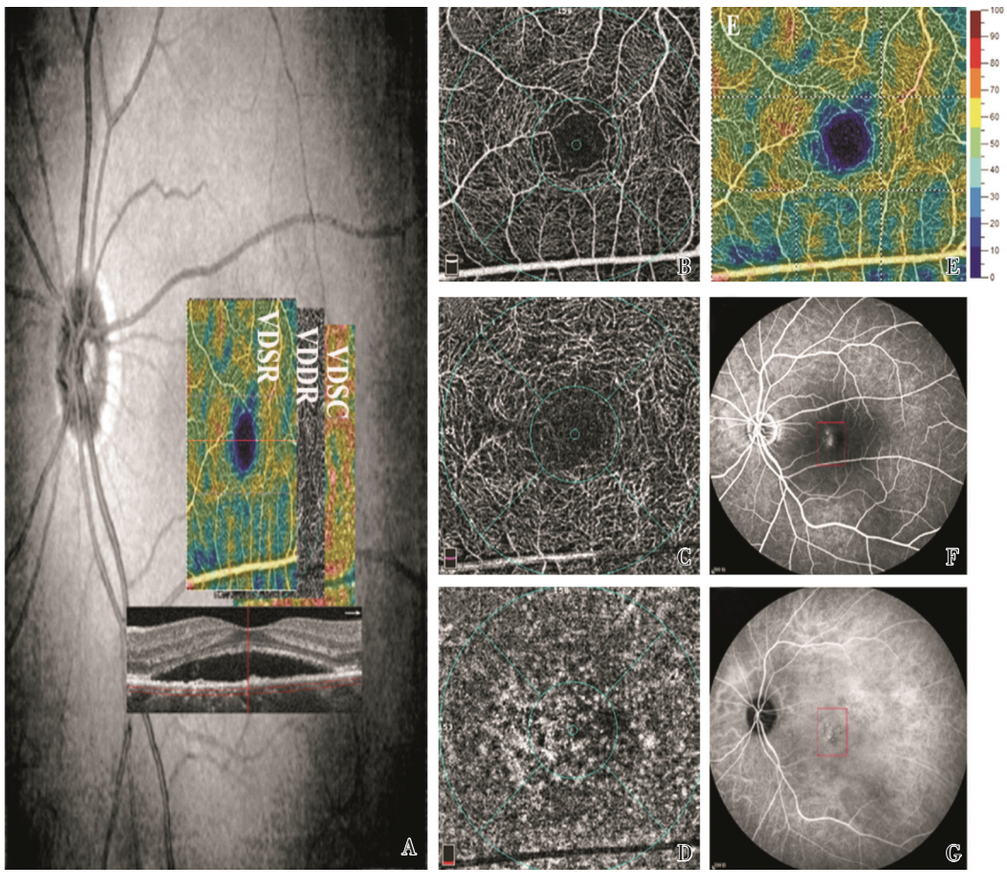
Characteristics	Acute group	Normal group	Z value	P value
VDSR	48.8(46.9 ~ 50.5, 3.6)	48.5(46.9 ~ 49.8, 2.9)	−0.269	0.788
VDDR	53.8(52.4 ~ 55.1, 2.7)	54.5(52.6 ~ 56.2, 3.6)	−0.967	0.334
VDSC	57.6(53.6 ~ 59.5, 6.0)	62.6(61.7 ~ 64.0, 2.4)	−5.975	< 0.001[1)]

VDSR: vessel density of superficial retina; VDDR: vessel density of deep retina; VDSC: vessel density of superficial choroid. 1) P < 0.05 indicates statistically significant difference.

Table 4 Subgroup analysis of retinochoroid microcirculation of chronic CSC eyes and normal eyes [$M(P_{25}$~$P_{75}, Q)$]

Characteristics	Chronic group	Normal group	Z value	P value
VDSR	47.6(44.2 ~ 49.3, 5.1)	48.5(46.9 ~ 49.8, 2.9)	−2.057	0.042[1)]
VDDR	52.9(50.2 ~ 54.9, 4.7)	54.5(52.6 ~ 56.2, 3.6)	−2.090	0.037[1)]
VDSC	59.2(57.1 ~ 62.0, 4.9)	62.6(61.7 ~ 64.0, 2.4)	−4.124	< 0.001[1)]

VDSR: vessel density of superficial retina; VDDR: vessel density of deep retina; VDSC: vessel density of superficial choroid. 1)P < 0.05 indicates statistically significant difference.



A: The en face projection slab of the different layers of retinochoroid capillaries and B scan on OCTA; B, E: Vessel density evaluation of the superficial retinal layer on OCTA, defines as 3 microns below the inner limiting membrane (ILM) to 15 microns below the inner plexiform layer (IPL); C: Vessel density evaluation of the deep retinal layer, defines as 15-70 microns below the IPL; D: Vessel density evaluation of the superficial choroid layer, defines as 30-60 microns below the RPE; F: Middle-phase fluorescein angiography of the left eye of CSC patient, a hyperfluorescent was visible; G: Middle-phase of indocyanine green angiography showed a hyperfluorescent area.

Fig.3 OCTA images of the left eye of a 42-year-old male patient with a history of acute central serous chorioretinopathy for 4 months

3 Discussion

CSC is a posterior segment disease that represents a common cause of vision threat in the middle-aged population [6]. In the diagnostic tools FFA and ICGA remain to be the golden standard for diagnosis of CSC currently, but they are limited for being invasive test that require intravenous administration of dye and imaging up to 20- 30 minutes [15-17]. Lack of quantification is another limitation of FFA and ICGA. The updated OCTA in comparison is a non-invasive technique that acquires volumetric angiographic information in 5-6 seconds, and the observation of vascular microcirculation in different layers are more intuitive [8-9]. OCTA is showing promising image technique in diagnosis of retinal and choroidal diseases as well as microcirculation quantification which allow us achieve a new insight in the pathogenesis of diseases.

Our data has shown that the density of retinal capillaries acquired by OCTA were not changed obviously between CSC eyes and normal eyes. But the VDSR and VDDR were lower in chronic CSC eyes compared with normal eyes in subgroup analysis. While there was no statistical differences in VDSR, VDDR between acute CSC eyes and normal control. 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 chronic CSC patients were more severe than acute CSC patients [18-19]. Therefore, early intervention should recommend and may help reduce the risk of structural and functional further impairment in patients with early stage of CSC.

It is still unclear in terms of the exact pathogenesis of CSC. Some scholars reported that the ratio of the hyperpermeability in the early phase of ICGA was significantly larger than that of normal eyes[15-16]. But the limitation of these previous studies were lack of quantification evidence. Some other studies showed abnormality of retinal pigment epithelium may be the cause of CSC[1,4]. Our data showed that the vessel density of superficial choroid layer in CSC group was lower than that in control group. The same conclusion was also reached in subgroup analysis in this study and literature reported previously[20-21]. This phenomenon happened in CSC firstly proved that the photoreceptor and retinal pigment epithelium were connected with a decreased nutrition supply. 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/sensory retina detachment. Atrophy of outretina such as the external limiting membrane/ellipsoid zone may develop if the pathology last over a long term.

The present study still contains limitations: 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 of acute CSC patients can also help to confirm our conclusion. Although patients with PED were excluded from this study by average diameters greater than 400 microns, the presence of undetected PED would create a 'dark area' on the superficial choroidal layer, leading to the underestimations of vessel density. In addition, the existence of 'SRF' may also be a factor in the decline of VDSC, but it's hard to evaluate its exact influence, and it has rarely been mentioned in the existing literatures[21-22].

In conclusion, our study found that the abnormal microcirculation in CSC was existed. The VDSC in CSC was decreased. To our knowledge, the VDSR and VDDR were firstly observed to be attenuated in chronic CSC. 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.

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