Correlation between macular edema recurrence and macular capillary network destruction in branch retinal vein occlusion

Ji Hye Jang (mjmom99@naver.com)  
Keimyung University Dongsan Medical Center  
https://orcid.org/0000-0002-9501-9892

Yu Cheol Kim  
Keimyung University School of Medicine

Jae Pil Shin  
Kyungpook National University School of Medicine

Research article

Keywords: Macular edema, Macular capillary network, Vessel density, Branch retinal vein occlusion, Optical coherent tomography angiography

Posted Date: October 1st, 2019

DOI: https://doi.org/10.21203/rs.2.15437/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License

Version of Record: A version of this preprint was published on August 24th, 2020. See the published version at https://doi.org/10.1186/s12886-020-01611-w.
Abstract

Purpose: To evaluate the correlation between changes of the macular capillary network and macular edema (ME) recurrence in branch retinal vein occlusion (BRVO) using swept-source optical coherence tomography (SS-OCT) angiography.

Methods: We reviewed the data of 43 patients with treatment-naive ME associated with BRVO. Patients who received intravitreal bevacuzumab injection were divided into two groups based on ME recurrence after 6 months after edema resolution. The perifoveal capillary morphology and the macular capillary vessel density (VD) were retrospectively analyzed with en face SS-OCT angiography image after ME resolution.

Results: In the ME recurrence group (n=22), a broken the perifoveal capillary ring in the superficial capillary plexus (SCP) and deep capillary plexus (DCP) was more common than the no ME recurrence group (p = 0.047 and p = 0.002). The destruction of the perifoveal capillary ring of the DCP (30.0° vs 87.3°, p = 0.001) was more severe than that of the SCP (17.3° vs 69.5°, p = 0.006) in the ME recurrence group compared with the no ME recurrence group. The hemi-VD disparity between the affected areas and the unaffected areas in the SCP and DCP showed significant differences (p = 0.031 and p = 0.017), while macular VD showed no differences between the groups.

Conclusions: The destroyed perifoveal capillary ring and the hemi-VD disparity were related to the recurrence of ME in BRVO. Therefore, these factors can be helpful in predicting ME recurrence.

Background

Macular edema (ME) is the most common cause of visual loss in patients with branch retinal vein occlusion (BRVO). ME occurs from the physical destruction of the inner blood-retinal barrier caused by elevated venous pressure as a result of vein occlusion in the arteriovenous crossing site [1,2]. With respect to the natural progression of BRVO, ME occurs in 5–15% of the cases within one year from the initial onset, and while spontaneous resolution is achieved in less than half of the cases, recovery of visual acuity to 20/40 or better is rare [3].

Other factors involved in the onset of ME include increased vascular permeability caused by vascular endothelial growth factors (VEGFs) or various inflammatory cytokines [4,5]. Increased levels of intravitreal VEGFs are associated with nonperfusion areas of the retinal capillaries and the severity of ME [5,6]. However, many cases still require re-treatment due to recurrence or persistence of ME despite intravitreal anti-VEGF and/or steroid injection therapy [7–9]. Yoo et al. [10] reported that recurrent ME requires more aggressive treatment and spontaneous resolution without any treatment is very rare.

ME related to retinal vascular disorders is known to be associated with regulation of the flow of fluid in macular capillaries, according to Spaide’s [11] new theory. Edema in BRVO mainly happens in the same areas of altered macular capillary flow [11]. Tsuboi et al. [12] reported that persistent macular edema can
be related to the difference in capillary loss between the deep capillary plexus (DCP) and the superficial capillary plexus (SCP). However, there is a lack of data on the relationship between changes in the macular capillary network and ME recurrence.

Optical coherence tomography (OCT) is a very important diagnostic tool for ME caused by RVO [13,14]. It takes images of cross-sections of the macular region to provide information about changes in macular thickness, changes in intraretinal cysts, accumulation of subretinal fluid and photoreceptor damage. However, OCT has the disadvantage of being unable to show changes in the foveal avascular zone (FAZ) or the different layers in the capillary network.

In contrast, OCT angiography (OCTA) with no contrast agent utilized, uses light with a wavelength of 840–1050 nm, to amplify and calculate the difference in the signals emitted from moving and non-moving tissues to detect the flow of erythrocytes inside the blood vessels, thereby producing reconstructed images of the retinal and choroidal vascular structure. The data obtained from the retinal volume scan are reconstructed as en face image, while also providing information about the capillary morphology and area of the FAZ [15–17]. Therefore, using SS-OCT images, we analyzed the changes in macular capillary structure following treatment for BRVO-induced ME and investigated the factors associated with ME recurrence.

**Methods**

The present study retrospectively analyzed the medical records and images of patients who were diagnosed with treatment-näive ME associated with BRVO at the Department of Ophthalmology, Dongsan Medical Center, Keimyung University between October 2016 and March 2018. Comparative analysis was performed with the patients divided into two groups with and without recurrence of ME during 6 months after the resolution of initial ME. The present study was performed in accordance with the principles of the Declaration of Helsinki and was approved by the Keimyung University Institutional Review Board ( IRB no. 2018–09–039).

Patients with any of the following conditions were excluded from the study: 1) previous diagnosis and treatment for BRVO, 2) other retinal diseases, which may affect macular thickness such as age-related macular degeneration, diabetic retinopathy, central retinal vein occlusion, epi-retinal membrane, 3) high myopia ( axial length ≥ 26.5mm or refractive error ≥ –6 dioper), 4) glaucoma, 5) previously received pars plana vitrectomy. Patients were also excluded in cases of voluntary termination of follow-up prior to ME resolution and difficulty in analyzing data due to poor image quality.

The locations of vein occlusion proposed by Hayreh et al. [18] were used to divide the occlusion into two types: major BRVO and macular BRVO. ME was diagnosed using swept source-OCT (SS-OCT; Swept Source DRI-OCT Triton™, Topcon, Tokyo, Japan) and macular thickening was defined as central macular thickness (CMT) of ≥ 300 um with intraretinal cyst or subretinal fluid in the macular region. OCT was performed during each visit to check for the presence of edema and changes in macular thickness.
Resolution of ME was defined as a CMT < 300 um with concave macular contour. All patients were treated with intravitreal bevacizumab injection for ME. During the follow-up periods, intravitreal bevacizumab injection was repeated as needed until ME resolution was achieved.

**Perifoveal capillary network morphology analysis using OCTA**

Changes in the morphology of perifoveal capillary network (FAZ area, perifoveal capillary ring) were analyzed using OCTA (Swept Source DRI-OCT Triton™, Topcon, Tokyo, Japan) and imaging was performed by a single experienced examiner on the same day.

The images of the macular region (3 x 3 mm) were automatically acquired with four slabs, divided into SCP, DCP, outer retina, and choriocapillaris using the IMAGEnet 6 software (version 1.17, Topcon, Tokyo, Japan). The range of the SCP included 2.6 um below the internal limiting membrane to 15.6 um below the inner plexiform layer, while that of the DCP included between 15.6  to 70.2  below the inner plexiform layer.

Analyzed images were obtained after resolution of ME to eliminate segmentation errors in the retinal layer due to macular swelling. The image with signal strength intensity (SSI) values $\geq$ 50 were selected and the FAZ area and perifoveal capillary ring morphology analyzed.

The FAZ area was obtained from automatically calculated values from two examiners using a caliper contained in the program to manually draw along the inner boundaries of the SCP and DCP (Figure 1). The perifoveal capillary ring was defined as the boundary of FAZ, which was enclosed retinal capillaries. Changes in the perifoveal capillary ring were divided into two types: (I) intact (0 clock hour) if the inner boundary of the capillary plexus was not broken after resolution of ME and (II) ring loss or destruction if the inner boundary was broken. The degree of ring loss was marked as the clock hour and then converted by multiplying 30° with each hour (Figure 2).

**Macular capillary vessel density analysis using Image J**

VD in the macular capillary network was analyzed by the Image J software program (version 1.52a, National Institutes of Health, Bethesda, Maryland, USA; available at [http://imagej.nih.gov/ij/](http://imagej.nih.gov/ij/)) using SCP and DCP images of 3 x 3 mm macular region acquired by OCTA. For visualization of the capillaries, a 320 x 320 pixel image was converted to an 8-bit image and processed by binarization after marking with gray values between 0 and 255, and the average gray value of all pixels was used as the VD (Figure 3).

Moreover, to analyze the hemi-VD disparities between the affected areas and the unaffected areas in BRVO, the SCP & DCP images were divided into upper and lower portions of the image. The hemi-VD values respectively measured by binarization of the 320 x 160 pixel area (3 x 1.5 mm) and the hemi-
vessel density disparity was calculated by the difference of VD between hemi-superior area and hemi-inferior area (Figure 4).

**Statistical analysis**

The SAS program (version 9.4, SAS Institute Inc. Cary, North Carolina, USA) was used for statistical analysis with \( p \)-value < 0.05 considered as statistically significant. The values measured by two examiners were considered reliable if ICC was \( \geq 0.8 \). The mean of SSI values in *en face* OCTA images were no significant differences between the two groups. (the mean of SSI values = 59.05 vs 60.62) \( (p = 0.32) \)

The superficial and deep FAZ areas, average VD, and hemi-VD disparity in SCP and DCP between the two groups were analyzed using the Wilcoxon rank-sum test. The superficial and deep perifoveal capillary ring loss were analyzed using the Chi-square test and the extent of capillary ring loss was analyzed using the Wilcoxon rank-sum test.

**Results**

The patient population included a total of 43 patients: 21 patients with no ME recurrence and 22 patients with ME recurrence following intravitreal anti-VEGF injection therapy for BRVO-induced ME. The demographics and clinical characteristics of the eyes with or without ME recurrences in BRVO are summarized in Table 1.

There were no statistically significant differences in the mean ages \( (p = 0.318) \), sex \( (p = 0.667) \), involvement of eye \( (p = 0.897) \), the location of vein occlusion \( (p = 0.650) \), the presence of macular hemorrhage \( (p = 0.665) \), the pre-treatment BCVA (logMAR) after resolution of ME \( (p = 0.371) \), mean CMT before and after resolution of ME \( (p = 0.170, p = 0.502) \) and the mean duration until resolution of ME \( (p = 0.313) \) between the groups with and without recurrence of ME.

However, BCVA at six months after resolution of ME showed a significantly better visual improvement in the no ME recurrence group \( (p = 0.037) \) and the mean number of injections until resolution of ME was higher in the recurrence group, showing that the recurrence group required additional injections to achieve resolution of ME \( (p = 0.028) \).

The change of the morphology of the perifoveal capillary network (FAZ area, perifoveal capillary ring) between the groups is summarized in Table 2. The mean FAZ in the SCP \( (p = 0.035) \) and the DCP \( (p = 0.063) \) areas was wider in the ME recurrence group compared with the no ME recurrence group. With respect to intact perifoveal capillary ring, the recurrence group had a significantly higher number of cases with perifoveal capillary ring loss in the SCP and DCP \( (p = 0.047, p = 0.002) \). The mean extents of perifoveal capillary ring loss in the SCP \( (p = 0.006) \) and DCP \( (p = 0.001) \) were more severe in the ME recurrence group compared with the no ME recurrence group.
The mean VD in the SCP \((p = 0.298)\) and the DCP \((p = 0.190)\) was no significant differences regardless of ME recurrence. Otherwise, the hemi-VD disparity between the unaffected and affected areas in SCP \((p = 0.031)\) and the DCP \((p = 0.017)\) showed statistically significant differences between the groups (Table 3).

**Discussion**

This retrospective study aimed to investigate how changes in the macular capillary morphology and the macular vessel density affect recurrence of ME associated with BRVO. Using *en face* OCTA images after resolution of ME, the recurrence group showed a less intact perifoveal capillary ring and a broader range of ring loss than the no ME recurrence group. Moreover, the recurrence group also showed a larger hemi-VD disparity between the unaffected and affected areas in the SCP and DCP and a lower hemi-VD in the affected area in the DCP, when compared with the no ME recurrence group.

The most common causes of visual loss in BRVO cases are known to be ME and macular ischemia [19, 20], however, the definition of macular ischemia remains unclear, but the occurrence of ME and macular ischemia are closely related [21,22]. Sim et al. [21] defined macular ischemia as an expansion of the FAZ and non-perfusion in perimacular capillaries. Meanwhile, Finkelstein [22] reported that the macular ischemia is associated with the destruction of the perifoveal capillary ring, while Wakabayashi et al. [23] defined capillary ring loss of \(\geq 1/4\) as the destruction of the FAZ. In our study, although a definition of macular ischemia was not provided, we analyzed whether the changes in the capillary network (the FAZ area, capillary ring morphology) and macular vascular density (VD in 3 x 3 mm macular region, the hemi-VD disparity) affect ME recurrence.

The mean superficial and deep FAZ areas in healthy people is 0.2–0.4 mm\(^2\) and 0.3–0.6 mm\(^2\), respectively, with the deep FAZ areas being wider than superficial FAZ areas [24–26]. Changes in FAZ area and VD have been reported as important biomarkers for the progression of diabetic retinopathy or retinal vascular diseases and prognosis of visual acuity [27–29]. These factors are more useful to OCT angiography than fluorescein angiography [30–31].

Wakabayashi et al. [23] reported that smaller FAZ areas resulted in better visual acuity after resolution of ME, and Parodi et al. [26] reported that the association between ME and visual loss was weak, but an increase in the FAZ area was closely associated with visual loss. As shown, most of the previous studies reported associations between the FAZ and the prognosis of visual acuity in retinal vascular disease [17, 23, 26–29]. However, studies on the association between the FAZ area and the ME recurrence are lacking. Our study found that the recurrence group had wider superficial and deep FAZ areas after resolution of ME when compared with the no ME recurrence group, with greater statistical significance in the superficial FAZ area values. Unfortunately, we did not analyze whether the FAZ areas changes over time after ME resolution, therefore, additional studies are needed to establish the changes that occur in FAZ areas following ME resolution.
In our study, the extent of perifoveal capillary ring loss in the SCP and DCP was significantly higher in the recurrence group when compared with the no ME recurrence group, indicating that ring destruction was more severe at DCP than SCP level in the recurrence group. Destruction of the capillary ring actually had a greater effect on ME recurrence than FAZ enlargement. Identification of DCP status by OCTA is very important for identifying macular ischemia [32]. Deep capillaries play a role as a watershed zone that supplies blood to the outer plexiform and inner nuclear layers [24], and supplies the necessary oxygen to the inner segments of visual cells under scotopic conditions [33]. Destruction of a capillary ring is an indicator of macular ischemia, where destruction of superficial and deep perifoveal capillary ring promotes secretion of VEGFs, which may cause ME to occur more readily due to increased vascular permeability.

The VD of capillary network in 3 x 3 mm macular region and the hemi-VD disparity were calculated, which indirectly reflects the degree of macular capillary perfusion. Hasegawa and colleagues [34] reported that patients with severe macular VD reduction in en face OCTA SCP images had less edema recurrence and need less intravitreal anti-VEGF injections. Sakimoto and colleagues [35] divided the macular perfusion into the three grades using FAG: full perfusion area, partial perfusion area, and nonperfusion area. They found that partial perfusion area with the dilated and irregular capillary net was a source of macular edema.

In this study, we checked the macular VD using both SCP and DCP images in en face OCTA. Our results showed no difference in the macular VD between the recurrence and no ME recurrence groups, but the recurrence group showed a greater hemi-VD disparity between the hemi-superior areas and hemi-inferior areas in the SCP and DCP than the no ME recurrence group. Moreover, macular capillary loss in the affected areas with BRVO in the DCP was especially higher in the ME recurrence group. How can we get the opposite results about between the capillary loss and edema recurrence? We think that the hemi-VD disparity does not mean non-perfusion area. Rehak and colleagues [36] found that alteration of retinal VEGF gene expression and dysfunction of water homeostasis of Müller cells are not restricted in vein-occluded area but also involved in neighboring non-occluded area in rat animal model of BRVO. We consider that macular edema occurs often until restoration of damaged retinal vessels after vein occlusion. So, the hemi-VD disparity beween hemi-superior and hemi-inferior macular area might reflect the disturbances of edema control in entire macular area. and contributes the development of macular edema.

This study had some limitations. Because the images were acquired from just a single round of OCTA, excluding images with poor image qualities from the analysis therefore, a relatively small number of samples were retrospectively analyzed. The study did not identify the range of retinal nonperfusion area by fluorescein fundus angiography, while VD measured by OCTA used only a 3 x 3 mm macular region. So, future studies are needed to examine the change of macular capillary network morphology over time after ME resolution using wide-viewing OCT angiography image.

Conclusions
In conclusion, the perifoveal capillary ring destructions and the hemi-VD disparities were related to the recurrence of ME in BRVO. The more the destruction of the foveal capillary ring, the greater the hemi-VD disparity, the lower the hemi-VD in the affected areas of BRVO, which may be correlated with a higher risk of ME recurrence. Therefore, the finding of the macular capillary ring morphology and vessel density change with naïve ME associated with BRVO can be helpful in predicting ME recurrence.

**Abbreviations**

BRVO: Branch retinal vein occlusion; CMT: Central macular thickness; DCP: Deep capillary plexus; FAG: Fluorescein angiography; FAZ: Foveal avascular zone; ME: Macular edema; OCT: Optical coherence tomography; OCTA: Optical coherence tomography angiography; SCP: Superficial capillary plexus; SSI: Signal strength intensity; SS-OCT: Swept-source optical coherence tomography; VD: Vessel density; VEGF: Vascular endothelial growth factor; VD: Vessel density.

**Declarations**

**Acknowledgments**

Not applicable

**Authors contributions**

Data acquisition: JJH and KYC

Analysis and interpretation of data: JJH, KYC and SJP

Write the manuscript: JJH

Revise the manuscript: JJH and SJP

All authors have read and approved the content and agree to submit for publication in the journal.

**Funding**

This work has no financial support.

**Availability of data and materials**

The data are available form the corresponding author on reasonable request.
Ethical approval and consent of participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by the Keimyung University Institutional Review Board (IRB no. 2018–09–039).

Informed consent

For this type of study, formal consent is not required.

Consent for publications

Not applicable

Competing interests

J. H.J received payment for lectures from Bayer, Novartis outside the submitted work.; Y. C.K reports honorarism from Allergan, Bayer, Novartis and Santan, and research grant from Bayer, outside the submitted work; J. P.S has nonfinancial supports.

References

1. Silva RM, Faria de Abreu JR, Cunha-Vaz JG. Blood-retina barrier in acute retinal branch vein occlusion. Graefes Arch Clin Exp Ophthalmol. 1995;233(11):721–6.
2. Rehak J, Rehak M. Branch retinal vein occlusion: pathogenesis, visual prognosis, and treatment modalities. Curr Eye Res. 2008;33(2):111–31.
3. Rogers SL, McIntosh RL, Lim L, et al. Natural history of branch retinal vein occlusion: an evidence-based systematic review. Ophthalmology. 2010;117(6):1094–101.
4. Tolentino MJ, Miller JW, Gragoudas ES, et al. Intravitreous injections of vascular endothelial growth factor produce retinal ischemia and microangiopathy in an adult primate. Ophthalmology. 1996;103(11):1820–8.
5. Noma H, Funatsu H, Yamasaki M, et al. Pathogenesis of macular edema with branch retinal vein occlusion and intraocular levels of vascular endothelial growth factor and interleukin–6. Am J Ophthalmol. 2005;140(2):256–61.
6. Daruich A, Matet A, Moulin A, et al. Mechanisms of macular edema: Beyound the surface. Prog Retina Eye Res. 2018;63:20–68.
7. Prager F, Michels S, Kriechbaum K, et al. Intravitreal bevacizumab (avastin) for macular edema secondary to retinal vein occlusion: 12-month results of a prospective clinical trial. Br J Ophthalmol.
8. Tadayoni R, Waldstein SM, Boscia F, et al. Sustained benefits of ranibizumab with or without laser in branch retinal vein occlusion: 24-month results of the BRIGHTER study. Ophthalmology. 2017;124(12):1778–1787.

9. Yoon YH, Kim JW, Lee JY, et al. Dexamethasone intravitreal implant for early treatment and retreatment of macular edema related to branch retinal vein occlusion: the multicenter COBALT study. Ophthalmologica. 2018;240(2):81–89.

10. Yoo SJ, Kim JH, Lee TG, et al. Natural short-term course of recurrent macular edema following intravitreal bevacizumab therapy in branch retinal vein occlusion. Korean J Ophthalmol. 2017;31(2):95–101.

11. Spaide RF. Retinal vascular cystoid macular edema: Review and new theory. Retina. 2016;36(10):1823–42.

12. Tsuboi K, Ishida Y, Kamei M. Gap in capillary perfusion on optical coherence tomography angiography associated with persistent macular edema in branch retinal vein occlusion. Invest Ophthalmol Vis Sci. 2017;58(4):2038–43.

13. Spaide RF, Lee JK, Klancnik JK Jr, Gross NE. Optical coherence tomography of branch retinal vein occlusion. Retina. 2003;23(3):343–7.

14. Hoeh AE, Ruppenstein M, Ach T, Dithmar S. OCT patterns of macular edema and response to bevacizumab therapy in retinal vein occlusion. Graefes Arch Clin Exp Ophthalmol. 2010;248(11):1567–72.

15. Nagiel A, Sadda SR, Sarraf D. A promising future for optical coherence tomography angiography. JAMA Ophthalmol. 2015;133(6):629–30.

16. Kashani AH, Chen CL, Gahm JK, et al. Optical coherence tomography angiography: A comprehensive review of current methods and clinical applications. Prog Retin Eye Res. 2017;60:66–100.

17. Tsai G, Banaee T, Conti FF, Singh RP. Optical coherence tomography angiography in eyes with retinal vein occlusion. J Ophthalmic Vis Res. 2018;13(3):315–332.

18. Hayreh SS, Zimmerman MB, Podhajsky P. Incidence of various types of retinal vein occlusion and their recurrence and demographic characteristics. Am J Ophthalmol. 1994;117(4):429–41.

19. Scott IU, VanVeldhuisen PC, Oden NL, et al. Baseline predictors of visual acuity and retinal thickness outcomes in patients with branch retinal vein occlusion: Standard care versus corticosteroid for retinal vein occlusion study report 10. Ophthalmology. 2011;118(2):345–52.

20. Hayreh SS, Zimmerman MB. Branch retinal vein occlusion: natural history of visual outcome. JAMA Ophthalmol. 2014;132(1):13–22.

21. Sim DA, Keane PA, Zarranz-Ventura J, et al. Predictive factors for the progression of diabetic macular ischemia. Am J Ophthalmol. 2013;156(4):684–92.

22. Finkelstein D. Ischemic macular edema. Recognition and favorable natural history in branch vein occlusion. Arch Ophthalmol. 1992;110(10):1427–34.
23. Wakabayashi T, Sato T, Hara-Ueno C, et al. Retinal microvasculature and visual acuity in eyes with branch retinal vein occlusion: Imaging analysis by optical coherence tomography angiography. Invest Ophthalmol Vis Sci. 2017;58(4):2087–2094.

24. Provis JM, Dubis AM, Maddess T, Carroll J. Adaptation of the central retina for high acuity vision: cones, the fovea and the avascular zone. Prog Retin Eye Res. 2013;35:63–81.

25. Coscas F, Sellam A, Glacet-Bernard A, et al. Normative data for vascular density in superficial and deep capillary plexuses of healthy adults assessed by optical coherence tomography angiography. Invest Ophthalmol Vis Sci. 2016;57(9):OCT211–23.

26. Parodi MB, Visintin F, Della Rupe P, Ravalico G. Foveal avascular zone in macular branch retinal vein occlusion. Int Ophthalmol. 1995;19(1):25–8.

27. Falavarjani KG, Shenazandi H, Naseri D, et al. Foveal avascular zone and vessel density in healthy subjects: an optical coherence tomography angiography study. J Ophthalmic Vis Res. 2018;13(3):260–265.

28. Al-Sheikh M, Akil H, Pfau M, Sadda SR. Swept-Source OCT angiography imaging of the foveal avascular zone and macular capillary network density in diabetic retinopathy. Invest Ophthalmol Vis Sci. 2016;57(8):3907–13.

29. Adhi M, Filho MA, Louzada RN, et al. Retinal capillary network and foveal avascular zone in eyes with vein occlusion and fellow eyes analyzed with optical coherence tomography angiography. Invest Ophthalmol Vis Sci. 2016;57(9):OCT486–94.

30. Spaide RF, Klancnik JM Jr, Cooney MJ. Retinal vascular layers imaged by fluorescein angiography and optical coherence tomography angiography. JAMA Ophthalmol. 2015;133(1):45–50.

31. Mochi T, Anegondi N, Girish M, Jayadev C, Sinha Roy A. Quantitative comparison between optical coherence tomography angiography and fundus fluorescein angiography images: effect of vessel enhancement. Ophthalmic Surg Lasers Imaging Retina. 2018;49(11):e175-e181.

32. Rahimy E, Sarraf D. Paracentral acute middle maculopathy spectral-domain optical coherence tomography feature of deep capillary ischemia. Curr Opin Ophthalmol. 2014;25(3):207–12.

33. Birol G, Wang S, Budzynski E, Wangsa-Wirawan ND, Linsenmeier RA. Oxygen distribution and consumption in the macaque retina. Am J Physiol Heart Circ Physiol. 2007;293(3):H1696–704.

34. Hasegawa T, Murakawa S, Maruko I, Kogure-Katakura A, Iida T. Correlation between reduction in macular vessel density and frequency of intravitreal ranibizumab for macular oedema in eyes with branch retinal vein occlusion. Br J Ophthalmol. 2019;103(1):72–77.

35. Sakimoto S, Kamei M, Suzuki M, et al. Relationship between grades of macular perfusion and foveal thickness in branch retinal vein occlusion.Clin Ophthalmol. 2013;7:39–45.

36. Rehak M, Hollborn M, Iandiev I, et al. Retinal gene expression and Müller cell responses after branch retinal vein occlusion in the rat. Invest Ophthalmol Vis Sci. 2009;50(5):2359–67.

Tables
Table 1. Demographics and clinical characteristics of study eyes
| Characteristics                              | no ME recurrence group (n=21) | ME recurrence group (n=22) | *p*-value |
|---------------------------------------------|------------------------------|-----------------------------|-----------|
| Mean age (year)                             | 60.29 ± 14.26                | 64.00 ± 9.08                | 0.318*    |
| Male / Female (no)                          | 8 / 13                       | 7 / 15                      | 0.667†    |
| Right eye / Left eye (no)                   | 9 / 12                       | 9 / 13                      | 0.897†    |
| Occlusion site, no (%)                      |                              |                             | 0.650†    |
| Major BRVO                                  | 10 (47.6%)                   | 12 (54.5%)                  |           |
| Macular BRVO                                | 11 (52.4%)                   | 10 (45.5%)                  |           |
| Presence of macular hemorrhage, no          | 14 (66.7%)                   | 16 (72.7%)                  | 0.665†    |
| Mean logMAR BCVA at first visit             | 0.17 ± 0.21                  | 0.33 ± 0.31                 | 0.037*    |
| Mean logMAR BCVA at 6 months                | 494.43 ± 164.62              | 550.82 ± 161.31             | 0.170*    |
| Mean CMT before treatment                   | 2.87 ± 2.16                  | 2.30 ± 1.63                 | 0.313*    |
| Mean CMT at ME resolution                   | 2.05 ± 1.12                  | 2.86 ± 1.32                 | 0.028*    |
| Mean time to ME resolution, months          | 8.38 ± 3.14 (6 - 15)         | 11.09 ± 4.82 (6 - 21)       | 0.036*    |
| Mean number of intravitreal injections       |                              |                             |           |
| Mean follow-up period, months (range)       |                              |                             |           |
Values are presented as mean ± standard deviation unless otherwise indicated. ME = macular edema; BRVO = branch retinal vein occlusion; log MAR = logarithm of the minimum angle of resolution; BCVA = best corrected visual acuity; CMT = central macular thickness.

* Statistics by Wilcoxon rank-sum test; † Statistics by Chi-square test.

Table 2. The perifoveal capillary network morphology of en face swept-source optical coherence tomography angiography images in groups with or without macular edema recurrence in branch retinal vein occlusion
| OCT angiography parameters | no ME recurrence | ME recurrence group (n=22) | p-value |
|----------------------------|------------------|-----------------------------|---------|
|                            |                  |                             |         |
| **Superficial capillary plexus** |                  |                             |         |
| Average FAZ area           | 0.40 ± 0.11 ‡    | 0.52 ± 0.26 ‡               | 0.035*  |
| Intact perifoveal capillary ring, no (%) | 12 (57.1%)       | 6 (27.3%)                   | 0.047†  |
| Extent of the destructed capillary ring, no (%) | 6 (28.6%)        | 3 (13.6%)                   |         |
| 1 clock hour               | 3 (14.3%)        | 5 (22.7%)                   |         |
| 2 clock hours              | 0 (0.0%)         | 2 (9.1%)                    |         |
| 3 clock hours              | 0 (0.0%)         | 2 (9.1%)                    |         |
| 4 clock hours              | 0 (0.0%)         | 0 (0.0%)                    |         |
| 5 clock hours              | 0 (0.0%)         | 4 (18.2%)                   |         |
| 6 clock hours              | 17.3             | 69.5                        | 0.006*  |
| Average extent of capillary ring loss, ° |                   |                             |         |
| **Deep capillary plexus**   |                  |                             |         |
| Average FAZ area           | 0.48 ± 0.12 ‡    | 0.60 ± 0.26 ‡               | 0.063*  |
| Intact perifoveal capillary ring, no (%) | 11 (52.4%)       | 2 (9.1%)                    | 0.002†  |
| Extent of the destructed capillary ring, no (%) | 5 (23.8%) | 5 (22.7%) |
| 1 clock hour | 2 (9.5%) | 2 (9.1%) |
| 2 clock hours | 2 (9.5%) | 4 (18.2%) |
| 3 clock hours | 0 (0.0%) | 5 (22.7%) |
| 4 clock hours | 0 (0.0%) | 1 (4.6%) |
| 5 clock hours | 1 (4.8%) | 3 (13.6%) |
| 6 clock hours | 30.0 | 87.3 | 0.001* |

Average extent of capillary ring loss, °.

Values are presented as mean ± standard deviation unless otherwise indicated. OCT = optical coherence tomography; ME = macular edema; FAZ = foveal avascular zone.

* Statistics by Wilcoxon rank-sum test; † Statistics by Chi-square test.

**Table 3. The macular capillary density of *en face* swept-source optical coherence tomography angiography images in groups with or without macular edema recurrence in branch retinal vein occlusion**
| OCT angiography parameters | no ME recurrence group (n=21) | ME recurrence group (n=22) | p-value* |
|---------------------------|-------------------------------|-----------------------------|----------|
| **Superficial capillary plexus** |                               |                             |          |
| Macular vessel density (3 x 3 mm² area) | 76.70 ± 9.06 | 78.07 ± 7.66 | 0.298    |
| Hemi-vessel density (3 x 1.5 mm² area) |                               |                             |          |
| Hemi-vessel density in the unaffected area | 81.49 ± 9.82 | 84.40 ± 9.72 | 0.215    |
|                                     | 72.23 ± 16.62 | 71.32 ± 9.87 | 0.544    |
| Hemi-vessel density in the affected area | 9.26 ± 10.68 | 13.08 ± 8.81 | 0.031    |
| Hemi-vessel density disparity |                               |                             |          |
| **Deep capillary plexus** |                               |                             |          |
| Macular vessel density (3 x 3 mm² area) | 73.71 ± 7.39 | 71.87 ± 6.22 | 0.190    |
| Hemi-vessel density (3 x 1.5 mm² area) |                               |                             |          |
| Hemi-vessel density in the unaffected area | 81.68 ± 7.70 | 82.55 ± 9.20 | 0.512    |
|                                     | 65.57 ± 9.50 | 68.82 ± 8.38 | 0.040    |
| Hemi-vessel density in the affected area | 14.10 ± 12.42 | 21.73 ± 12.10 | 0.017    |
| Hemi-vessel density disparity |                               |                             |          |
Values are presented as mean ± standard deviation unless otherwise indicated. OCT = optical coherence tomography; ME = macular edema.

* Statistics by Wilcoxon rank-sum test.

Table 1. Demographics and clinical characteristics of study eyes
| Characteristics                              | no ME recurrence group (n=21) | ME recurrence group (n=22) | \( p \)-value |
|---------------------------------------------|------------------------------|---------------------------|---------------|
| Mean age (year)                             | 60.29 ± 14.26               | 64.00 ± 9.08              | 0.318*        |
| Male / Female (no)                          | 8 / 13                      | 7 / 15                    | 0.667†        |
| Right eye / Left eye (no)                   | 9 / 12                      | 9 / 13                    | 0.897†        |
| Occlusion site, no (%)                      |                              |                           | 0.650†        |
| Major BRVO                                  | 10 (47.6%)                  | 12 (54.5%)                |               |
| Macular BRVO                                | 11 (52.4%)                  | 10 (45.5%)                |               |
| Presence of macular hemorrhage, no          | 14 (66.7%)                  | 16 (72.7%)                | 0.665†        |
| Mean logMAR BCVA at first visit             | 0.17 ± 0.21                 | 0.33 ± 0.31               | 0.037*        |
| Mean logMAR BCVA at 6 months                | 494.43 ± 164.62             | 550.82 ± 161.31           | 0.170*        |
| Mean CMT before treatment                   | 2.87 ± 2.16                 | 2.30 ± 1.63               | 0.313*        |
| Mean CMT at ME resolution                   | 2.05 ± 1.12                 | 2.86 ± 1.32               | 0.028*        |
| Mean time to ME resolution, months          | 8.38 ± 3.14 (6 - 15)        | 11.09 ± 4.82 (6 - 21)     | 0.036*        |
| Mean number of intravitreal injections      |                              |                           |               |
| Mean follow-up period, months (range)       |                              |                           |               |
Values are presented as mean ± standard deviation unless otherwise indicated. ME = macular edema; BRVO = branch retinal vein occlusion; log MAR = logarithm of the minimum angle of resolution; BCVA = best corrected visual acuity; CMT = central macular thickness.

* Statistics by Wilcoxon rank-sum test; † Statistics by Chi-square test.

Table 2. The perifoveal capillary network morphology of en face swept-source optical coherence tomography angiography images in groups with or without macular edema recurrence in branch retinal vein occlusion
| OCT angiography parameters | no ME recurrence | ME recurrence group (n=22) | \( p \)-value |
|---------------------------|------------------|----------------------------|-------------|
| **Superficial capillary plexus** |                 |                            |             |
| Average FAZ area          | 0.40 ± 0.11  †   | 0.52 ± 0.26  †             | 0.035*      |
| Intact perifoveal capillary ring, no (%) | 12 (57.1%) | 6 (27.3%) | 0.047† |
| Extent of the destructed capillary ring, no (%) | 6 (28.6%) | 3 (13.6%) |          |
| 1 clock hour              | 3 (14.3%)       | 5 (22.7%)                  |             |
| 2 clock hours             | 0 (0.0%)        | 2 (9.1%)                   |             |
| 3 clock hours             | 0 (0.0%)        | 2 (9.1%)                   |             |
| 4 clock hours             | 0 (0.0%)        | 0 (0.0%)                   |             |
| 5 clock hours             | 0 (0.0%)        | 4 (18.2%)                  |             |
| 6 clock hours             | 17.3            | 69.5                       | 0.006*      |
| Average extent of capillary ring loss, ° |          |                            |             |

**Deep capillary plexus**

| Average FAZ area          | 0.48 ± 0.12  †   | 0.60 ± 0.26  †             | 0.063*      |
| Intact perifoveal capillary ring, no (%) | 11 (52.4%) | 2 (9.1%) | 0.002‡ |
Extent of the destructed capillary ring, no (%)  

|                | 1 clock hour | 2 clock hours | 3 clock hours | 4 clock hours | 5 clock hours | 6 clock hours |
|----------------|--------------|---------------|---------------|---------------|---------------|--------------|
| 5 (23.8%)      | 2 (9.5%)     | 0 (0.0%)      | 1 (4.8%)      | 30.0          | 0.001*        |

Average extent of capillary ring loss, °.

Values are presented as mean ± standard deviation unless otherwise indicated. OCT = optical coherence tomography; ME = macular edema; FAZ = foveal avascular zone.

* Statistics by Wilcoxon rank-sum test; † Statistics by Chi-square test.

Table 3. The macular capillary density of en face swept-source optical coherence tomography angiography images in groups with or without macular edema recurrence in branch retinal vein occlusion
| OCT angiography parameters | no ME recurrence group (n=21) | ME recurrence group (n=22) | p-value* |
|---------------------------|-------------------------------|---------------------------|----------|
| **Superficial capillary plexus** |                               |                           |          |
| Macular vessel density (3 x 3 ³ area) | 76.70 ± 9.06 | 78.07 ± 7.66 | 0.298 |
| Hemi-vessel density (3 x 1.5 ³ area) |                               |                           |          |
| Hemi-vessel density in the unaffected area | 81.49 ± 9.82 | 84.40 ± 9.72 | 0.215 |
|                                           | 72.23 ± 16.62 | 71.32 ± 9.87 | 0.544 |
| Hemi-vessel density in the affected area | 9.26 ± 10.68 | 13.08 ± 8.81 | 0.031 |
| Hemi-vessel density disparity |                               |                           |          |
| **Deep capillary plexus** |                               |                           |          |
| Macular vessel density (3 x 3 ³ area) | 73.71 ± 7.39 | 71.87 ± 6.22 | 0.190 |
| Hemi-vessel density (3 x 1.5 ³ area) |                               |                           |          |
| Hemi-vessel density in the unaffected area | 81.68 ± 7.70 | 82.55 ± 9.20 | 0.512 |
|                                           | 65.57 ± 9.50 | 68.82 ± 8.38 | 0.040 |
| Hemi-vessel density in the affected area | 14.10 ± 12.42 | 21.73 ± 12.10 | 0.017 |
| Hemi-vessel density disparity |                               |                           |          |
Values are presented as mean ± standard deviation unless otherwise indicated. OCT = optical coherence tomography; ME = macular edema.

* Statistics by Wilcoxon rank-sum test.

**Figures**

![Figure 1](image)
The macular capillary network parameter in en face $3 \times 3$ swept-source optical coherence tomography angiography. The foveal avascular zone area in the superficial capillary plexus (A) and deep capillary plexus (B) are automatically measured if it is manually drawn along the inner boundary of the capillary network (C & D).

Figure 2

The morphology of the perifoveal capillary ring after resolution of the macular edema in branch retinal vein occlusion in en face $3 \times 3$ swept-source optical coherence tomography angiography. (A & B) These
images show slight perifoveal capillary loss with an intact of the capillary ring in the superficial capillary plexus and deep capillary plexus. (C & D) These images show disruptions of the perifoveal capillary ring in the superficial capillary plexus and deep capillary plexus.

Figure 3

Assessment of macular vessel density by the binarization process using the Image J program from en face 3 × 3 Swept-source optical coherence tomography angiography image. (A & B) These images show large capillary loss in the inferior region in superficial capillary plexus and deep capillary plexus. (C & D)
The vessel density is calculated at the 320 × 320-pixel area in binarized images of superficial capillary plexus and deep capillary plexus.

Figure 4

Assessment of hemi-vessel density disparity of the superficial capillary plexus (SCP) and deep capillary plexus (DCP). (A) En face 3 × 3 OCTA image of the SCP is divided into two regions, a hemi-superior macular area (B) and a hemi-inferior macular area (C) by the horizontal blue line. A hemi-vessel density disparity of the SCP is obtained from the differences in the vessel densities between the binarized hemi-superior SCP image (D) and the binarized hemi-inferior SCP image (E). (F) En face 3 × 3 OCTA image of the DCP is divided into a hemi-superior macular area (G) and a hemi-inferior macular area (H) by the blue line. A hemi-vessel density disparity of the DCP is obtained from the differences in the vessel densities between the binarized hemi-superior DCP image (I) and the binarized hemi-inferior DCP image (J).