

Retinal Microvasculature and Visual Acuity in Eyes With Branch Retinal Vein Occlusion: Imaging Analysis by Optical Coherence Tomography Angiography

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Submitted: November 30, 2016
Accepted: February 28, 2017

Citation: 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;58:2087-2094. DOI: 10.1167/iops.16-21208

PURPOSE. To investigate microvascular changes in the superficial capillary plexus (SCP) and deep capillary plexus (DCP) in eyes with resolved branch retinal vein occlusion (BRVO) and their association with best-corrected visual acuity (BCVA).

METHODS. Eighty-five eyes (82 consecutive patients) with BRVO after resolution of the macular edema were retrospectively evaluated. All patients underwent optical coherence tomography angiography (OCTA) for assessment of microvascular changes, including capillary telangiectasia, microaneurysm, and disruption of the foveal avascular zone (FAZ). The areas of vascular perfusion and FAZ in the SCP and DCP were quantitatively evaluated. Best-corrected visual acuity was measured on the same day as OCTA examination. The correlation between BCVA and OCTA findings was assessed.

RESULTS. In eyes with resolved BRVO, the mean vascular perfusion areas in the SCP and DCP within a 3×3 -mm area were 3.75 ± 0.49 and 3.80 ± 0.55 mm², respectively. The mean FAZ areas of the SCP and DCP were 0.57 ± 0.36 and 0.76 ± 0.38 mm², respectively. Better BCVA was significantly associated with a larger vascular perfusion area in the SCP ($P < 0.001$) and DCP ($P < 0.001$), and a smaller FAZ area in the SCP ($P = 0.025$) and DCP ($P = 0.017$). Stepwise multiple regression analysis revealed that the vascular perfusion area in the DCP was the most important parameter significantly correlated with BCVA ($R^2 = 0.33$, $P < 0.001$).

CONCLUSIONS. Preservation of the deep retinal vasculature is crucial for better visual function in BRVO.

Keywords: branch retinal vein occlusion, optical coherence tomography angiography, macular edema, foveal avascular zone, optical coherence tomography

Branch retinal vein occlusion (BRVO) is a common retinal vascular disorder in middle-aged and elderly people with a history of hypertension, diabetes mellitus, smoking, or open-angle glaucoma.¹⁻⁶ Patients with BRVO develop varying degrees of retinal hemorrhage, retinal ischemia, tortuous retinal vessels, and macular edema due to compression of the retinal vein by a thickened retinal arteriole wall at the site of arteriovenous crossing.^{7,8} Macular edema is a predominant cause of vision loss in BRVO.⁹ Laser photocoagulation, intravitreal anti-vascular endothelial growth factor (VEGF), and corticosteroids such as dexamethasone have been reported to be effective in reducing macular edema and improving vision in patients with BRVO.¹⁰⁻¹⁵ However, poor visual recovery has been reported despite complete resolution of the macular edema after treatment.^{10,16} In such cases, the possible mechanisms accounting for persistent visual impairment, for example, potential abnormalities in the retinal microvasculature, cannot be identified by conventional optical coherence tomography (OCT).

Optical coherence tomography angiography (OCTA) is a new imaging modality that allows noninvasive visualization of retinal blood flow without use of exogenous dyes.¹⁷⁻²⁰ The layer-specific imaging capabilities of OCTA have the potential to

simultaneously visualize both superficial and deep retinal capillaries by segmentation of each layer.²⁰ Because it is difficult to visualize layer-specific vascular patterns by fluorescein angiography (FA), OCTA may provide a better understanding of the relationship between layer-specific retinal microvascular changes and the visual prognosis in various retinal vascular diseases. To date, several studies using OCTA have reported abnormal vascular changes in BRVO, including microaneurysms, telangiectasia, and retinal capillary nonperfusion, especially in the deep retinal layer.²¹⁻²³ A possible association between retinal vascular density and visual acuity (VA) has also been reported.²⁴ However, the most important vascular parameters that are significantly associated with VA after treatment of the macular edema have not been fully clarified because of the limited number of patients evaluated in previous research.

The purpose of this study was to evaluate OCTA parameters, including capillary telangiectasia, microaneurysm, disruption of the foveal avascular zone (FAZ), and quantitative areas of vascular perfusion and FAZ, after treatment of macular edema in BRVO, and assess their relationship with the visual outcome in a relatively large series of patients. We also investigated the possible association between vascular perfusion status and



structural changes in the fovea detected by spectral-domain OCT (SD-OCT).

PATIENTS AND METHODS

The procedures used in this study conformed to the tenets of the Declaration of Helsinki, and were approved by the institutional review board of Osaka University Graduate School of Medicine (10039). All patients were informed of the nature and possible consequences of the procedures, and signed informed consent was obtained from all patients.

A consecutive series of patients who showed complete resolution of center-involved macular edema associated with BRVO and underwent OCTA examination at the Department of Ophthalmology of Osaka University Hospital between September 2014 and April 2016 were enrolled in this observational study. All patients had a history of BRVO with retinal hemorrhage and macular edema extending to the fovea diagnosed by SD-OCT. All patients underwent successful treatment of the macular edema and were followed up for more than 5 months. The treatment included intravitreal ranibizumab, intravitreal aflibercept, laser photocoagulation, sub-Tenon's injection of triamcinolone acetonide, or observation. Some patients had received a combination of two or more treatments for complete resolution of their macular edema. Eyes treated with pars plana vitrectomy with internal limiting membrane peeling were excluded.

All patients underwent comprehensive ophthalmic evaluation including measurement of best-corrected visual acuity (BCVA), binocular indirect ophthalmoscopy, contact lens slit-lamp biomicroscopy, and fundus photography.

Retinal Microvasculature Imaging by OCTA

Optical coherence tomography angiography images were acquired with AngioVue (Optovue RTVue XR Avanti; Optovue, Inc., Fremont, CA, USA) using automated segmentation algorithms on the same day as the clinical examination. A 3 × 3-mm (9 mm²) area, centered on the fovea, was scanned in all eyes. The AngioVue software automatically segments the vascular area into four layers, that is, the superficial capillary plexus (SCP), deep capillary plexus (DCP), outer retina, and choroidal levels. Default autosegmentation of the SCP images includes the vasculature from the internal limiting membrane to 15 μm below the inner plexiform layer (IPL). Deep capillary plexus images include the vasculature from 15 to 70 μm below the IPL.

We qualitatively assessed the microvascular changes in the SCP and DCP, including capillary telangiectasia (dilation), microaneurysm, and disruption of the FAZ based on the previous report.²¹⁻²³ The disruption of the FAZ was defined as loss of the intact perifoveal capillary arcade greater than one quadrant. Image analyses were performed by two masked observers (TW, CH-U). When there was disagreement, a third investigator (TS) was consulted for the final decision. We also quantitatively evaluated the SCP and DCP using the AngioAnalytics software, which measures the flow area and nonflow area of each layer. For quantitative analysis, the vascular area (mm²) was measured as the area of visible perfusion in the SCP and DCP within a 3 × 3-mm area. The FAZ area was also measured in the SCP and DCP within a 3 × 3-mm area. Eyes with pre-existing macular disease, media opacity, or diabetes mellitus that can interfere with OCTA examinations and imaging interpretation were excluded from data analysis. Optical coherence tomography angiography images with poor quality (a signal strength index ≤ 50), motion artifacts, or

TABLE 1. Patient Characteristics

No. eyes	85
No. patients	82
Age, y, mean ± SD (range)	69.2 ± 9.1 (45-86)
Sex, no. (%)	
Men	26 (32)
Women	56 (68)
Eye, no. (%)	
Right	43 (51)
Left	42 (49)
Lens status	
Phakia	66 (78)
Pseudophakia	19 (22)
Superior/inferior, no. (%)	
Superior	54 (64)
Inferior	31 (36)
Initial BCVA before treatment	
Landolt C acuity chart, mean (range)	0.48 (0.06-1.5)
LogMAR, mean ± SD	0.32 ± 0.28
Initial CRT before treatment, μm, mean ± SD (range)	504 ± 149 (301-1002)
Previous treatment, no. (%)	
Intravitreal ranibizumab	42 (49)
Intravitreal aflibercept	42 (49)
Laser photocoagulation	41 (48)
STTA	3 (4)
Observation: no treatment	6 (7)
Posttreatment BCVA at OCTA examination	
Landolt C acuity chart, mean (range)	0.76 (0.15-1.5)
LogMAR, mean ± SD	0.12 ± 0.22
Posttreatment CRT at OCTA examination, μm, mean ± SD (range)	246 ± 34 (154-307)
Duration of follow-up, mo, mean ± SD (range)*	14.3 ± 12.8 (5-68)

BCVA, best-corrected visual acuity; CRT, central retinal thickness; OCTA, optical coherence tomography angiography; SD, standard deviation; STTA, sub-Tenon's injection of triamcinolone acetonide.

* Follow-up duration from the initial presentation of branch retinal vein occlusion (BRVO) to OCTA examination after treatment of the macular edema.

incorrect autosegmentation were also excluded from the data analysis.

SD-OCT Examination

Spectral-domain OCT images were acquired by Cirrus SD-OCT examination (Carl Zeiss Meditec, Inc., Dublin, CA, USA) before and after treatment of the macular edema. Central retinal thickness (CRT) was measured automatically as the average retinal thickness in the central area within a diameter of 1 mm. The integrity of the photoreceptor layer was evaluated as preservation of the continuous back-reflection line corresponding to the external limiting membrane (ELM), ellipsoid zone (EZ), and cone interdigitation zone (CIZ).

Image Analysis

Data were collected on ophthalmic history, initial BCVA before treatment, initial CRT before treatment, previous treatment for macular edema, posttreatment OCTA images, posttreatment BCVA at OCTA examination, posttreatment

TABLE 2. Optical Coherence Tomography Angiography Parameters in Resolved Branch Retinal Vein Occlusion

Parameter	85 Eyes
SCP, no. (%)	
Microaneurysm	5 (6)
Telangiectasia	43 (51)
Disrupted FAZ	34 (40)
DCP, no. (%)	
Microaneurysm	25 (29)
Telangiectasia	76 (89)
Disrupted FAZ	48 (56)
Quantitative retinal vascular area within 3 × 3 mm, mm ²	
SCP, mean ± SD (range)	3.75 ± 0.49 (2.46–4.68)
DCP, mean ± SD (range)	3.80 ± 0.55 (2.45–4.90)
Quantitative FAZ area within 3 × 3 mm, mm ²	
SCP, mean ± SD (range)	0.57 ± 0.36 (0.23–2.16)
DCP, mean ± SD (range)	0.76 ± 0.38 (0.23–2.20)

SD, standard deviation.

CRT, photoreceptor status at OCTA examination, and duration of follow-up. The main outcome measures included in the data analysis were posttreatment BCVA and OCTA imaging of the SCP and DCP on the same day as the posttreatment BCVA measurement.

For statistical analysis, the BCVA was measured using the Landolt C acuity chart and analyzed on a logarithm of minimal angle of resolution (logMAR) scale. Univariate and multivariate regression were used to investigate the associations between logMAR BCVA and OCTA parameters such as vascular area and FAZ area. Forward stepwise regression analysis was further performed to identify the factor most significantly related to BCVA. All analyses were conducted using SigmaStat software version 3.1 (SPSS, Inc., Chicago, IL, USA) and JMP Pro Software (SAS, Inc., Cary, NC, USA). $P < 0.05$ indicated statistical significance.

RESULTS

One hundred six eyes of 103 consecutive patients with resolved BRVO were enrolled initially. Twenty-one eyes were

excluded because of epiretinal membrane (3 eyes), proliferative diabetic retinopathy (1 eye), autosegmentation error (6 eyes), motion artifact (8 eyes), and low image quality due to progressed cataract (3 eyes). Therefore, 85 eyes of 82 patients (26 men, 56 women) met the study criteria for subsequent data analysis. The baseline characteristics of the 85 eyes with resolved BRVO are summarized in Table 1. The data for both initial BRVO presentation before treatment and at the time of OCTA examination after treatment are included. The mean patient age was 69.2 ± 9.1 (range, 45–86) years. Initial mean logMAR BCVA was 0.32 ± 0.28 . All patients underwent treatment of center-involved macular edema by intravitreal ranibizumab (42 eyes), intravitreal aflibercept (42 eyes), laser photocoagulation (41 eyes), sub-Tenon's injection of triamcinolone acetonide (3 eyes), or observation (6 eyes). The mean time interval between initial presentation with BRVO and OCTA was 14.3 (range, 5–68) months. At the time of OCTA, the mean logMAR BCVA improved to 0.12 ± 0.22 with resolution of macular edema in all eyes.

OCTA Findings and VA

Although all patients showed complete resolution of macular edema, OCTA detected microaneurysm in 5 eyes (6%), capillary telangiectasia in 43 (51%), and disruption of the FAZ in 34 (40%) in the SCP (Table 2). In the DCP, OCTA showed microaneurysm in 25 eyes (29%), capillary telangiectasia in 76 (89%), and disruption of the FAZ in 48 (56%; Table 2).

The mean vascular perfusion area in the SCP and DCP was 3.75 ± 0.49 (range, 2.46–4.68) mm² and 3.80 ± 0.55 (range, 2.45–4.90) mm², respectively. The mean FAZ area of the SCP and DCP was 0.57 ± 0.36 (range, 0.23–2.16) mm² and 0.76 ± 0.38 (0.23–2.20) mm², respectively (Table 2).

Univariate and Multivariate Regression Analysis

The vascular perfusion area in the SCP ($P < 0.001$), FAZ area in the SCP ($P = 0.025$), disruption of the FAZ in the SCP ($P = 0.001$), vascular perfusion area in the DCP ($P < 0.001$), FAZ area in the DCP ($P = 0.017$), microaneurysm in the DCP ($P = 0.020$), telangiectasia in the DCP ($P = 0.008$), and disruption of the FAZ in the DCP ($P = 0.001$) were significantly associated with posttreatment VA (Table 3). Among these OCTA parameters, the vascular perfusion area in the DCP ($P = 0.008$) was significantly associated with posttreatment VA in

TABLE 3. Univariate and Multivariate Regression Analyses of the Association Between Best-Corrected Visual Acuity and Optical Coherence Tomography Angiography Parameters in Eyes With Resolved Branch Retinal Vein Occlusion

Variable	Univariate Linear Regression			Multivariate Linear Regression	
	Regression Coefficient	R ²	P Value	Regression Coefficient	P Value
OCTA parameters					
SCP					
Retinal perfusion area, mm ²	−0.240	0.277	<0.001	0.164	0.291
FAZ area, mm ²	0.15	0.059	0.025	−0.080	0.547
Microaneurysm, yes vs. no	−0.020	0.0004	0.852		
Telangiectasia, yes vs. no	0.093	0.043	0.056		
Disrupted FAZ, yes vs. no	0.154	0.115	0.001	0.042	0.56
DCP					
Retinal perfusion area, mm ²	−0.234	0.333	<0.001	−0.358	0.008
FAZ area, mm ²	0.153	0.067	0.017	−0.062	0.605
Microaneurysm, yes vs. no	0.123	0.064	0.02	0.036	0.434
Telangiectasia, yes vs. no	0.207	0.082	0.008	0.052	0.458
Disrupted FAZ, yes vs. no	0.154	0.117	0.001	0.064	0.341

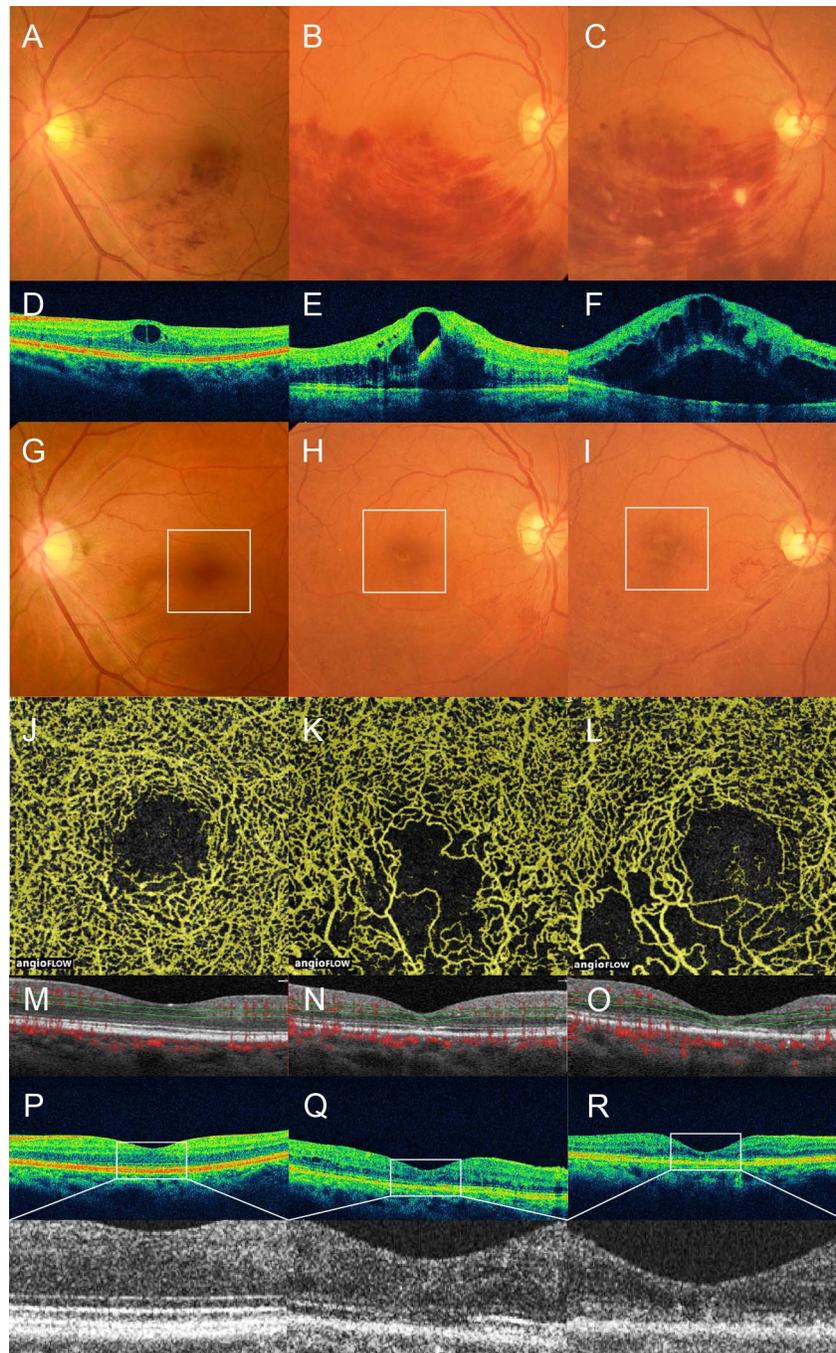


FIGURE. Patterns of the retinal microvasculature in the deep capillary plexus (DCP) obtained by optical coherence tomography angiography (OCTA) in resolved branch retinal vein occlusion. (A–C) The fundus photograph at initial presentation in a 55-year-old female, a 69-year-old female, and a 64-year-old female, respectively. (D–F) The horizontal spectral-domain OCT (SD-OCT) images at initial presentation show center-involved macular edema in patients with (A) to (C). The central retinal thickness (CRT) is 311, 665, and 1002 μm , respectively. (G–I) The fundus photograph after resolution of the macular edema in patients with (A) to (C). The OCTA images in the DCP (J–L) and corresponding structural OCT image (M–O). The area of OCTA image is denoted by a *white inset* on the fundus photograph. The flow area (*yellow line*) automatically measured by the software is 4.59, 4.03, and 3.33 mm^2 , and the decimal visual acuity is 1.5, 0.8, and 0.2, respectively. (P–R) The horizontal SD-OCT images at the time of OCTA examination in patients with (A) to (C). The CRT is 294, 212, and 154, respectively. Magnification of the horizontal SD-OCT image shows intact external limiting membrane (ELM), photoreceptor ellipsoid zone (EZ), and cone interdigitation zone (CIZ) in (P). The horizontal SD-OCT shows preserved ELM but disruption of the EZ and CIZ in (Q). The horizontal SD-OCT shows thinning of the retina with disruption of the ELM, EZ, and CIZ in (R).

multivariate regression analysis. Stepwise multiple regression analysis also indicated that the vascular perfusion area in the DCP was the most important factor significantly correlated with posttreatment VA ($R^2 = 0.33$, $P < 0.001$; Fig.).

Association Between Retinal Perfusion and Foveal Structure

To investigate the potential reason why retinal perfusion in the DCP was associated with VA, we assessed the relationship

TABLE 4. Association Between Deep Retinal Perfusion Area Evaluated by Optical Coherence Tomography Angiography and Foveal Structure

Variable	Univariate Linear Regression			Multivariate Linear Regression	
	Regression Coefficient	R ²	P Value	Regression Coefficient	P Value
Initial CRT before treatment, μm	-0.0016	0.191	<0.001	-0.0005	0.293
CRT at OCTA examination, μm , mean \pm SD	0.0038	0.054	0.033	0.0007	0.713
Photoreceptor integrity*	0.321	0.279	<0.001	0.237	0.004

* Photoreceptor integrity was defined as 4 = ELM(+)/EZ(+)/CIZ(+), eyes with a preserved external limiting membrane (ELM), ellipsoid zone (EZ), and cone interdigitation zone (CIZ); 3 = ELM(+)/EZ(+)/CIZ(-), eyes with a preserved ELM and EZ, but with disrupted CIZ; 2 = ELM(+)/EZ(-)/CIZ(-), eyes with a preserved ELM but with disrupted EZ and CIZ; 1 = ELM(-)/EZ(-)/CIZ(-), eyes with disrupted ELM, EZ, and CIZ.

between retinal perfusion in the DCP and structural changes in the fovea detected by SD-OCT.

Univariate analysis revealed that the vascular perfusion area in the DCP was significantly associated with the CRT before treatment ($P < 0.001$; Table 4); that is, worse macular edema was associated with less vascular perfusion in the DCP after treatment. The vascular perfusion area in the DCP was also significantly associated with the CRT at OCTA examination ($P = 0.033$) and photoreceptor integrity ($P < 0.001$), indicating that adequate perfusion preserves both retinal morphology and survival of photoreceptors. In multivariate regression analysis, the vascular perfusion area in the DCP was most significantly associated with photoreceptor integrity ($P = 0.004$).

Conversely, when we divided the eyes into four subgroups based on photoreceptor integrity, that is, preserved ELM, EZ, and CIZ (13 eyes), preserved ELM and EZ but disrupted CIZ (39 eyes), preserved ELM but disrupted EZ and CIZ (21 eyes), and disrupted ELM, EZ, and CIZ (12 eyes), the mean vascular perfusion area differed significantly between the groups in both the SCP and DCP (Supplementary Table S1). The mean vascular perfusion area was 4.06 ± 0.47 , 3.89 ± 0.43 , 3.57 ± 0.43 , and 3.29 ± 0.40 , respectively, in the SCP ($P < 0.001$) and 4.23 ± 0.51 , 3.94 ± 0.46 , 3.54 ± 0.50 , and 3.33 ± 0.48 in the DCP ($P < 0.001$). In addition, the mean area of the FAZ differed significantly in the SCP (0.42 ± 0.16 , 0.51 ± 0.29 , 0.61 ± 0.41 , and 0.83 ± 0.52 , respectively, $P = 0.034$) between the groups. The mean area of the FAZ in the DCP differed between the groups (0.63 ± 0.21 , 0.73 ± 0.37 , 0.80 ± 0.39 , and 0.95 ± 0.48 , respectively, $P = 0.189$); however, the difference was not statistically significant.

DISCUSSION

Recent OCTA analysis has identified the significance of microvascular changes in the DCP in several retinal vascular diseases, including BRVO,²¹⁻²³ macular telangiectasia,²⁵ and diabetic macular edema,^{26,27} based on the depth-resolved imaging technique. In eyes with BRVO, microvascular abnormalities such as capillary telangiectasia, microaneurysm, non-perfusion, and enlargement of the FAZ are more common in the DCP than in the SCP.^{21-23,28} However, the relative importance of each of these microvascular findings in determining VA has not been elucidated in BRVO. In the present study, we not only qualitatively assessed the microvascular changes in the retinal capillary networks but also quantified the area of vascular perfusion and FAZ in eyes with BRVO and identified the factor most significantly associated with VA in BRVO.

Our results indicate that microvascular abnormalities, including capillary telangiectasia, microaneurysm, and disruption of the FAZ, are more common in the DCP than in the SCP, as previously reported.^{21-23,28} In addition, we identified that better vascular perfusion and a smaller FAZ area in both the

SCP and the DCP were significantly associated with better VA after treatment of macular edema in BRVO. Further, we identified that the vascular area in the DCP was the parameter most significantly correlated with VA ($R^2 = 0.33$, $P < 0.001$, forward stepwise regression analysis). Thus, preservation of retinal perfusion, especially in the DCP, seems to be crucial for better VA in BRVO.

Several previous studies have investigated the relationship between retinal perfusion and VA in BRVO.²⁹⁻³² Sophie et al.³¹ reported that the area of posterior retinal nonperfusion measured by FA was significantly associated with worse VA in patients with BRVO treated with intravitreal ranibizumab. Chung et al.³² also reported that visual recovery was correlated with less macular ischemia evaluated by FA after treatment of the macular edema with bevacizumab. The result of the present study is compatible with those reports indicating that better vascular perfusion is associated with better VA. However, because of the limited depth resolution, the DCP has not been evaluated previously in FA. The ability of OCTA to visualize the SCP and DCP separately and to quantify the area of perfusion offers additional information over FA, that is, that vascular perfusion of not only the SCP as detected by FA, but also the DCP, is important for VA.

Interpreting OCTA images has been well documented based on histologic analysis of the retinal vasculature.^{20,33-36} In the normal human retina, the main branches of the central retinal artery and the central retinal vein lie horizontally within the retinal nerve fiber layer (RNFL). The arterial branches then supply a total of four (two superficial and two deep) layers of the capillary networks in the perifoveal region, that is, (1) the RNFL, (2) the retinal ganglion cell layer (GCL) and superficial portion of IPL, (3) the deep portion of IPL and superficial portion of inner nuclear layer (INL), and (4) the deep portion of INL.³⁴ The SCP in the OCTA represents the retinal arterioles, venules, and capillary networks in the first through third of these. On the other hand, the DCP in the OCTA indicates the capillary networks at the fourth. Therefore, the significance of the DCP in the visual outcome in our series seems to highlight the importance of preserving capillaries at the outer boundary of INL in eyes with BRVO. At the outer boundary of INL (border of the deep portion of INL and outer plexiform layer [OPL]), the photoreceptor axon terminals form ribbon synapses with the horizontal cells and bipolar cells.³⁷⁻⁴¹ Therefore, the capillaries in the DCP seem to be important for nutritional and oxygen support of the synaptic connections responsible for transmission of visual signals.⁴² Because the area of the INL and OPL is located in the so-called watershed zone where the oxygen level is significantly lower than that in the inner and outer retinal layer and may be particularly vulnerable to ischemia,⁴³⁻⁴⁷ hypoperfusion in the DCP may cause acute nutritional deficiency in the synaptic connections, resulting in decreased VA as shown in the present study.

In our series, retinal hypoperfusion in the DCP was associated with retinal thinning and disruption of the

photoreceptor layer. Two potential mechanisms may be responsible for this phenomenon. First, because ischemia in the DCP was associated with the severity of macular edema before treatment, the macular edema may have caused irreversible damage to the entire retinal tissue, including the photoreceptors. Second, because the DCP has been reported to contribute 10% to 15% of the oxygen supply to the photoreceptors,⁴⁷ ischemia in the DCP may have gradually influenced the photoreceptor integrity.^{48,49} Therefore, in addition to nutritional deficiency in the synaptic connections, photoreceptor damage may also be responsible for visual impairment in eyes with ischemia in the DCP.

Several experimental studies of laser-induced BRVO in the Rhesus monkey have reported that venous dilation and tortuosity may occur immediately after obstruction.⁵⁰⁻⁵³ These studies suggest that deep retinal capillaries without the coverage of vascular smooth muscle cells are more severely affected by high venous pressure, leading to dilation and opening of the endothelial gaps. Subsequently, increased vascular permeability leads to retinal edema in the RNFL, GCL, INL, and OPL. Retinal hemorrhage also develops due to extravasation of erythrocytes from the dilated capillaries. Retinal edema in turn increases the retinal tissue pressure and may further reduce perfusion by compressing the capillaries, especially in the deep layer.^{50,51} Finally, there is a loss of endothelial cells and pericytes, and the acellular capillaries are invaded by glial cells, producing permanent capillary closure.⁵⁴ In the current series, hypoperfusion in the DCP was associated with the severity of macular edema before treatment. This suggests that the severe occlusion associated with BRVO may have caused increased fluid leakage and subsequent deep capillary ischemia, as reported in animal studies.^{50,51} In our study, although we did not assess the OCTA images before treatment, the once-closed capillaries associated with severe macular edema may not have achieved complete reperfusion because the deep capillary ischemia remained even after successful treatment of the macular edema. Preservation of the DCP may occur in cases where the capillary damage and subsequent macular edema are not prominent. Indeed, preservation of the DCP was associated with less macular edema before treatment in our study (Fig.). In such cases, the VA was favorable. This finding seems to support the experimental results in eyes with mild venous occlusion.

High intraocular levels of VEGF has been shown to be responsible for development of macular edema in retinal vein occlusion.⁵⁵ According to the recent literature, high levels of VEGF also promote retinal hemorrhages and worsening of the nonperfusion area in eyes with BRVO.⁵⁶ Although we did not measure intraocular VEGF concentrations, the severe macular edema and concomitant capillary ischemia seen in the present study may have been caused by high levels of intraocular VEGF associated with severe venous occlusion. Further studies are needed to elucidate whether a prompt and aggressive treatment regimen with anti-VEGF could not only resolve macular edema⁵⁷ but also prevent worsening of ischemia in the DCP and hence preserve the final VA.

The limitations of this study include its retrospective design, nonstandardized treatment protocol for treating macular edema, and the lack of preoperative OCTA information, which is important but usually difficult to assess in eyes with macular edema. In addition, we could analyze only a limited area (3 × 3 mm) of retinal perfusion, which is important for central vision but may not reflect the whole disease process in BRVO. Nevertheless, this study suggests that vascular perfusion in the DCP detected by OCTA is a key parameter responsible for VA in patients with BRVO. We also found a significant association between vascular perfusion in the DCP and photoreceptor

integrity, which has been reported to be associated with visual outcome after treatment of BRVO.^{58,59} Without definitive treatments for increasing capillary perfusion, our findings may provide only a better understanding of the microvascular changes and a possible reason for the differences in VA after resolution of macular edema. However, this information may be valuable for developing novel therapeutic strategies to maintain normal capillary perfusion or regenerate new capillaries in the future.

In summary, OCTA is a useful noninvasive tool for evaluation of deep capillary perfusion not identifiable on clinical examination including FA. The vascular perfusion status in the DCP detected by OCTA is a key finding and accounts for the better VA after treatment of macular edema in BRVO.

Acknowledgments

Disclosure: **T. Wakabayashi**, None; **T. Sato**, None; **C. Hara-Ueno**, None; **Y. Fukushima**, None; **K. Sayanagi**, None; **N. Shiraki**, None; **M. Sawa**, None; **Y. Ikuno**, None; **H. Sakaguchi**, None; **K. Nishida**, None

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