CAPILLARY NETWORK ANOMALIES IN BRANCH RETINAL VEIN OCCLUSION ON OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY

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Purpose: To analyze the foveal microvasculature features in eyes with branch retinal vein occlusion (BRVO) using optical coherence tomography angiography based on split spectrum amplitude decorrelation angiography technology.

Methods: A total of 10 BRVO eyes (mean age 64.2 ± 8.02 range between 52 years and 76 years) were evaluated by optical coherence tomography angiography (XR-Avanti; Optovue). The macular angiography scan protocol covered a $3 \text{ mm} \times 3 \text{ mm}$ area. The focus of angiography analysis were two retinal layers: superficial vascular network and deep vascular network. The following vascular morphological congestion parameters were assessed in the vein occlusion area in both the superficial and deep networks: foveal avascular zone enlargement, capillary non-perfusion occurrence, microvascular abnormalities appearance, and vascular congestion signs. Image analyses were performed by 2 masked observers and interobserver agreement of image analyses was 0.90 ($\kappa = 0.225$, $P < 0.01$).

Results: In both superficial and deep network of BRVO, a decrease in capillary density with foveal avascular zone enlargement, capillary non-perfusion occurrence, and microvascular abnormalities appearance was observed ($P < 0.01$). The deep network showed the main vascular congestion at the boundary between healthy and nonperfused retina.

Conclusion: Optical coherence tomography angiography in BRVO allows to detect foveal avascular zone enlargement, capillary nonperfusion, microvascular abnormalities, and vascular congestion signs both in the superficial and deep capillary network in all eyes. Optical coherence tomography angiography technology is a potential clinical tool for BRVO diagnosis and follow-up, providing stratigraphic vascular details that have not been previously observed by standard fluorescein angiography. The normal retinal vascular nets and areas of nonperfusion and congestion can be identified at various retinal levels. Optical coherence tomography angiography provides noninvasive images of the retinal capillaries and vascular networks.

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Retinal vein occlusion is the second most common retinal vascular disorder after diabetic retinopathy and is considered to be an important cause of visual loss.^{1,2}

Branch retinal vein occlusion (BRVO) is an acute cause of visual impairment secondary to thrombotic

events, external compression, or vessel wall pathology.^{3,4} It is hypothesized that in BRVOs, a combination of compression of veins at artero-venous crossings, degenerative changes within venous walls, and hypercoagulability may interact.

Occlusion of the major veins of the retinal circulation leads to increased intraluminal pressure, hemorrhage, and edema.⁵ Although the most common cause of decreased vision in BRVO is macular edema, thrombosis results in engorged veins frequently accompanied by variable amounts of retinal nonperfusion.

The assessment of the foveal microvasculature using fluorescein angiography has shown enlargement of intercapillary spaces in retinal vein occlusion areas,⁶

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Table 1. Macular Area (3 mm² × 3 mm²) Details of Superficial and Deep Network in the Branch Retinal Vein Occlusion Eyes by OCT-A

Eye/Gender/Age/	BCVA (ETDRS)	Comorbidities (Y/N)		Age of BRVO (Months)	OCT-Angiography								VC Mainly Signs (Superficial/Deep)	
		Diabetes	Hypertension		FAZ Enlargement (Superficial/Deep)		CN-P Occurrence (Superficial/Deep)		MA Appearance (Superficial/Deep)					
					#1	#2	#1	#2	#1	#2	#1	#2		
#1 RE/F/52	85	Y	Y	72	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	N/Y	N/Y	
#2 LE/M/60	80	Y	Y	18	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	N/Y	N/Y	
#3 LE/F/67	34	N	N	8	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	N/Y	N/Y	
#4 RE/M/70	63	N	N	20	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	N/Y	N/Y	
#5 LE/M/67	68	N	Y	26	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	N/Y	N/Y	
#6 RE/F/53	25	N	N	6	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	N/Y	N/Y	
#7 LE/M/58	30	N	N	48	Y/N	Y/Y	Y/N	Y/Y	Y/Y	Y/N	Y/Y	N/Y	N/Y	
#8 RE/M/68	70	N	N	72	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	N/Y	N/Y	
#9 RE/M/71	75	N	N	12	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	N/Y	N/Y	
#10 LE/F/76	75	N	Y	24	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	N/Y	N/Y	

Morphological features of FAZ enlargement (Y/N), CN-P occurrence (Y/N), and MA appearance (Y/N) in the area of vein occlusion were evaluated #1 and #2 are the estimation of 2 independent observers. Interobserver agreement was high (0.9).

BCVA, best correct visual acuity.

but the ability to detect microvasculature alterations has been limited by the superposition of the capillary networks and leakage.⁷

Recently, a new method of analysis by split spectrum amplitude decorrelation angiography technology has been introduced to evaluate and study the retinal microvasculature.^{8–10} Optical coherence tomography angiography (OCT-A) allows separating the superficial and deep vascular network, whereas the deep capillary network is barely visible on fluorescein angiography as reported by Spaide et al.⁹

The aim of this study was to assess foveal microvascular changes in BRVO using OCT-A.

Methods

This study was conducted in compliance with the tenets of the Declaration of Helsinki. Informed consent was obtained routinely from all examined patients to participate in this research. The main inclusion criterion was diagnosis of BRVO. The exclusion criteria included presence of any other retina disorders, a history of vitreous surgery, or presence of media opacities such as vitreous hemorrhage. The following data were collected, during the same examination: best corrected visual acuity, slit-lamp biomicroscopy, fundus examination, and OCT-A images. The AngioVue OCT-A device (Optovue, Inc., Fremont, CA) was used to obtain amplitude decorrelation angiography images. This instrument has an A-scan rate of 70,000 scans per second, using a light source centered on 840 nm and a bandwidth of 50 nm. Each OCT-A volume contains 304 Fx 304 A-scans with 2 consecutive B-scans captured at each fixed position before proceeding to the next sampling location. The split-spectrum amplitude decorrelation angiography was used to extract OCT-A information corresponding to each layer of interest. Each OCT-A volume was acquired in 2.9 seconds and 2 orthogonal OCT-A volumes were acquired to minimize motion artifacts.

A total of 10 BRVO eyes of 10 patients (mean age 64.2 ± 8.02; range between 52 years and 76 years) (F:M = 4:6) were evaluated by OCT-A (XR-Avanti; Optovue) in this observational study. The macular angiography scan protocol covered a 3 mm × 3 mm area. Angiography analysis was performed, focusing on two intraretinal layers: superficial vascular network and deep vascular network. The following vascular morphological details were assessed in both the superficial and deep network of the vein occlusion area: foveal avascular zone (FAZ) enlargement, capillary nonperfusion (CN-P), microvascular abnormalities (MA), and vascular congestion (VC).

Statistical Analysis

The FAZ enlargement, CN-P occurrence, MA appearance, and VC signs of superficial and deep vascular network images assessed by two independent observers were compared by Cohen kappa coefficient. Image analyses were performed by two masked observers and interobserver agreement of image analyses was 0.90 ($\kappa = 0.225$, $P < 0.01$).

Results

All 10 eyes of 10 patients with BRVO were evaluated using AngioVue OCT-A. The images included in the study were of sufficient quality for analysis and assessment. All eyes presented focal ischemia in the retinal area of involvement by BRVO.

Optical coherence tomography angiography allowed the detection of BRVO clinical features such as vascular tortuosity and caliber changes. Specific alterations of the foveal microvasculature were also detected by OCT-A such as FAZ enlargement, CN-P occurrence, MA appearance, and VC signs. The OCT-A images were evaluated independently by 2 trained readers (M.R. and M.C.S.) to define OCT-A characteristics of the macular area. Demographic and OCT-A details are summarized in Table 1. The interobserver agreement of image analyses for both superficial and deep network was high, at 0.90 ($\kappa = 0.225$, $P < 0.01$).

Foveal Avascular Zone Enlargement

Foveal avascular zone enlargement was observed both in superficial and deep network.

Capillary Non-Perfusion Occurrence

The CN-P areas were mainly shown by OCT-A in the superficial capillary network.

Microvascular Abnormalities Appearance

Microvascular abnormalities were represented by multiple intraretinal loops in the area of retina ischemia in correspondence of the superficial network. In the deep network was more evidently marked capillary congestion.

Vascular Congestion Signs

Vascular congestion was mainly observed in deep vascular network.

The superficial and deep vascular networks were both abnormal in all eyes; however, microvasculature alterations differed significantly between the two plexuses on OCT-A.

The differences between the region of BRVO involvement and healthy retina were well depicted by OCT-A. Beside the area of vascular occlusion in superficial vascular network, BRVO led to capillary dropout with CN-P areas around and outside the FAZ (Figure 1). Further, the main VC area was observed in

Fig. 1. A. Branch retinal vein occlusion in en-face OCT. B. B-scan trough of the fovea. C. Optical coherence tomography angiography of superficial network. D. Deep network. While the OCT and face shows the distribution area of cystoid space along the inferior vascular arcade, the B-scan revealed macular edema and subfoveal neuroretinal detachment. The vascular situation can be assessed only in OCT-A. The asymmetry between the region of BRVO involvement and the healthy retina is finely detected in OCT-A, both superficial and deep network. Beside the area of vascular occlusion in superficial vascular network, BRVO leads to capillary rarefaction with CN-P areas around and outside the FAZ.

Fig. 2. A. Detail of microvasculature anomaly around the FAZ that does not define precisely the layer involved in fluorescein angiography. The OCT-A defined the exact localization of the vascular congestion in the deep network (C) not observable in the superficial network (B).

the deep vascular network. Figure 2 shows microvascular anomalies around the FAZ that were not well defined in fluorescein angiography (Figure 2A). Instead the OCT-A defined more precisely the exact localization of the vascular congestion areas in deep network level (Figure 2C) not observable in the superficial network (Figure 2B). The CN-P areas were better delimited on OCT-A in the superficial capillary network outside the FAZ. (Figure 3) The composite images of 4-acquisition high-resolution protocol (3×3) distributed around the fovea show sinusoidal capillary course and multiple intraretinal loops in the area of retina ischemia in the superficial network whereas the deep network presents an intense alteration of the normal tiny fan patterns and marked capillary congestion. Figure 4 shows a case of BRVO at the

supero-temporal arcade. Foveal avascular zone, CN-P, and diffuse MA were evident in both the superficial (Figure 4A) and deep network (Figure 4B). The complete absence of flow in both networks in the area of branch retina vein occlusion reveals a severe ischemic process well defined by OCT-A. The B-scan in Figure 4, C and D shows the cut used for stratigraphy analysis.

In all, Figures VC was more marked in deep vascular network.

Discussion

BRVO symptoms depend on the site and severity of the occlusion. Some cases are asymptomatic, decreased

Fig. 3. Optical coherence tomography angiography composite of 4-acquisition protocol (3×3) distributed around the fovea. The images show the capillary FAZ enlargement, CN-P, and diffuse MA in the area of branch retina vein occlusion. The superficial network reveals sinuous capillary course and multiple intraretinal loops in the area of retina ischemia whereas the deep network presents a full subversion of fan pattern with marked capillary congestion. At the bottom the B-scan highlights the OCT-A image levels for superficial and deep network.

visual acuity being caused by macular edema and/or ischemia. Generally macular BRVO presents with a central visual field defect, whereas a major BRVO presents with a peripheral visual field defect corre-

sponding to the retinal quadrant that the affected vein drains.¹¹ Longstanding occlusion results in absolute scotomas, whereas short-term occlusion causes relative scotomas in areas of capillary non-perfusion.¹²

Fig. 4. Branch retinal vein occlusion on supero-temporal arcade. The superficial (A) and deep network (B) shows the FAZ enlargement, CN-P occurrence, and diffuse MA in the area of branch retina vein occlusion. The total absence of flow in both networks reveals severe ischemic process well defined by OCT-A. The B-scan in C and D show the section level used for stratigraphy analysis.

Although fundoscopy readily detects flame hemorrhages, dot and blot hemorrhages, cotton wool spots, hard exudates, retinal edema, and dilated tortuous veins in acute BRVO,^{13,14} OCT-A shows microvascular anomalies in detail.

In fact, the possibility to study the retina tissue by a stratigraphic analysis as the OCT-A, allows to choose the vascular layer to observe. Moreover, BRVO features such as venous collaterals and vascular sheathing are better depicted by OCT-A. In our study, we observed that in early BRVO, vascular congestion was mainly localized at the boundary of healthy tissue, in the deep vascular layers, whereas in stabilized or prolonged BRVO, the vascular congestion is partially restored. On the other hand, in long-standing BRVO, we found a larger area of involvement.

As recently described, the reason for evaluating the superficial and deep networks separately is the potential differential involvement of the two layers in some pathologies.^{10,15} According to Ishibazawa et al¹⁶ and Kuehlewein et al¹⁷ the nonperfused area is well defined by OCT-A. They reported the ischemic macular area identification in diabetic macular retinopathy.

In our series the identification of FAZ enlargement, CN-P appearance, MA presence, and VC signs are easy to assess by OCT-A. In fact, there was a good agreement between the two blinded examiners, as shown by the Cohen Kappa coefficient.

The detection of CN-P areas on OCT-A could be also due to a very slow blood flow in these areas of suffering, below the detection limit of 0.3 mm/second on OCT-A.¹⁸

The FAZ was also well visualized on OCT-A providing more precise delineation of this area and of its enlargement than on FA. Intraretinal MA as the abnormal shunts or anastomosis that developed at the edge of CN-P areas could have a more rapid blood flow which could enhance their detection by OCT-A.

All eyes showed VC at the level of the deep vascular network, at the margin of nonaffected areas.

In conclusion we observed microvascular alterations in BRVO in both superficial and deep vascular networks in our series. Foveal avascular zone enlargement, CN-P and MA were observable in both networks. VC was mainly observed in the deep network.

Our study has some limitations because of a small number of cases with various onsets of BRVO. Furthermore, an objective method to quantify FAZ enlargement, CN-P appearance, and MA presence may support our results. However, we found interesting to note in all cases a better identification of capillary features on OCT-A and their distribution in the superficial and deep capillary network. Larger

sample size and prospective studies are needed to further investigate OCT-A for BRVO in the clinical setting.

Optical coherence tomography angiography technology can be a useful clinical tool for BRVO diagnosis and follow-up, providing stratigraphic vascular details that have not been previously observed by standard fluorescein angiography. It helps quantify FAZ enlargement, CN-P appearance, MA presence, and vascular congestion. The normal retinal vascular nets as well as areas of nonperfusion and congestion can be identified at various retinal levels. Optical coherence tomography angiography provides noninvasive images of the retinal capillaries and their lesions at all vascular networks.

Key words: capillary non-perfusion, foveal avascular zone, foveal microvasculature, macular ischemia, microvascular abnormalities, optical coherence tomography angiography, split spectrum amplitude decorrelation angiography (SSADA).

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