

Choroidal thickness measurements with optical coherence tomography in branch retinal vein occlusion

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Abstract

• **AIM:** To evaluate central macular thickness (CMT) and mean choroidal thickness (MCT) in eyes with branch retinal vein occlusion (BRVO), before and after ranibizumab treatment using spectral domain –optical coherence tomography (SD-OCT).

• **METHODS:** Forty –two patients with unilateral BRVO and macular edema were included in this study. There were 25 men and 17 women. Using SD-OCT, choroidal thickness was measured at 500 µm intervals up to 1500 µm temporal and nasal to the fovea. MCT was calculated based on the average of the 7 locations. All the eyes with BRVO were treated with intravitreal ranibizumab (0.5 mg/0.05 mL). Comparisons between the BRVO and fellow eyes were analyzed using Mann-Whitney U test. Pre-injection and post-injection measurements were analyzed using Wilcoxon test and repeated measure analysis.

• **RESULTS:** At baseline, there was a significant difference between the BRVO and fellow eyes in MCT [BRVO eyes 245 (165–330) µm, fellow eyes 229 (157–327) µm] and CMT [BRVO eyes 463 (266–899) µm, fellow eyes 235 (148–378) µm (P=0.041, 0.0001, respectively)]. Following treatment, CMT [295 (141–558) µm] and MCT [229 (157–329) µm] decreased significantly compared to the baseline measurements (P=0.001, 0.006, respectively). Also BCVA (logMAR) improved significantly (P=0.0001) in the BRVO eyes following treatment. After treatment CMT [BRVO eyes 295 (141–558) µm, fellow eyes 234 (157–351) µm] and MCT [BRVO eyes 229 (157–329) µm, fellow eyes 233 (162–286) µm] values did not reveal any significant difference in BRVO eyes and fellow eyes (P=0.051, 0.824, respectively).

• **CONCLUSION:** In eyes with BRVO, CMT and MCT values are greater than the fellow eyes, and decrease significantly following ranibizumab injection.

• **KEYWORDS:** branch retinal vein occlusion; choroidal thickness; macular edema; optical coherence tomography; ranibizumab

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INTRODUCTION

Retinal vein occlusion (RVO) is one of the most frequent major retinal vascular disease after diabetic retinopathy^[1]. Venous thrombus formation as a result of RVO and leads to poor venous drainage, dilation and tortuosity of the large retinal veins and increased retinal capillary pressure. These changes result in exudation of blood, fluid, lipid into retina, leading to macular edema^[2]. Macular edema is a frequent cause of visual loss that should be the main treatment target^[3]. Treatment strategies for macular edema consist of focal laser photocoagulation^[4-5], intravitreal steroids^[6], and injection of anti-vascular endothelial growth factor (VEGF) protein compounds^[7-8]. Macular edema in patients with RVO seems to be closely related to VEGF levels in the vitreous^[9-10]. Thus, inhibiting VEGF seems to be a reasonable therapeutic approach^[8,11].

The choroid is a highly vascular tissue that is directly influenced by intraocular pressure as well as perfusion pressure^[12]. Choroidal blood flow is the highest of any tissue in the body to satisfy the normal metabolic demands of the outer retina^[13]. RVO is accompanied with retinal hypoxia which leads to increased VEGF expression in the retinal pigment epithelium, pericytes and microvascular endothelial cells^[14]. VEGF induces vessel dilatation and increased ocular blood flow through a mechanism involving nitric oxide production, and is proposed to increase the choroidal thickness^[15].

The aim of this study was to compare the mean choroidal thickness (MCT) and central macular thickness (CMT) in eyes with branch retinal vein occlusion (BRVO) before and

after the treatment with intravitreal ranibizumab, and compare the results with the unaffected fellow eyes.

SUBJECTS AND METHODS

In this retrospectively designed cross-sectional study, the data of consecutive patients with unilateral BRVO and macular edema, who were diagnosed between January 2012 and June 2015, were evaluated. This study adhered to the tenets of Declaration of Helsinki and was approved by the Baskent University Institutional Review Board and Ethics Committee (KA13/272).

The primary outcome measure was to evaluate the changes in MCT and CMT, before and after intravitreal injection of ranibizumab in patients with BRVO. Secondary outcome measure was to compare these values with the normal fellow eyes.

Ophthalmologic examination included best corrected visual acuity (BCVA), slit lamp biomicroscopy, and retinal examination, in addition to fundus fluorescein angiography (FFA) and spectral domain-optical coherence tomography (SD-OCT) examinations. The diagnosis of BRVO was determined according to the clinical picture and FFA as dilated and tortuous veins, flame-shaped hemorrhages, dot and blot hemorrhages, retinal edema and cotton wool spots affecting the part of the retina drained by the obstructed vein.

The BRVO eyes with macular edema, exceeding 250 microns were included in the study and compared with the fellow eyes without any macular or retinal disease. The exclusion criterias were any history of vitreous surgery, intravitreal injection of either any anti-VEGF agent or steroid, and findings of vitreo-macular traction or epiretinal membrane, as well as macular edema due to any reason other than BRVO. BRVO eyes were treated with 3 doses of intravitreal injection of ranibizumab (Lucentis; Genentech; San Francisco, CA, USA) (0.5 mg/0.05 mL) at one month intervals.

Optical coherence tomography (OCT) measurements were performed by the same experienced technician using a high speed and high resolution SD-OCT device ($\lambda=840$ nm, 26 000 A-scans/s and 5 μm axial resolution), Optovue RTVue software V.3.5 (Optovue Inc., Fremont, California, USA). Macular thickness analysis were performed by the MM5 (5 \times 5 mm² grid of 11 horizontal and 11 vertical lines with 668 A-scans each and an inner 3 \times 3 mm² grid of 6 horizontal and 6 vertical lines with 400 A-scans each). For choroidal analysis, horizontal B-scan images centered on the fovea were selected. Each B-scan image is constructed from a number of line scans through the same retinal locations and each line scan consists of 1024 A-scans. By automatically inverting the image, the chorioretinal interface became adjacent to zero delay. The retina cross-line scan has 32 frames averaged, 16 per direction without tracking^[16].

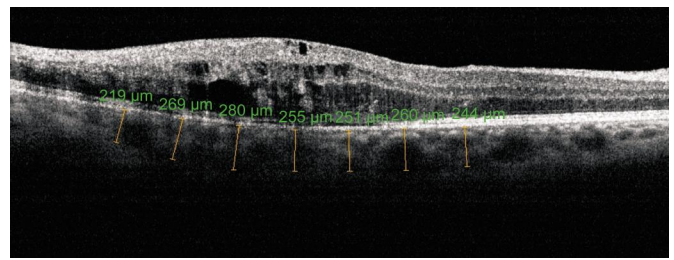


Figure 1 Baseline choroidal thickness measurements of a patient with BRVO.

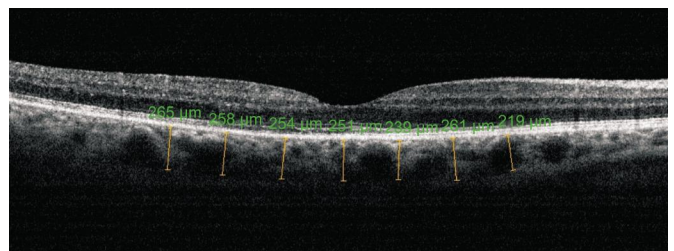


Figure 2 Choroidal thickness measurements of a patient with BRVO after intravitreal ranibizumab treatment.

The choroidal thickness was measured from the posterior edge of the retinal pigment epithelium (RPE) to the choroid-sclera junction at the fovea and at 500 μm intervals up to 1500 μm temporal as well as nasal to the fovea at 7 locations (Figure 1). The MCT was calculated based on all 7 measurements for each eye (Figures 1, 2). Choroidal thickness measurements were performed by two masked physicians (Coban-Karatas M and Ulas B). The average of two measurements was taken for the analysis. Also reliability statistics for two examiners was performed. The BCVA (in logMAR) and CMT as well as MCT measurements were evaluated at baseline (zero visit) and 1mo following the third intravitreal injection (follow-up visit), and the measurements at each time point were compared.

Statistical Analysis Statistical analysis was performed using the statistical package SPSS software (Statistical Package for the Social Sciences, version 17.0, SPSS Inc, Chicago, III, USA). For each continuous variable, normality was checked by Kolmogorov Smirnov and Shapiro-Wilk tests and by histograms. Comparisons between the eye with BRVO and fellow eye were performed with Mann-Whitney U test for the data not normally distributed. Pre-injection and post-injection measurements were analyzed using Wilcoxon test. Values of P less than 0.05 were considered statistically significant. Reliability statistics and inter-observer correlation was evaluated by Cronbach's alpha.

RESULTS

There were 42 patients with unilateral BRVO, with a mean age of 59.2 ± 7.5 y (range 42 to 81y). Twenty-five (59.5%) were male and 17 (40.5%) were female. Systemic disease questioning revealed hypertension in 28 patients (66.7%) and diabetes mellitus in 6 patients (14.3%). None of the patients had retinopathy in the fellow eye.

Table 1 Comparison of median (minumum and maximum) values of eyes with BRVO and fellow eyes before and after treatment

Measured data	Study eye		Control eye		² P
	Med (min-max)	¹ P	Med (min-max)	¹ P	
BCVA (zero visit)	0.7 (0.2-2.0)	0.0001	0.1 (0.0-0.3)	0.515	0.0001
BCVA (follow-up visit)	0.4 (0.0-1.2)		0.1 (0.0-0.3)		
CMT (zero visit)	463 (266-899)	0.001	235 (148-378)	0.861	0.0001
CMT (follow-up visit)	295 (141-558)		234 (157-351)		
MCT (zero visit)	245 (165-330)	0.006	229 (157-327)	0.826	0.041
MCT (follow-up visit)	229 (157-329)		233 (162-286)		

BCVA: Best corrected visual acuity; CMT: Central macular thickness; MCT: Mean choroidal thickness. ¹Comparison between pre and post values using Wilcoxon test; ²Comparison of the eye with BRVO and fellow eye using Mann-Whitney U test. Values of P less than 0.05 were considered statistically significant.

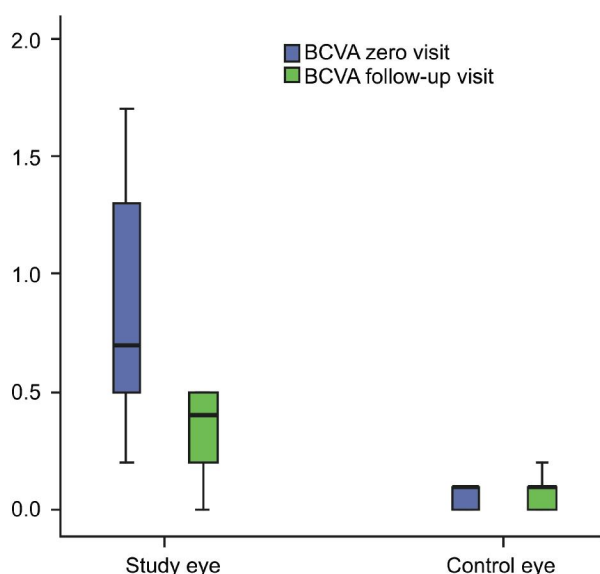


Figure 3 BCVA (LogMAR) improved significantly at the follow-up visit in BRVO eyes.

At the zero visit BCVA ranged from 2.0 to 0.2 (logMAR) (median, 0.7), and at the follow-up visit it improved to 1.2 to 0.0 (logMAR) (median 0.4) ($P=0.0001$; Figure 3).

At the zero visit, the median (min-max) MCT was 245 μm (165-330 μm) in BRVO eyes, and 229 μm (157-327 μm) in the fellow eyes. The study eyes showed greater MCT compared to the control eyes ($P=0.041$). Similarly, study eyes showed greater CMT compared to the control eyes ($P=0.0001$). The median (min-max) of CMT was 463 μm (266-899 μm) in the study eyes and 235 μm (148-378 μm) in the control eyes (Table 1).

At the follow-up visit CMT and MCT improved significantly in the study eyes ($P=0.001$, 0.006, respectively) compared to the measurements at zero visit (Figures 4, 5). The median (min-max) values for MCT was 229 μm (157-329 μm), and for CMT was 295 μm (141-558 μm) at the follow-up visit. There was no difference at the follow-up visit between the study and the control eyes for CMT and MCT values ($P=0.051$, 0.824 respectively) (Table 1). In the control eyes, also no difference was found in CMT and MCT values at zero visit and follow-up visit ($P=0.861$, 0.826 respectively).

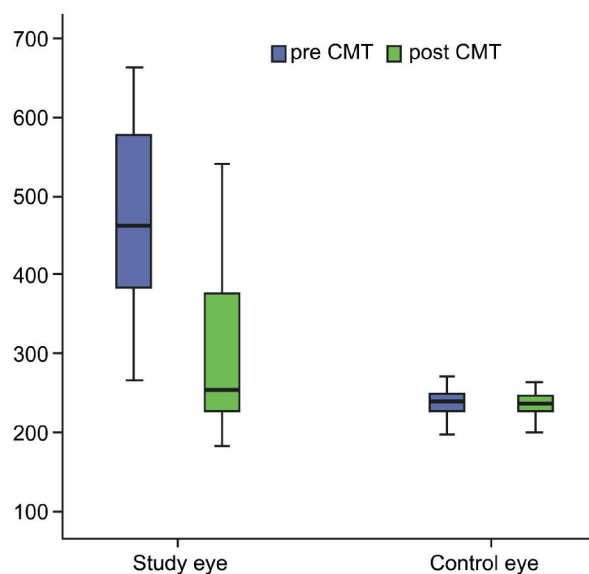


Figure 4 CMT improved significantly at the follow-up visit in BRVO eyes In the control eyes, no difference was found in CMT values at zero visit and follow-up visit.

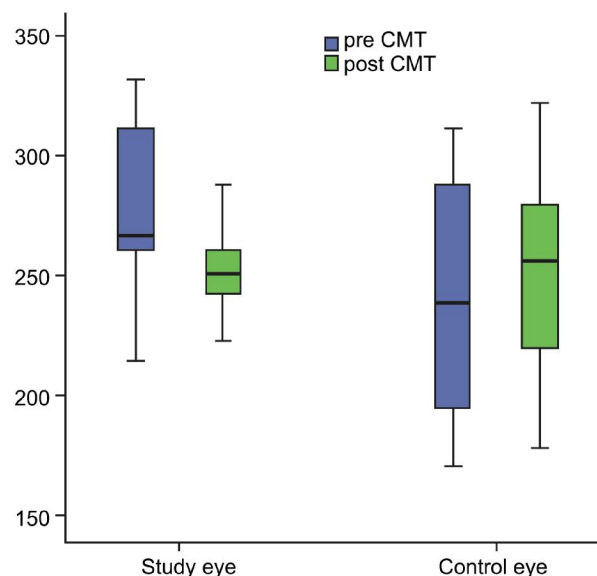


Figure 5 MCT improved significantly at the follow-up visit in BRVO eyes In the control eyes, no difference was found in MCT values at zero visit and follow-up visit.

The reliability statistics of two masked physicians were evaluated by Cronbach's alpha (Cronbach's alpha=0.934,

95% CI 0.90-0.05). Inter-observer correlation was higher than 90%. The differences between the measurements of two masked physicians were not more than 5%.

DISCUSSION

Until recently, the choroid could only be evaluated with indocyanine green angiography^[17-18], laser Doppler flowmetry^[19] and ultrasound^[20]. Although, it is possible to diagnose choroid vessel abnormalities and changes in the blood flow with these techniques, SD-OCT enabled us to achieve 3-dimensional anatomic information about RPE and choroid layers^[21-22]. OCT is a noninvasive imaging modality used to acquire high-resolution cross sectional scans of the retina. Recently, Spaide *et al*^[21] described a new acquisition technique, namely enhanced depth imaging (EDI), using Spectralis OCT device (Heidelberg Engineering, Heidelberg, Germany). Herein, placing the acquired structures deeper close to zero delay, allowed a better visualization of the choroid^[21].

Due to increased interest in choroidal imaging with OCT, other methods have been used to try to better visualize and measure the choroid, including use of swept-source OCT^[23] and longer wavelength OCT^[24-25]. All of these methods, however, potentially cause loss of clear visualization of the retinal surface where other pathologies such as vitreo-macular traction or epiretinal membrane might be present and contributing to poor vision^[26].

A high reliability and reproducibility of choroidal thickness measurements across three SD-OCT systems (Cirrus *vs* Spectralis, Cirrus *vs* RTVue, Spectralis *vs* RTVue) in normal subjects^[16]. Twenty-eight subjects of young healthy adults with no retinal and choroidal pathology and normal vision were analyzed. Choroidal thickness in normal eyes was manually measured in 5 areas. Measurements from any pair of three instruments were strongly correlated. There was good reproducibility between choroidal thickness of images acquired by Cirrus, Spectralis and RTVue^[16].

In RTVue software "chorioretinal" mode achieves the same purpose as EDI described by Spaide *et al*^[21] with a slightly different approach. RTVue's 'chorioretinal' mode moves the zero delay closer to the choroid and achieves the same effect as EDI without inverting the retinal image^[27]. Using this technique, we found that eyes with BRVO showed significantly greater MCT and CMT compared to the fellow control eyes before the treatment (zero visit). At the follow-up visit (one month following the third injection) CMT and MCT values improved in the BRVO eyes compared to the zero visit measurements. In the control eyes, however, no difference in CMT and MCT between zero and follow-up visit was found. This could be explained by increased expression of VEGF leading to increased thickness of choroid in patients with BRVO.

Several studies focused on choroidal thickness measurements in various diseases of the retina and choroid such as

Vogt-Koyanagi-Harada disease^[28], polypoidal choroidal vasculopathy^[29] and central serous chorioretinopathy^[30]. It was demonstrated that choroidal thickness can be measured by SD-OCT, and choroidal thickness disparity exists among patients with the clinical diagnosis of wet and dry age-related macular degeneration^[12]. Imamura *et al*^[30] reported that the choroidal thickness in central serous chorioretinopathy was significantly greater than the choroidal thickness in normal eyes. EDI SD-OCT revealed a very thick choroid in patients with central serous chorioretinopathy. This finding provides additional evidence that central serous chorioretinopathy may be caused by increased hydrostatic pressure in the choroid.

In a recent study, subfoveal choroidal thickness in patients with central retinal vein occlusion (CRVO) using EDI OCT was evaluated retrospectively. Thirty-six patients with macular oedema were treated with intravitreal bevacizumab (1.25 mg/0.05 mL). Mean subfoveal choroidal thickness after intravitreal bevacizumab was 227.7 ±65.1 µm, which was thinner than that before intravitreal bevacizumab therapy (266.9±79.0 µm; *P*<0.01, paired *t* test). Subfoveal choroidal thickness of CRVO eyes was significantly greater than that of fellow eyes and decreased significantly after intravitreal bevacizumab treatment. Enhanced depth imaging optical coherence tomography can be used to evaluate choroidal involvement in CRVO and may assist noninvasive diagnosis and management of this disease^[31].

In the present study, with SD-OCT we demonstrated that both MCT and CMT parameters were greater in BRVO patients and decreased significantly after ranibizumab treatment. Choroidal thickness significantly increases in eyes with unilateral BRVO and can return to normal levels following anti-VEGF treatment. This could be explained by increased expression of VEGF leading to increased thickness of choroid in patients with BRVO.

Being a retrospective study, with a small sample size are the shortcomings of this study. However, we believe that our results could be a sample for future studies on BRVO.

In conclusion, using the SD-OCT software, which enables the measurement of choroidal thickness, this study demonstrated that choroidal thickness in BRVO eyes with macular edema was significantly greater than the fellow eyes and decreased following the treatment with three doses of an anti-VEGF agent (ranibizumab). According to our results, we believe that SD-OCT is an effective non-invasive tool to evaluate the choroid and detect choroidal changes in pathologic states such as BRVO. Future studies with larger patient numbers are needed to support our findings.

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