Microvascular and functional changes according to the fundus location of the affected arteriovenous crossing in patients with branch retinal vein occlusion

Gurcan Dogukan Arslan, Dilek Guven¹, Mehmet Demir², Abdurrahman Alpaslan Alkan³, Delil Ozcan¹

Purpose: The aim of this study was to evaluate the structural and functional changes occurring in patients with branch retinal vein occlusion (BRVO) according to the distance of the affected arteriovenous (AV) crossing to the centers of the fovea and optic disc by optic coherence tomography angiography (OCTA).

Methods: Forty-five patients with unilateral BRVO and 45 age- and sex-matched healthy controls were included in this retrospective observational study. Images of the macula (3 mm × 3 mm) and affected AV crossing sites were obtained by OCTA. The fovea-AV crossing distance (FAVD), optic disc-AV crossing distance (DAVD), and optic disc-fovea distance (DFD) were measured. Results: The DAVD/DFD ratio was positively correlated with the vessel density in the superficial and deep affected hemifields (r = 0.430, P < 0.05 and r = 0.308, P < 0.05, respectively) and negatively correlated with the superficial foveal avascular zone and logarithm of the minimum angle of resolution (logMAR) visual acuity (r = -0.412, P < 0.05 and r = -0.356, P < 0.05, respectively). The DAVD/DFD ratio was not correlated with the logMAR visual acuity, superficial FAZ area or vessel densities in the affected hemifield (all P > 0.05). Conclusion: The affected AV crossing site that was further away from the fovea had better visual acuity and quantitative microvascular parameters in the affected hemifields. However, this correlation was not observed for the distance between the affected AV crossing site and the optic disc.

Key words: Arteriovenous crossing, branch retinal vein occlusion, optical coherence tomography angiography, visual function

Branch retinal vein occlusion (BRVO) is the most commonly encountered retinal vascular disease after diabetic retinopathy. Various degrees of retinal hemorrhage, retinal ischemia, and macular edema may occur in patients with BRVO. Vessel density in the superficial capillary plexus (SCP), deep capillary plexus (DCP), and foveal avascular zone (FAZ) has recently been evaluated by optical coherence tomography angiography (OCTA), and the ability of this imaging technique to reveal capillary vessel pathology has been assessed in these patients with BRVO. Furthermore, the macula has been examined in healthy fellow eyes of patients to account for the effects of comorbid diseases.

BRVO occurs most often at an arteriovenous (AV) crossing site and is described as first-degree or second-degree focal occlusion of a retinal vein. Some researchers have suggested that venous flow is impaired because of mechanical compression of the vein by a rigid arterial wall. AV crossings have been investigated in many studies and their role in the pathogenesis of BRVO has been examined.

A previous study that investigated the pathophysiology of BRVO using fundus photography and intravenous fluorescein angiography identified one of the factors affecting visual function to be the extent and location of the venous drainage area involved. Moreover, the extent of retinal ischemia in retinal vein occlusions has been associated with a worse prognosis. Other important factors were reported to be the proportion of impaired perifoveal collaterals and the effectiveness of collateral drainage. We already know that the extent of the venous drainage area affected, amount of cotton wool spots, and size of the edematous areas in the macula are greater when occlusions are closer to the optic disc (approaching the vascular root). On the other hand, damage to the perifoveal collaterals is enhanced in eyes with occlusions closer to the fovea. Nonetheless, to the best of our knowledge, there is no study in the literature that has investigated the relationship between the distances of the occlusion sites from the fovea and the optic disc using quantitative microvascular parameters, and visual function.

The aims of this study were (1) to evaluate the structural and functional changes that occur in patients with unilateral BRVO, and (2) to evaluate the importance of the fundus location of the affected AV crossing in patients with BRVO. This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

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Department of Ophthalmology, Tatvan State Hospital, Bitlis, ¹Department of Ophthalmology, University of Health Sciences Sisli Hamidiye Etfal Training and Research Hospital, Istanbul, ²Department of Ophthalmology, Ercis Sehit Ridvan Cevik State Hospital, Van, Turkey

Correspondence to: Dr. Gurcan Dogukan Arslan, Department of Ophthalmology, Tatvan State Hospital, 45 Hal Street, Tatvan, Bitlis, Turkey. E-mail: mr.dogukan2@gmail.com

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BRVO according to the distance of the affected AV crossing sites from the centers of the fovea and optic disc using OCTA and (2) to compare the microvascular structures of the macula between eyes with BRVO, fellow eyes, and control eyes.

**Methods**

**Participants and data collection**

This retrospective observational study included patients admitted to our hospital with BRVO between April 2017 and May 2019. The study was approved by our institution’s ethics committee and performed in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from each study participant after explanation of the nature and possible consequences of the study.

Forty-five eyes of 45 patients with BRVO and 45 eyes of 45 control subjects were enrolled in the study. Patients with major BRVO involving the temporal sector were included in the study if they had been followed for 1–3 years and had a foveal thickness of ≤ 300 µm without macular edema. The patients received 0.5 mg/0.05 ml intravitreal ranibizumab (Lucentis; Novartis, Basel, Switzerland and Genentech Inc., South San Francisco, California) injections if they had macular edema that exceeded 300 µm of central retinal thickness. Focal laser photocoagulation (532 nm) was performed only for closure of leaky microaneurysms causing macular edema that were located between 500 and 3000 microns from the center of the fovea (Carl Zeiss Meditec AG, Jena, Germany). The parameters for laser photocoagulation were as follows: duration, 100 ms; spot size diameter, 80-100 µm; sufficient power (70–120 mW) to produce a medium white burn. The exclusion criteria were as follows: Patients who received any other form of treatment (scatter laser photocoagulation, steroid therapy, surgical intervention, or intravitreal anti-vascular endothelial growth factor agent injections other than ranibizumab), co-existing ocular diseases (diabetic retinopathy, retinal arterial occlusion, glaucoma, or epiretinal membrane), serous retinal detachment, macular vein occlusion, a history of vitrectomy or glaucoma surgery, keratoconus, high myopia (more severe than −6 diopters), and an area of occlusion within the optic disc or its boundaries.

The control group consisted of 45 eyes of 45 patients matched for age and sex, without additional systemic or ocular pathology, who had attended the ophthalmology outpatient clinic and had a logarithm of the minimum angle of resolution (logMAR) best-corrected visual acuity of 0.05 (equivalent to 20/22 on a Snellen chart).

Complete ophthalmic examinations were performed for all participants. The best-corrected visual acuity was calculated as logMAR and Snellen chart values. Biomicroscopic anterior segment and fundus examinations were performed. Subsequently, fundus fluorescein angiography imaging was performed, and digitally colored fundus images were obtained (Kowa, VX-10-i, Kowa Optimed, Inc., Torrance, California). Red-free digital images of the fundus were recorded.

**OCTA imaging**

Images of the macula (3 mm × 3 mm) were obtained by OCTA as previously described using the AngioVue software of the RTVue XR Avanti spectral-domain OCT (SD-OCT) system (OptoVue, Fremont, California). The corresponding OCT B-scan images co-registered simultaneously with the OCTA data. Affected AV crossing sites were also identified by OCTA. The same experienced technician performed the OCTA data collection and processing for all study participants.

AngioVue uses a split-spectrum amplitude-decorrelation angiography algorithm (SSADA) to detect vascular density and capture the OCTA images. This system has an A-scan repetition rate of 70 kHz, a wavelength of 840 nm, a tissue resolution of 5 µm axially, and a beam width of 15 µm. The device produces two optical coherence tomography units, each consisting of 304 × 304 A-scans, with two B-scans captured in 3 seconds. The software generates 3 × 3-mm² en face images of the microvascularplexuses centered on the fovea. As described previously, the SCP in the macula was automatically measured by the device as the distance between 3 µm below the internal limiting membrane and 15 µm below the internal plexiform layer (IPL), whereas the DCP in the macula was automatically measured as the distance between 15 µm below the IPL and 70 µm below the IPL.

Vascular density was defined as the percentage area occupied by blood vessels. Vessel density in the macula was calculated for the whole field, the affected (superior or inferior) hemifield, and the unaffected hemifield. Non-flow function in the OCTA software was used for the FAZ area measurements. The FAZ area was calculated from the automated segmentation results using the automated OCTA algorithm with no manual adjustments. However, if the FAZ area differs from the expected value because of disease or normal variation, the segmentation may not be accurate. Automatic segmentation error might cause artifacts and contribute to abnormal findings. Therefore, caution is necessary when interpreting abnormalities detected on OCTA. Foveal thickness was evaluated in the central circle measuring 1 mm in diameter. Images with a low signal strength index (<70) were excluded, as were those with motion and blink artifacts.

The FAZ area and the vessel density in the SCP and DCP in the macula were examined. The whole field and the affected and unaffected hemifields of eyes with BRVO were compared with the corresponding quadrants in fellow eyes and control eyes.

**Analysis of distances by OCTA**

B-scan OCT imaging allows a detailed *in vivo* analysis of the interior of the retina, especially the fovea. The patients in our study did not have macular edema and had normal foveal contour. The foveal center in our patients was identified as the deepest point of the foveal pit and the thinnest position of the inner retinal layer. The foveal center is marked on B-scan OCT images and automatically on their corresponding macula OCTA (3 mm × 3 mm) projection maps.

Fundus and OCTA images for each patient were combined by aligning the retinal vessels [Fig. 1]. Measurements on the processed images were obtained using Image software (V.1.49, National Institutes of Health, Bethesda, MD, USA). Based on 3-mm distances at the edges of the OCTA image of the macula, the fovea-AV crossing distance (FAVD), optic disc-AV

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crossing distance (DAVD), and optic disc-fovea distance (DFD) were measured [Fig. 1]. In view of interindividual variation in distances according to the macula size, the FAVD/DFD and DAVD/DFD ratios were calculated using the fixed DFD distance.

The FAVD/DFD ratio was used to show the distance to the fovea. The DAVD/DFD ratio was used to show the distance to the optic disc. Whether or not there were any correlations between the FAVD/DFD and DAVD/DFD ratios and the OCTA parameters (superficial FAZ area and vessel density in the SCP and DCP) was investigated.

Statistical analysis
The descriptive data are presented as the mean and standard deviation, range, frequency, or rate, as appropriate. Best corrected visual acuity values were converted to logMAR values for statistical analysis. The OCTA data for the BRVO and fellow eyes were compared using the Wilcoxon test. The Mann–Whitney U test was used to compare the OCTA data between the BRVO and control eyes and between the fellow eyes and control eyes. Pearson’s correlation coefficient was used for the correlation analysis. All statistical analyses were performed using SPSS version 22.0 (IBM Corp., Armonk, New York). The values of P < 0.05 were considered reflective of statistical significance.

Results

Patient characteristics
The demographic and clinical characteristics of the participants are shown in Table 1. Twenty-three patients (51.5%) were female and 22 (48.9%) were male. The mean patient age was 64.3 ± 9.0 years. There was no difference in the age or sex distribution between patients with BRVO and controls (both P > 0.05). The BRVO was in the superior half of the retina in 35 patients and in the inferior half of the retina in 10 patients. Thirty-four patients (75.6%) had hypertension and the mean duration of follow-up was 20.4 ± 6.9 (range: 12–36) months.

Comparisons between eyes with BRVO, fellow eyes, and control eyes
Comparisons of OCTA data for the macula between eyes with BRVO and corresponding fields in fellow eyes and control eyes are shown in Table 2. The vessel density in the SCP and DCP was significantly lower in eyes with BRVO than in fellow eyes or control eyes in all fields of the macula (all P < 0.05). There was no significant difference in SCP vessel density in any of the fields between the fellow eyes and control eyes. However, the DCP vessel density was significantly lower in all fields in fellow eyes than in control eyes (all P < 0.05). The mean FAZ area was significantly larger in eyes with BRVO than in fellow eyes (P < 0.05) or control eyes (P < 0.05).

Changes according to the distance between the affected AV crossings and the fovea
The mean distance between the AV crossings and the fovea was 4.5 ± 0.6 mm. As shown in Fig. 2a, there was a significant negative correlation between logMAR visual acuity and FAVD/DFD values (r = −0.356, P < 0.05). The FAVD/DFD ratio was positively correlated with the vessel density in the superficial and deep affected hemifields (r = 0.430, P < 0.05, Fig. 2b, and r = 0.308, P < 0.05, Fig. 2c, respectively). However, the FAVD/DFD ratio was not correlated with vessel density in the superficial or deep unaffected hemifield [Fig. 2d and e]. There was a significant negative correlation between the FAZ area and the FAVD/DFD values (r = −0.412, P < 0.05; Fig. 2f).

Changes according to the distance between the affected AV crossings and the optic disc
The mean distance between the center of the optic disc and the AV crossing sites was 3.5 ± 1.4 mm and that between the center of the optic disc and the fovea was 4.9 ± 0.3 mm. As shown in Fig. 3a, there was no significant correlation between logMAR visual acuity and the DAVD/DFD values. The DAVD/DFD ratio was not correlated with vessel density in the superficial or deep affected hemifields [Fig. 3b and c]. However, the DAVD/DFD ratio was negatively correlated with vessel density in the superficial and deep unaffected hemifields (r = −0.442, P < 0.05, Fig. 3d, and r = −0.313, P < 0.05, Fig. 3e, respectively). There was no significant correlation between the FAZ area and the DAVD/DFD values [Fig. 3f].

Discussion

BRVO is a retinal vascular disease characterized by first-degree or second-degree focal occlusion. It is most frequently observed around the temporal vascular arcade. The upper temporal vascular arcade is more commonly affected than the lower temporal vascular arcade.\(^2\)\(^3\)\(^4\) However, peripheral occlusions are relatively rarely encountered because of their tendency to have an asymptomatic course.\(^5\)\(^6\) Occlusions are usually identified at AV crossings\(^7\) and are associated with pathology such as macular edema and macular ischemia.\(^8\)\(^9\) Therefore, in this study, we aimed to show the affected AV crossings, which are important in the pathogenesis of BRVO...
Table 1: Demographic and clinical characteristics of the study participants

|                          | BRVO group (n=45) | Control group (n=45) |
|--------------------------|-------------------|----------------------|
| Age in years, mean±SD (range) | 64.3±8.4 (48-79) | 62.4±9.2 (47-79) |
| Sex, n (%)               |                   |                      |
| Female                   | 23 (51.1)         | 23 (51.1)            |
| Male                     | 22 (48.9)         | 22 (48.9)            |
| Comorbidity, n (%)       |                   |                      |
| Hypertension             | 34 (75.6)         | -                    |
| Previous treatment, n    |                   |                      |
| Intravitreal ranibizumab | 25                | -                    |
| Focal laser photocoagulation | 4             | -                    |
| Ranibizumab + focal laser | 16             | -                    |
| Follow-up duration in months, mean±SD (range) | 20.4±6.9 (12.0-36.0) | -                    |
| Foveal thickness in µm, mean±SD (range) | 254.5±29.2 (156-296) | 231.8±18.5 (178-260) |
| BCVA in logMAR, mean±SD  | 0.26±0.16         | 0.01±0.02            |

BCVA, best-corrected visual acuity; BRVO, branch retinal vein occlusion; logMAR, logarithm of the minimum angle of resolution; SD, standard deviation

Table 2: Comparison of optical coherence tomography angiography data for the macula between eyes with BRVO and corresponding fields in fellow eyes and control eyes

|                                | Mean±SD  | P          |
|--------------------------------|----------|------------|
|                                | BRVO group | Control group |
| SCP VD whole-field (%)         |           |            |
| BRVO eye                       | 39.3±3.8  | 46.2±4.0   | <0.05*    |
| Fellow eye                     | 44.8±3.7  | 46.2±4.0   | 0.092†    |
| P                              | <0.05‡    |            |
| SCP VD affected hemifield (%)  |           |            |
| BRVO eye                       | 37.0±4.6  | 46.0±4.1   | <0.05*    |
| Fellow eye                     | 44.7±3.8  | 46.0±4.1   | 0.054‡    |
| P                              | <0.05‡    |            |
| SCP VD unaffected hemifield (%)|           |            |
| BRVO eye                       | 41.4±4.4  | 46.5±3.9   | <0.05*    |
| Fellow eye                     | 44.9±3.7  | 46.5±3.9   | 0.082‡    |
| P                              | <0.05‡    |            |
| DCP VD whole-field (%)         |           |            |
| BRVO eye                       | 42.1±4.6  | 51.3±3.7   | <0.05*    |
| Fellow eye                     | 48.8±3.2  | 51.3±3.7   | <0.05*    |
| P                              | <0.05‡    |            |
| DCP VD affected hemifield (%)  |           |            |
| BRVO eye                       | 39.9±5.5  | 51.4±3.9   | <0.05*    |
| Fellow eye                     | 48.8±3.3  | 51.4±3.9   | <0.05*    |
| P                              | <0.05‡    |            |
| DCP VD unaffected hemifield (%)|           |            |
| BRVO eye                       | 44.4±5.6  | 51.2±3.8   | <0.05*    |
| Fellow eye                     | 48.9±3.2  | 51.2±3.8   | <0.05*    |
| P                              | <0.05‡    |            |
| Superficial FAZ area (mm²)     |           |            |
| BRVO eye                       | 0.39±0.18 | 0.28±0.09  | <0.05*    |
| Fellow eye                     | 0.29±0.10 | 0.28±0.09  | 0.6†      |
| P                              | <0.05‡    |            |

BRVO, branch retinal vein occlusion; DCP, deep capillary plexus; FAZ, foveal avascular zone; OCTA, optical coherence tomography angiography; SCP, superficial capillary plexus; SD, standard deviation; VD, vessel density. *Significance between BRVO eyes and control eyes (Mann-Whitney U test). †Significance between fellow eyes and control eyes (Mann-Whitney U test). ‡Significance between BRVO eyes and fellow eyes (Wilcoxon test). Bold values are statistically significant
and its prognosis. We measured the distances between the affected AV crossing sites and the centers of the fovea and optic disc identified by OCTA. We then compared these distances between the optic disc and fovea (using the FAVD/DFD and DAVID/DFD ratios) given that this distance is known to vary in healthy individuals.\[^{28}\]  

In this study, we found that the vessel density was greater in the superficial and deep plexuses of the affected hemifield, FAZ area was smaller (approached control group values), and visual acuity was better with greater fovea-affected AV crossing distances. Better visual acuity and quantitative vessel parameters were observed when the occlusion was more distant from the fovea. Our findings suggest that impairment of foveal vascularity and visual acuity were more prominent in eyes with occlusions closer to the fovea. Parodi et al.\[^{29}\] found an irregular enlargement of the FAZ using fluorescein
angiography in eyes with BRVO. Furthermore, the FAZ area correlated negatively with visual acuity in the eyes in that study. When looking at the capillary ring surrounding the FAZ, Hayreh et al. evaluated the association of capillary foveal ring (intact or broken) with improvement in visual acuity after macular edema had resolved. They found that visual acuity improved in 81% of eyes with an intact perifoveal capillary ring and in 58% of those with a broken ring.[30]

In previous studies, a short distance of occlusion from the disc margin was found to be associated with increased retinal hemorrhage and development of refractory macular edema.[31,32] Although it was expected that there would be more congestion and ischemic areas in occlusions located close to the vascular root, the FAZ area and visual acuity were not associated with the optic disc-affected AV crossing distance. However, the vessel density was greater in the
superficial and deep plexuses of the unaffected macular hemifield when the optic disc-affected AV crossing distance was smaller. The order of AV crossing at which the vein was occluded in BRVO was previously counted from the optic disc onwards as a first-order or second-order AV crossing.[8,33] In the study by Staurenghi et al.,[34] 26% of patients with BRVO had first-order occlusions and 74% had second-order occlusions. They argued that symptoms may be reduced because of the greater distance from the macula, causing underestimation of the prevalence of first-order occlusions. In this study, although the FAZ area and visual acuity values were significantly correlated with the distance between the affected AV crossings and the center of fovea, they were not significantly correlated with the distance of the AV crossings to the center of the optic disc. Feist et al. observed that occlusions of AV crossings were more common in the temporal quadrants than in the nasal quadrants and that temporal occlusions would be more likely to become symptomatic than would nasal occlusions distant from the macula.[35] In our study, we found better visual acuity and central macular quantitative vessel parameters when the affected AV crossing was more distant from the fovea in patients with BRVO.

In this study, we found that the vessel density was significantly lower in the superficial and deep whole fields in eyes with BRVO than in either fellow eyes or control eyes, which is consistent with the findings of previous studies.[8,36] In addition, the vessel density in the DCP was significantly lower in fellow eyes than in control eyes without any significant difference in vessel density in the SCP.

Hypertension is a known risk factor for BRVO and was present in 75% of our patients. Therefore, we suspect that the vessel density in the DCP was lower in the fellow eyes of patients because of vascular thinning that occurred as a result of chronic hypertension. This finding is consistent with that in a study performed in patients with hypertension by Donati et al.[37] who observed a significant reduction in vessel density in the deep DCP and attributed this change in the microvascular network to thinning of the retinal vessels and loss of capillaries as a result of endothelial injury. Moreover, Koulimis et al.[9] showed that the caliber of capillaries in the unaffected fellow eye was significantly lower in patients with retinal vein occlusion than in healthy control eyes. They suggested that this finding may represent a manifestation of chronic hypertension and attendant vascular attenuation.

This study has some limitations mainly because the study design was retrospective in nature, the duration of observation varied among patients and nonstandardized treatment protocol was used for treating macular edema. Moreover, measurements of the deep FAZ area could not be obtained (due to the OCTA software). Furthermore, we could only analyze a limited field (3 mm × 3 mm) in the macula, which is important for central vision but may not be representative of the vascular disorder overall. Finally, the study excluded patients with macular vein occlusion. Hence, our findings may not be generalizable to all types of BRVO.

Conclusion

Our study shows that quantitative vessel parameters and visual acuity values vary significantly according to the change in distance between the affected AV crossings and the fovea in eyes with BRVO. There was better visual acuity, greater capillary density in the affected macular hemifield, and a smaller FAZ area (approaching control values) as the distance between the affected AV crossing site and the fovea became greater. However, the proximity of affected AV crossings to the optic disc was not associated with visual acuity, the FAZ area, or vessel density in the affected hemifield. Therefore, we believe that our findings may permit clinicians to predict the prognosis of the disease based on the location of the occlusion determined via clinical examination. Further studies that include larger patient samples are needed to confirm the present findings.

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Conflicts of interest

There are no conflicts of interest.

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