Comparison of subfoveal choroidal thickness in eyes with CRVO and BRVO

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Abstract

Backgroud: To evaluate the subfoveal choroidal thickness (SFCT) in eyes with macular edema secondary to retinal vein occlusion（RVO）and to investigate the short-term response after a single intravitreal Ranibizumab injection. What is more, to compare the SFCT and SFCT change in eyes with central RVO (CRVO) and branch RVO (BRVO). Methods: The observational case series had collected treatment-naïve patients with unilateral macular edema secondary to RVO retrospectively (19 CRVO and 17 BRVO). They had received at least one intravitreal ranibizumab (IVR) injection after newly diagnosed. The SFCT values before IVR and after 2 weeks of IVR were collected and analyzed. Paired t test was performed to compare the difference between RVO eye and its unaffected fellow eye, and to compare the SFCT change between before IVR and after 2 weeks of IVR. In further, the SFCT and SFCT change in eyes with CRVO and BRVO were also evaluated with independent t test. Results: Mean SFCT in CRVO eyes at the onset was 326.03±30.86 μm, which was significantly greater than that in contralateral fellow eyes ($p<0.01$, paired t test), and decreased to 294.15±30.83 μm rapidly after 2 weeks of IVR ($p<0.01$, paired t test). Similarly, the SFCT in BRVO eyes was significant thicker than its contralateral eyes at the onset, and reduced after IVR. However, our findings showed that there was no significant difference on the SFCT at the onset and SFCT change after IVR between CRVO eyes and BRVO eyes. Conclusions: The SFCT in eyes with macular edema secondary to RVO (CRVO or BRVO,respectively) was significantly greater than that in fellow eyes, and decreased significantly within a short time in response to a single IVR injection. It indicated choroid was involved in the progress of macular edema secondary to RVO. Our study collected recent-onset and treatment- naïve patients, it may help to elucidate the conflicting results of SFCT in RVO eyes reported by previous studies. In further, the study first showed that the SFCT may have no relationship with RVO subtypes. However, further study is need to investigate the exact relationship between SFCT and RVO subtypes.

Background

Retinal vein occlusion (RVO) is a retinal vascular disorder characterized by obstruction of the retinal venous system by thrombus formation, is often associated with hypertension or coagulation abnormalities1, 2. It is a common cause of visual handicap in the elderly throughout the world3, generally be subdivided into central RVO (CRVO) ,branch RVO (BRVO) and hemi RVO (HRVO) according to the location of blockage4. Moreover, both CRVO and BRVO can be further classified into non-ischemic subtype and ischemic subtype based on the amount of retinal capillary perfusion5. Macular edema is one of the prominent complication in patients with ischemic RVO and can cause severe impairment of central vision6. Various treatment modalities have been used to treat macular edema, anti- vascular endothelial growth factor (VEGF) therapy had been demonstrated to be safe and effective among these available therapies7-10.

Macular edema secondary to RVO may have abnormal choroidal vasculature, duing to hydrostatic pressure and VEGF level11. Several studies had reported choroidal thickness in CRVO or BRVO, some studies found that there was no significant difference between affected RVO eyes and contralateral

unaffected eyes in subfoveal choroidal thickness (SFCT)11. However, some other studies showed that SFCT in affected RVO eyes was significantly thicker than that in contralateral unaffected eyes 12 13. In further, certain reports had investigated SFCT change after various treatments, such as intravitreal dexamethasone implant and anti-VEGF agents 14, 15. However, the results were also contradictory. Most of the studies reported that the SFCT was decreased significantly after anti-VEGF treatment12, 16, while a few studies reported that anti-VEGF treatment could not reduce SFCT 9. Thus, these contradictory results need be further investigated.

VEGF level and hydrostatic pressure are demonstrated as the main factors which contributed to SFCT change.11 Elevated VEGF level could lead to increased capillary permeality and leakage in retina and choroid2, 17, is critically involved in the pathogenesis of macular edema secondary to RVO18, 19. Franco-Cardenas and colleagues showed that ischemic index in CRVO was much higher than BRVO20, on the other hand, Yasuda and colleagues had found that aqueous VEGF concentration in CRVO eyes was significantly higher than BRVO21, those studies suggested retinal ischemia was more manifest in CRVO than BRVO. Therefore, we assumed that CRVO may had thicker SFCT than BRVO. However, it is still unclear that whether there is difference in choroidal thickness between CRVO and BRVO.

In order to elucidate the contradictory results reported by previous studies, the present study collected treatment-naïve and recent-onset RVO patients retrospectively. It was aimed to further evaluate the SFCT change in eyes with macular edema secondary to RVO (CRVO or BRVO, respectively), and to investigate the short-term response to a single intravitreal Ranibizumab injection. What is more, to compare the SFCT and SFCT change in eyes with CRVO and BRVO.

Methods

The present study was a retrospective observational case series. We had collected 36 patients with unilateral macular edema secondary to CRVO (19 subjects) or BRVO (17 subjects). Each diagnosis was based on the comprehensive ophthalmic examinations. Inclusion criteria was as the following: (1) the patient's age was ranged from 50 to 70 years old; (2) recent onset (less than 1.5 months) and treatment-naïve when presented to the hospital; (3) was ischemic subtype and had at least one intravitreal ranibizumab injection after newly diagnosed; (4) had at least 2 weeks follow up; (5) had comprehensive ophthalmic examination before and after treatment. Patients were excluded if their fellow eyes had any macular disorder such as age-related degeneration (AMD), polypoidal choroidal vasculopathy (PCV) or central serous chorioretinopathy (CSC). Patients were also excluded if the affected eyes or fellow eyes had any of the following criteria: (1) spherical equivalent was > 6D or pathologic myopia; (2) a history of pars plana vitrectomy or other intraocular surgery within half year. The present study followed the tenets of the declaration of Helsinki and was approved by the ethics committee in hospital. The subjects had been informed written consent on the study.

When presented to the hospital at the first time, those patients had undergone comprehensive ophthalmic examinations, include slit-lamp biomicroscopy, funduscopic, fluorescein angiography FA (Heidelberg

retina angiograph; Heidelberg Engineering Inc., Dossenheim, Germany), and enhanced depth imaging optical coherence tomography (EDI-OCT) (Heidelberg Engineering Inc,Dossenheim, Germany). Based on the above inclusion criteria, the RVO eyes had macular edema and were ischemic subtype (diagnosed by FA and OCT), in further, they had undergone at least one intravitreal ranibizumab injection (Lucentis, 0.05ml, 0.5 mg) after newly diagnosed. After that, the following treatment strategies were varied based on clinically relevant benefits and risks, patients' anticipated visit compliance, and the factor that whether the patient could afford the cost of ranibizumab treatment. The patients may be administered intravitreal ranibizumab injection monthly for 3 times, corticosteroids injection or laser photocoagulation during the follow -up period. In patients with macular edema secondary to CRVO, 9 had received continuous ranibizumab injection monthly for 3 months, whereas 6 BRVO eyes had received this treatment regimen. 5 patients (including 2 CRVO and 3 BRVO) had lost to follow-up. There were 8 patients in both CRVO and BRVO groups who were administered corticosteroids injection or laser photocoagulation duing to cost issue.

The demographic characteristics and SFCT values of these subjects were collected. SFCT was determined as the vertical distance from the hyperreflective line of the retinal pigment epithelium to the line of the inner surface of the sclera centered on the fovea, it was measured by 2 observers independently, and was recorded with the mean value. Statistical analysis was performed using Statistical Package for Social Science (SPSS) software (version 20.0, SPSS, Inc, Chicago, IL, USA). Continuous variables of the demographic characteristics were displayed as mean± standard deviation (SD), categorical variables were displayed as the number of subjects and its percentage. Difference between continuous variables was analyzed by independent *t* test, and Chi-square test was used for categorical variables. The SFCT values were displayed as mean± standard deviation (SD). The paired *t*-test was used to evaluate the differences between RVO eyes and fellow eyes, as well as between pre-injection and post-injection. SFCT difference between CRVO and BRVO was analyzed by the independent *t*-test. $p<0.05$ was considered statistically significant.

Results

Choroidal thickness was associated with the demographic characteristics of subjects. Ruiz-Medrano et al reported choroidal thickness decreased 10-15 μm with age getting each 10 years older22. In the present study, to avoid the effect of age and refractive error, the patients with age less than 50 years or more than 70 years were excluded, the spherical equivalent more than 6D were excluded. The demographic characteristics of all subjects were summarized in Table 1. No statistically difference was founded in age and gender distribution between CRVO subjects and BRVO subjects. (57.37±9.75 years, male 63.16% vs. 56.53±8.04 years, male 58.82%). Besides, there was no difference in the axial length and smoking percentage. Overall, the two groups between CRVO and BRVO were well balanced with respect to age, gender, and spherical equivalent. Among those eyes, no high myopia or pathological myopia was found among all the affected eyes and fellow eyes. 3 affected eyes and 4 unaffected fellow eyes were pseudophakia due to surgery in CRVO group, while 2 affected eyes and 2 unaffected fellow eyes were

pseudophakia in BRVO group. The frequency of systemic diseases (hypertension, diabetes, and abnormal coagulation) was similar between the two groups.

Table 1. The patients' demographic characteristics

	CRVO (n=19)	BRVO (n=17)	P
Age, years (Mean ± SD)	57.37±9.75	56.53±8.04	NS*
Gender, Male (%)	12（63.16%）	10（58.82%）	NS**
Axial length, mm (Mean ± SD)	23.55±1.06	23.92±1.03	NS*
Ever smoker (n, %)	6(31.58%)	8(47.06%)	NS**
Systemic diseases			NS**
Hypertension (n, %)	11(57.89%)	8(47.06%)	NS**
Diabetes (n, %)	3(15.79%)	4(23.53%)	NS**
Abnormal coagulation (n,%)	4(21.05%)	3(17.65%)	NS**

*= Independent *t* test;

**= Chi-square test.

Representative EDI-OCT images of CRVO group are shown in Fig 1A, B and C. Compared with unaffected eyes, the SFCT in macular edema eyes was significantly thicker than fellow eyes, the mean ± SD was 326.03±30.86 μm in CRVO eyes and 249.29±31.55 μm in fellow eyes (p<0.001,paired *t* test). However, after 2 weeks of intravitreal Lucentis injection, the mean SFCT in CRVO eyes reduced to 294.15±30.83 μm, significantly thinner than before (Fig 1D, p<0.001, paired *t* test).

Fig 1．Subfoveal choroidal thickness (SFCT) in patients with macular edema secondary to CRVO. A: The representative EDI-OCT image of unaffected contralateral eye; **B:** The representative EDI-OCT image of affected CRVO eye before intravitreal Ranibizumab (IVR) injection; **C:** The representative EDI-OCT image of affected CRVO eye after intravitreal Ranibizumab (IVR) injection; White arrowheads point the choroid-scleral junction. SFCT was determined as the vertical distance from the hyperreflective line of the retinal pigment epithelium to the line of the choroid-scleral junction centered on the fovea, it was measured by 2 observers independently, and was recorded with the mean value. **D:** Comparison of SFCT between the unaffected fellow eyes and CRVO eyes. **E:** Comparison of SFCT in CRVO eyes between pre-IVR injection and post-IVR injection. The values were displayed as mean± standard deviation (SD). The paired *t* test was used to evaluate the differences. *p<0.05 was considered statistically significant.

Similarly，the BRVO eyes showed significant greater SFCT than fellow eyes, the mean ± SD was 317.78±24.09 μm in BRVO eyes and 255.21 ±20.40 μm in fellow eyes (Fig 2D, p<0.001,paired *t* test), and

the SFCT in BRVO eyes (287.65±24.42μm) decreased rapidly after Ranibizumab (Fig 2E , p<0.001, paired *t* test).

Fig 2　Subfoveal choroidal thickness (SFCT) in patients with macular edema secondary to BRVO. A: The representative EDI-OCT image of unaffected contralateral eye; **B:** The representative EDI-OCT image of affected BRVO eye before intravitreal Ranibizumab (IVR) injection; **C:** The representative EDI-OCT image of affected BRVO eye after intravitreal Ranibizumab (IVR) injection; White arrowheads point the choroid-scleral junction. SFCT was determined as the vertical distance from the hyperreflective line of the retinal pigment epithelium to the line of the choroid-scleral junction centered on the fovea, it was measured by 2 observers independently, and was recorded with the mean value. **D:** Comparison of SFCT between the unaffected fellow eyes and BRVO eyes. **E:** Comparison of SFCT in BRVO eyes between pre-IVR injection and post-IVR injection. The values were displayed as mean± standard deviation (SD). The paired *t* test was used to evaluate the differences. *p<0.05 was considered statistically significant.

The affected eyes with macular edema showed a similar SFCT change in both CRVO eyes and BRVO eyes. In further, we compared the SFCT between CRVO groups and BRVO groups. Unexpectedly, although the SFCT in affected CRVO eyes (326.03 μm) was slightly thicker than the affected BRVO eyes (317.78 μm), no significant difference was showed between CRVO eyes and BRVO eyes (Fig 3 A, p >0.05, independent *t* test). The mean reduced SFCT value after IVR was 31.88 μm in CRVO eyes and 30.13 μm in BRVO eyes, there was also no significant difference in SFCT change between those two groups. (Fig 3 B, C, p>0.05, independent *t* test).

Fig 3　There was no significant difference on SFCT and SFCT change between CRVO group and BRVO group. A: Comparison of SFCT before IVR injection between CRVO group and BRVO group; **B:** Comparison of SFCT after IVR injection between CRVO group and BRVO group; **C:** Comparison of SFCT change between CRVO group and BRVO group. The independent *t* test was used to evaluate the differences. p>0.05 was considered no significant difference (NS).

Discussion

The present study showed that choroidal thickness in recent-onset treatment-naïve macular edema secondary to RVO eyes (including CRVO and BRVO) was significantly greater than that in unaffected fellow eyes, and decreased rapidly within a short term in response to single intravitreal Ranibizumab injection. Furthermore, our findings revealed that there was no significantly difference on SFCT between CRVO group and BRVO group, no matter at the onset or after intravitreal Ranibizumab injection. The study first investigated and compared the choroidal thickness change between these subtypes of RVO.

It is well known that EDI-OCT allowed a noninvasive technique to measure the choroidal thickness in vivo, which may provide a predicator to evaluate the disease severity and prognosis23, 24. Over the past several years, many studies have investigated the SFCT in macular-involved diseases. It was reported that idiopathic macular hole25 and dry AMD26 had reduced SFCT, whereas central serous chorioretinopathy (CSC) 27and Vogt- Koyanagi-Harada (VKH)28 had increased SFCT. Macular edema is

mainly secondary to diabetic retinopathy or RVO. Previous studies showed that SFCT was thinner in diabetic macular edema29, and was significantly related with the disease severity30, 31. With regard to macular edema with RVO, there had been several studies to investigate choroidal thickness and the role of choroid in the pathophysiology of RVO eyes. As was mentioned above, several studies demonstrated that the macular choroidal thickness in RVO eyes was greater than that its normal contralateral eyes12, 13, 23. In contrast, Du KF and colleges reported that no significant difference on SFCT was found in RVO eyes11. One of the explanation of the conflicting results is the difference phase of RVO, the patients recruited by Tsuiki and Coban Karatas were at acute phase, while the study conducted by Du KF included longstanding and acute phase, the discrepancy between those studies may be contributed to the effect of the longstanding RVO patients. Our findings were consistent with the speculation, the present study collected the resent-onset treatment-naïve patients with macular edema secondary to RVO, and the results showed SFCT was statistically increased in patients, who were at acute phase. Furthermore, several studies found that choroidal thickness in RVO decreased significantly following anti-VEGF treatment12, 13, 16, 32, however, Park Jongyeop and colleges reported no SFCT change was found in RVO eyes after anti-VEGF treatment9. The possible causes of the conflicting results might be the follow up period. Park Jongyeop evaluated SFCT in the long term (at 12 months) after treatment, while other studies evaluated it in the short term (ranged from 1 month to 6 months) after post-injection. Our study evaluated the SFCT at 2 weeks after injection, which was a much shorter follow up period. Our study still yield the similar finding with the studies evaluated in short term. The hypothesis is that the SFCT may decrease in short term after anti-VEGF treatment, and may restore in the long term. Further investigation is needed to demonstrate it.

The initial choroidal thickness can be served as biomarker of disease severity and predictor of prognosis30, 31, 33, 34. Although there were several studies to evaluate the choroidal thickness in RVO, they focused on CRVO or BRVO separately. To the best of our knowledge, there was no study to include CRVO group and BRVO group at the same time and to compare them, and no study showed the exact relationship between SFCT and RVO severity. CRVO and BRVO were the two main subtypes of RVO eyes35, 36. It had been demonstrated that CRVO eyes had higher ischemic index and VEGF expression compared with BRVO eyes. On the other hand, it was demonstrated that increased VEGF would induce vascular hyperpermeability and dilated vessel in choroid layer, which was the main cause of increased choroidal thickness37, 38. Thus, it was supposed that the more elevated VEGF level, the more increased choroidal thickness. In the present study, we speculated the SFCT of CRVO group may be greater than that of BRVO group. However, our findings showed no statistically difference was observed between them. The possible causes may be as following：(1).The subjects we collected were ischemic RVO patients with macular edema, VEGF level in both CRVO and BRVO group may be very high, and the difference was small; (2)The sample size in each group was too small to detect a significant difference; (3)Besides VEGF level, other unknown factors may be contribute to choroidal thickness change. Overall, the exact relationship between choroidal thickness and RVO severity require further investigations in the future study.

The present study had several limitations. First, the small sample size, short follow up period and retrospective study design are the drawbacks. The prospective study with large number of subjects and long term follow up is further required. Second, we only collected and investigated the patients with macular edema secondary to ischemic RVO, it may have selection bias, the patients obtained are not representative of the population of CRVO and BRVO, they only represent a small population of RVO who have the complication of macular edema. In order to further determine the exact relationship between SFCT and disease severity, the patients with non-ischemic RVO (including CRVO and BRVO), the patients without macular edema and the patients with other complications (such as neovascularization or glaucoma) should also be included in the future study.

Conclusion

In conclusion, in recent-onset treatment- naïve patients with macular edema secondary to RVO, SFCT was statistically greater than its unaffected contralateral eye and restored significantly in 2 weeks after a single IVR injection, it indicated subfoveal choroid may be involved in the progress of macular edema secondary to RVO eyes, moreover, our study may help to elucidate the conflicting results about the SFCT change in RVO eyes and after anti-VEGF treatment reported by previous studies.. In further, our findings first showed that SFCT and SFCT change had no significant difference between macular edema secondary to CRVO and BRVO. However, the exact relationship between SFCT and RVO severity is still need further investigation.

List Of Abbreviation

SFCT Subfoveal Choroidal Thickness

IVR Intravitreal Ranibizumab

RVO Retinal Vein Occlusion

CRVO Central Retinal Vein Occlusion

BRVO Branch Retinal Vein Occlusion

VEGF Vascular Endothelial Growth Factor

AMD Age-Related Degeneration

PCV Polypoidal Choroidal Vasculopathy

CSC Central Serous Chorioretinopathy

EDI-OCT Enhanced Depth Imaging Optical Coherence Tomography

Declarations

Ethics approval and consent to participate

The present study followed the tenets of the declaration of helsinki and was approved by the ethics committee of People's Hospital of Guangxi Zhuang Autonomous Region. The subjects had been informed and consent on the study.

Consent for publication

Not applicable

Availability of data and material

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Fen Tang and Fan Xu performed the measurements, Min Li and Qi Chen were involved in planning and supervised the work, Fen Tang, Haibin Zhong and Xin Zhao processed the experimental data, performed the analysis, drafted the manuscript and designed the figures. Mingliang Lv, Ke Yang, and Chaolan Shen performed the ophthalmic examinations. Hui Huang, Jiang Lv and Siming Zeng collected the demographic characteristics and the choroidal thickness. All authors discussed the results and commented on the manuscript.

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Figures

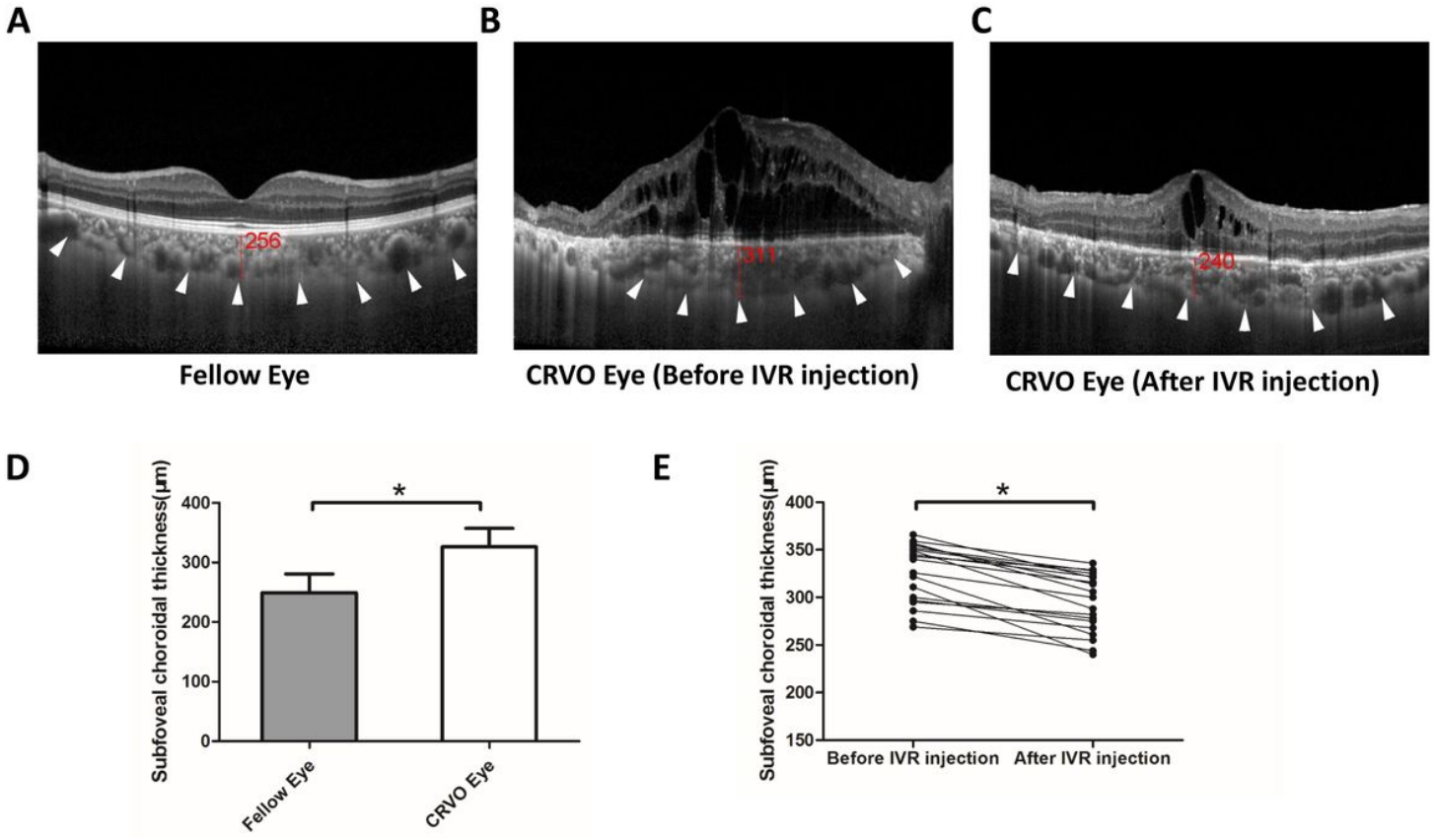

Figure 1

Subfoveal choroidal thickness (SFCT) in patients with macular edema secondary to CRVO. A: The representative EDI-OCT image of unaffected contralateral eye; B: The representative EDI-OCT image of affected CRVO eye before intravitreal Ranibizumab (IVR) injection; C: The representative EDI-OCT image of affected CRVO eye after intravitreal Ranibizumab (IVR) injection; White arrowheads point the choroid-scleral junction. SFCT was determined as the vertical distance from the hyperreflective line of the retinal pigment epithelium to the line of the choroid-scleral junction centered on the fovea, it was measured by 2 observers independently, and was recorded with the mean value. D: Comparison of SFCT between the unaffected fellow eyes and CRVO eyes. E: Comparison of SFCT in CRVO eyes between pre-IVR injection and post-IVR injection. The values were displayed as mean± standard deviation (SD). The paired t test was used to evaluate the differences. *$p<0.05$ was considered statistically significant.

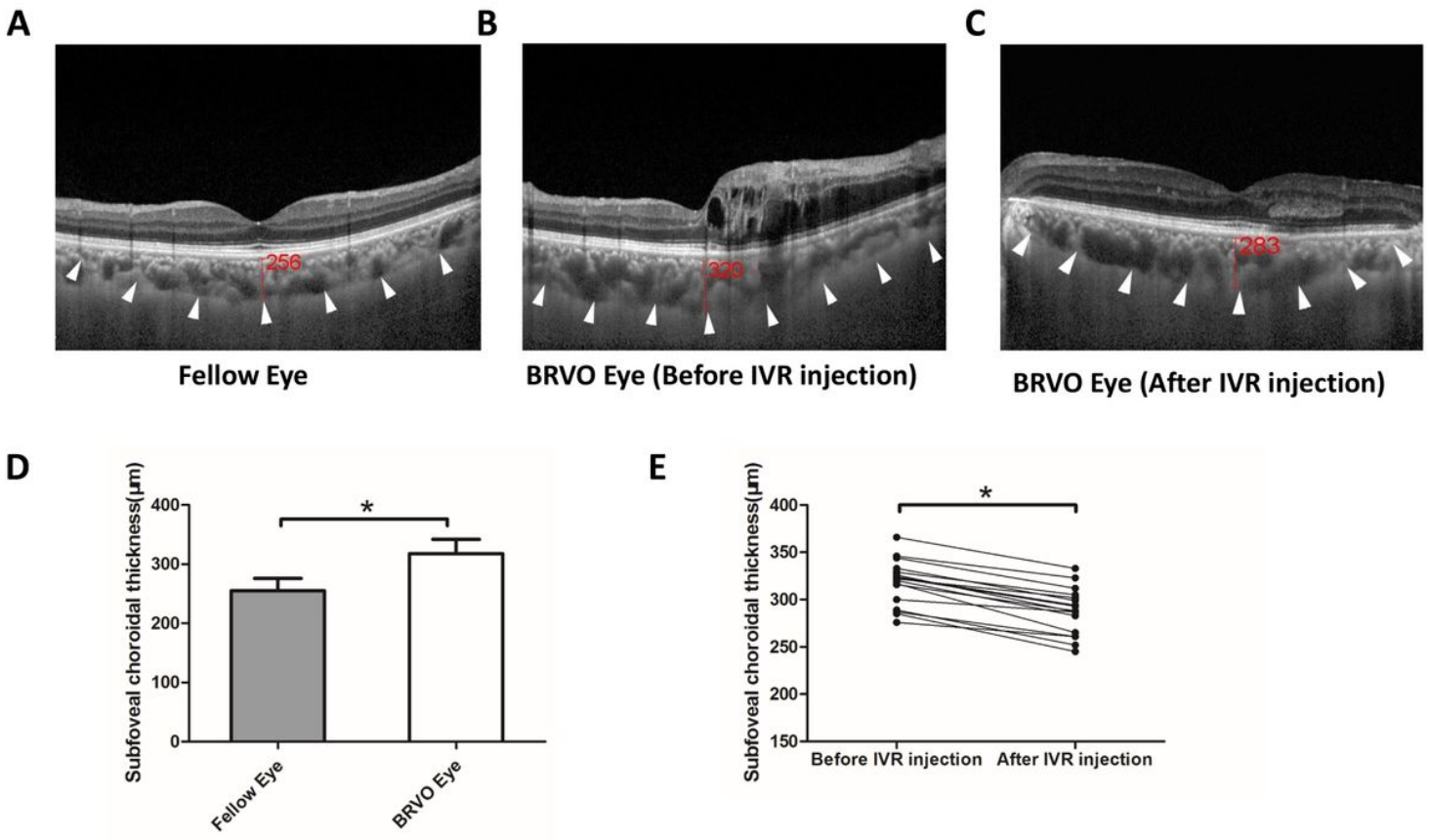

Figure 2

Subfoveal choroidal thickness (SFCT) in patients with macular edema secondary to BRVO. A: The representative EDI-OCT image of unaffected contralateral eye; B: The representative EDI-OCT image of affected BRVO eye before intravitreal Ranibizumab (IVR) injection; C: The representative EDI-OCT image of affected BRVO eye after intravitreal Ranibizumab (IVR) injection; White arrowheads point the choroid-scleral junction. SFCT was determined as the vertical distance from the hyperreflective line of the retinal pigment epithelium to the line of the choroid-scleral junction centered on the fovea, it was measured by 2 observers independently, and was recorded with the mean value. D: Comparison of SFCT between the unaffected fellow eyes and BRVO eyes. E: Comparison of SFCT in BRVO eyes between pre-IVR injection and post-IVR injection. The values were displayed as mean± standard deviation (SD). The paired t test was used to evaluate the differences. *$p<0.05$ was considered statistically significant.

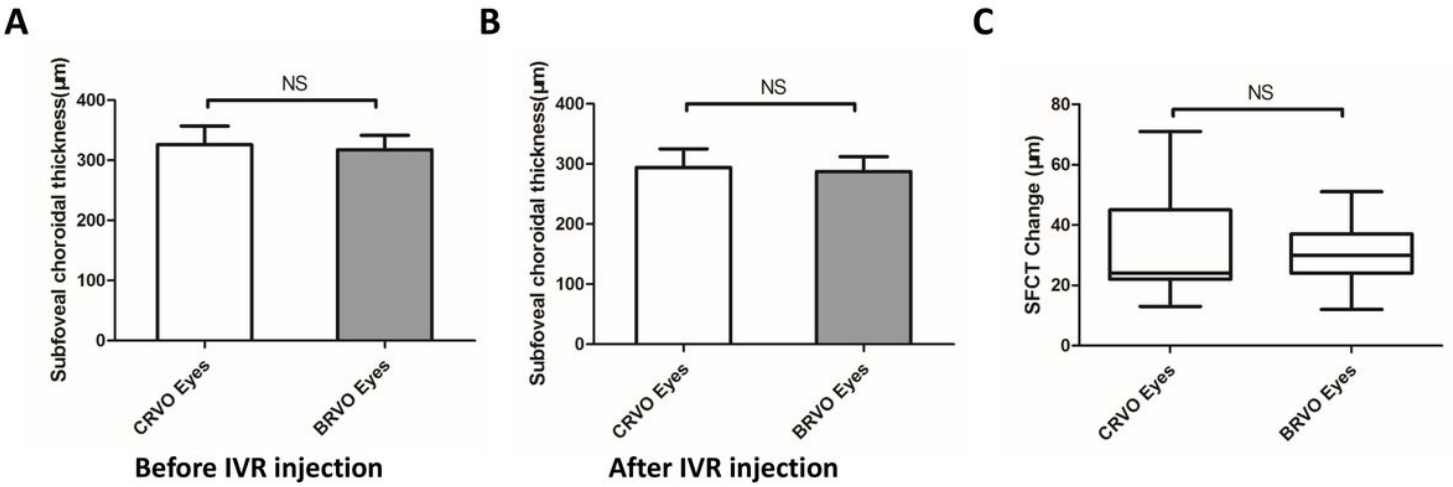

Figure 3

There was no significant difference on SFCT and SFCT change between CRVO group and BRVO group. A: Comparison of SFCT before IVR injection between CRVO group and BRVO group; B: Comparison of SFCT after IVR injection between CRVO group and BRVO group; C: Comparison of SFCT change between CRVO group and BRVO group. The independent t test was used to evaluate the differences. $p>0.05$ was considered no significant difference (NS).