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Original Article

Optical coherence tomography angiography analysis of microvascular network in retinal vein occlusion: superficial *vs*. deep capillary plexus

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Abstract

Introduction and aim: Optical coherence tomography angiography (OCTA) is a diagnostic imaging modality that provides distinct visualization of the vascular networks present in both the superficial and deep capillary plexuses. The present study employed OCTA to examine microvascular changes in the macular plexuses of retinal vein occlusion (RVO) patients, comparing them to unaffected eyes and a control group.

Materials and methods: We examined 35 patients with RVO and 35 healthy individuals, assessing both eyes of the RVO patients, resulting in 105 eyes examined overall. Data measurement of the superficial and deep capillary plexuses was performed using OCTA (Zeiss Cirrus HD-OCT 6000) and ImageJ software.

Results: The foveolar avascular zone (FAZ) exhibited an expanded area, a greater perimeter, and loss of circularity in contrast to healthy and unaffected eyes at both superficial and deep capillary plexuses. In RVO eyes, vascular density, perfusion density, and vascular length density were notably lower compared to both controls and fellow eyes, with similar reductions observed in fellow eyes compared to controls.

Conclusion: The study assessed OCTA parameters to analyze the macular microvascular network in RVO patients. The OCTA quantitative evaluation of the superficial and deep capillary plexuses in the macula of RVO eyes shows significant differences in FAZ and microvascular densities compared to fellow eyes and the control group. Similar differences were also observed in fellow eyes compared to the control group. OCTA offers quantitative information specific to layers about the microvascular alterations induced by RVO.

Keywords

foveolar avascular zone, microvascular density, retinal vasculature, retinal vascular occlusive disease

Introduction

Retinal vein occlusion (RVO) has an estimated global prevalence of 0.77 percent, posing a risk of blindness to approximately 28.06 million individuals worldwide. RVO is typically categorized into two forms: central vein occlusion (CRVO) and branch vein occlusion (BRVO) and is regarded as one of the most prevalent retinal vascular conditions.[1,2]

The use of fluorescein angiography (FA) allows visualization of the affected retinal vasculature in patients with RVO.[3] It is important to note that FA may be associated with a number of potential risks, adverse effects, and the possibility of severe outcomes. Additionally, its limitations preclude its use in analyzing the microcirculation in the macula's superficial and deep capillary plexuses separately. [4] The advantage of independently recording the vascular network makes optical coherence tomography angiography (OCTA) a valuable technique in patients with RVO, particularly for the quantitative analysis of the blood vessels.[5]

An OCTA macular scan in patients with RVO enables the detection of changes in both the macula's capillary plexuses and the foveal avascular zone (FAZ).[6-9] Analyzing the macula's vascular network with OCTA is considered to be as effective as using FA for RVO, providing layer-specific information that was previously unavailable with FA.[5]

The ability to examine quantitative aspects of the macula's microvascular network without invasive procedures makes OCTA an important tool for assessing patients with RVO.

Aim

The present study aims to analyze the microvascular changes in the macular superficial and deep capillary plexuses in eyes with RVO using OCTA.

Materials and methods

Participants

Patients diagnosed with RVO who presented to the University Eye Clinic at St George University Hospital in Plovdiv, Bulgaria, between January 2023 and July 2024 were studied prospectively. All patients with RVO were evaluated immediately after symptoms appeared and had never received anti-VEGF therapy.

The study included 35 patients with RVO and 35 healthy individuals. Both eyes of the patients with RVO were examined. Consequently, the patients were categorized into 35 eyes affected by RVO and 35 unaffected fellow eyes. In total, 105 eyes were investigated in this study. Nineteen eyes were identified with CRVO, while 16 were found to have BRVO, resulting in a percentage ratio of 54.3/45.7. **Table 1** is an overview of the demographic characteristics of the research subjects, indicating that the individuals in each group have comparable attributes.

Optical coherence tomography angiography

The Zeiss Cirrus HD-OCT 6000 device operates at a scan rate of 100 kHz, emitting light at a wavelength of 840 nm. It was utilized to evaluate the microvascular networks of participants within a 3×3 mm macular area centered on the fovea, using it as a fixation point. The Angiography 3×3 mm protocol analyzes the amplitude-decorrelation signal from two B-scans, visually representing macular blood flow and capillary networks.

Certain criteria were taken into account when choosing patients for the current research. Patients with RVO who also had additional retinal conditions were not included in the study, as their participation might adversely affect the recorded data and bias the research. Besides the initial criteria, OCTA scans were ruled out if they showed poor image quality or had non-transparent optical structures, resulting in significant distortions in OCTA scans.

Superficial and deep capillary plexus

Registering separate data from the superficial and deep capillary plexuses is enabled by the autonomous division and evaluation of retinal layers by the software. Although the automatic division of retinal layers allows for quantitative data recording of the superficial capillary plexus (SCP), the current version of the software does not support this for the deep capillary plexus (DCP). The software recognizes the inner plexiform layer (IPL) as the boundary between the SCP and DCP. The internal limiting membrane (ILM) defines the inner border of the SCP, while the outer plexiform layer (OPL) delineates the outer boundary of the DCP.[10]

With OCTA, various vascular network parameters, including vascular density (VD) and perfusion density (PD), as well as FAZ-related parameters, such as area, perimeter, and circularity, were evaluated in the SCP. For each separate ETDRS area enclosed by the Angiography 3×3 mm protocol – central, internal, and total, the software records individual values.

Because of software constraints, the DCP data was examined using ImageJ, a Java-based image processing tool developed by the National Institute of Health in the USA. [11] The software has been developed for the purpose of image analysis and is employed in a variety of scientific studies within the domains of medicine and biology. This open-source software can calculate VD and vascular length

Table 1. Demographic features of the groups

Parameter	RVO eyes, n = 35	Unaffected eyes, n=35	Control group, n=35
Age, mean±SD	62.83±12.86	62.83±12.86	59.77±5.92
Sex ratio male:female	23:12	23:12	21:14
Sex ratio (%)	65.7:34.3	65.7:34.3	60:40

SD: standard deviation; RVO: retinal vein occlusion; n: number of eyes density (VLD) by taking the count of pixels that represent blood vessels and dividing it by the total number of pixels within the analysis area. Additionally, the boundaries of FAZ can be manually chosen, and its size and shape can be determined **(Fig. 1)**.[12]

Statistical analysis

The OCTA and ImageJ data collected from macular vascular network analysis were statistically analyzed with SPSS version 19.0 (SPSS Inc, IBM). Quantitative comparisons between two groups were made using a Student's t-test, and multiple group comparisons were made using a One-Way ANOVA. A p-value of less than 0.05 was considered to indicate statistical significance.

Results

This research performed a comparison of quantitative parameters across three groups, concentrating on variables associated with the FAZ and the macular vascular network. **Table 2** presents a comparison of SCP and DCP measurements related to the FAZ, including area, perimeter, and circularity, among the groups.

Foveolar avascular zone

A statistically significant difference in FAZ parameters at SCP and DCP was observed when comparing 1) RVO eyes to the control group, 2) unaffected fellow eyes to the control group, and 3) all groups were compared simultaneously.

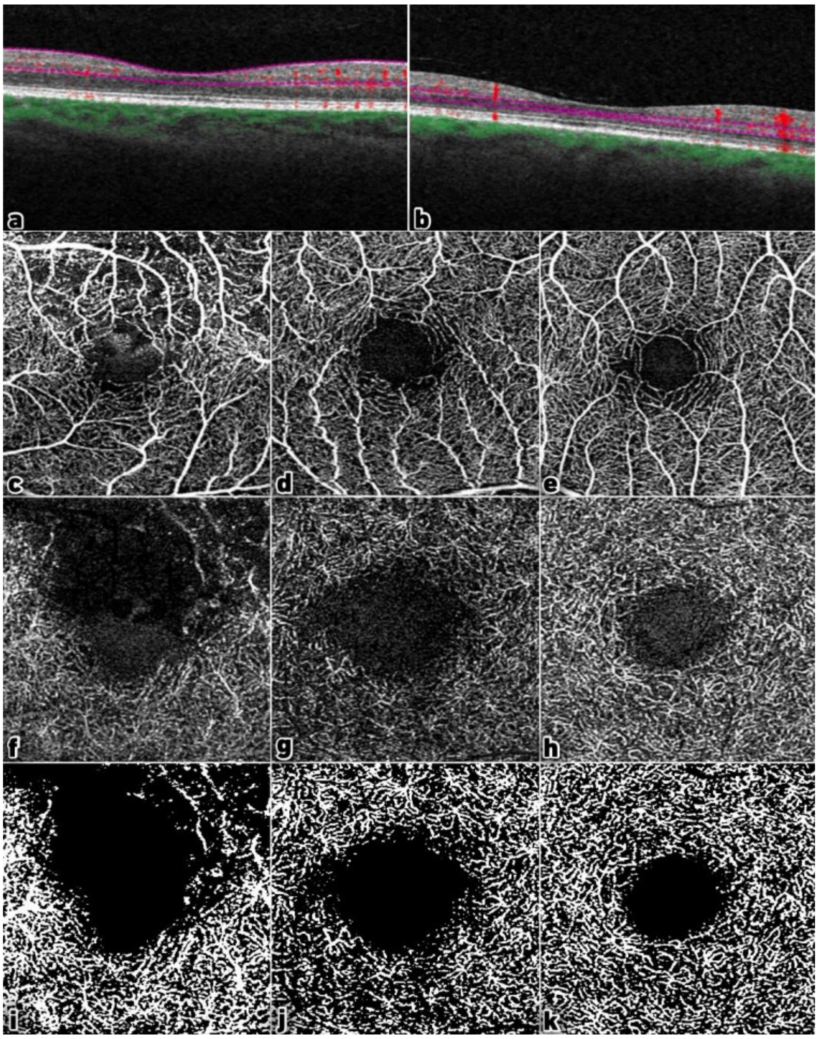

Figure 1. OCT B-scan image showing segmentation layers together with OCTA scans of the SCP and DCP covering a 3×3 mm area of the macula in the RVO eye, the unaffected fellow eye, and a normal eye. **a, b.** B-scans showing segmentation layers of SCP and DCP; **c, d, e.** En face OCTA scan of a 3×3 mm macular area for the SCP in an RVO eye, the fellow eye, and a normal eye; **f, g, h.** En face OCTA scan of a 3×3 mm macular area for the DCP in an RVO eye, the fellow eye, and a normal eye; **i, j, k.** Binarized en face images of the DCP from RVO eyes, fellow eyes, and the control group utilized in the quantification procedure.

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Table 2. Analysis of foveolar avascular zone (FAZ)

Parameters		Research groups	Mean±SD 95% CI	Pa	Pb	Pc	Pd
SCP FAZ	Area (mm²)	RVO eye	0.37±0.23 (0.29–0.45)	0.005	0.007	0.667	0.001
		Fellow eye	0.24±0.11 (0.21–0.28)				
		Control group	0.25±0.08 (0.23–0.28)				
	Perimeter (mm)	RVO eye	(2.91±0.95) 2.59–3.24	<0.001	<0.001	0.931	<0.001
		Fellow eye	2.17±0.50 (2.00–2.34)				
		Control group	2.16±0.43 (2.01–2.31)				
	Circularity	RVO eye	0.52±0.11 (0.48–0.55)	0.001	<0.001	0.008	<0.001
		Fellow eye	0.60±0.10 (0.57–0.64)				
		Control group	0.67±0.10 (0.63–0.70)				
DCP FAZ	Area (mm²)	RVO eye	2.15±0.68 (1.92–2.39)	<0.001	<0.001	0.108	<0.001
		Fellow eye	1.37±0.27 (1.28–1.46)				
		Control group	1.25±0.34 (1.14–1.37)				
	Perimeter (mm)	RVO eye	6.56±1.22 (6.14–6.98)	<0.001	<0.001	0.171	<0.001
		Fellow eye	5.07±0.57 (4.88–5.27)				
		Control group	4.85±0.77 (4.58–5.11)				
	Circularity	RVO eye	0.63±0.12 (0.59–0.67)	0.035	0.015	0.926	0.018
		Fellow eye	0.68±0.09 (0.65–0.71)				
		Control group	0.68±0.06 (0.66–0.70)				

SD: standard deviation; CI: confidence interval; Pa: RVO eyes compared to fellow eyes (unpaired student's t test); Pb: RVO eyes compared to control group (unpaired student's t test); Pc: fellow eyes compared to control group (unpaired student's t test); Pd: multiple group analysis (One-Way ANOVA test).

However, the FAZ parameters, when comparing fellow eyes to control groups, did not show a statistically significant difference. FAZ circularity at the SCP level was the only variable that showed significant difference when compared between the unaffected fellow eyes and the control group.

A comparison between eyes affected by RVO and the control group revealed a larger FAZ area, increased perimeter, and loss of circularity at both the SCP and DCP levels. Similar changes were detected in the unaffected eyes of RVO patients compared to the control group. The expansion of FAZ size was more evident at the DCP level than at the SCP level in RVO eyes compared to the control group.

Vascular density, perfusion density, and vascular length density

All three zones of the examined macular area at SCP level showed significant differences in vascular and perfusion density between RVO eyes and a control group. All analyzed parameters, except for the macula's central zones, revealed statistically significant differences between RVO eyes and their unaffected eyes. A comparison of unaffected fellow eyes and a control group revealed significantly reduced vascular density in the inner zone, as well as reduced perfusion density of the inner and total zone of the 3×3 macular zone.

Comparative analysis across all groups showed statistically significant differences in the macular vascular network at the DCP level when comparing total VD and VLD **(Table 3).**

Table 3. Analysis of the microvascular network of the macula

Parameters		Research groups	Mean±SD 95% CI	Pa	Pb	Pc	Pd
SCP VD (mm/mm^2)	Central	RVO eye	0.37±0.23 (0.29–0.45)	0.245	0.022	0.190	0.057
		Fellow eye	0.24±0.11 (0.21–0.28)				
		Control group	0.25±0.08 (0.23–0.28)				
	Inner	RVO eye	(2.91±0.95) 2.59–3.24	<0.001	<0.001	0.011	<0.001
		Fellow eye	2.17±0.50 (2.00–2.34)				
		Control group	2.16±0.43 (2.01–2.31)				
	Total	RVO eye	0.52±0.11 (0.48–0.55)	<0.001	<0.001	0.126	<0.001
		Fellow eye	0.60±0.10 (0.57–0.64)				
		Control group	0.67±0.10 (0.63–0.70)				
SCP PD (%)	Central	RVO eye	2.15±0.68 (1.92–2.39)	0.400	0.049	0.183	0.117
		Fellow eye	1.37±0.27 (1.28–1.46)				
		Control group	1.25±0.34 (1.14–1.37)				
	Inner	RVO eye	6.56±1.22 (6.14–6.98)	0.001	<0.001	0.008	<0.001
		Fellow eye	5.07±0.57 (4.88–5.27)				
		Control group	4.85±0.77 (4.58–5.11)				
	Total	RVO eye	0.63±0.12 (0.59–0.67)	0.003	<0.001	0.006	<0.001
		Fellow eye	0.68±0.09 (0.65–0.71)				
		Control group	0.68±0.06 (0.66–0.70)				

DCP VD (%)	Total	RVO eye	20.21±6.56 17.96–22.47	<0.001	<0.001	0.003	<0.001
		Fellow eye	27.16±4.51 25.62–28.71				
		Control group	30.17±3.74 28.88–31.45				
DCP VLD (%)	Total	RVO eye	3.30±0.97 2.96–3.63	0.004	<0.001	<0.001	<0.001
		Fellow eye	3.89±0.65 3.67–4.11				
		Control group	4.89±0.61 4.68–5.10				

SD: standard deviation; CI: confidence interval; SCP: superficial capillary plexus; DCP: deep capillary plexus; VD: vascular density; PD: perfusion density; VLD: vascular length density; Pa: RVO eyes compared to fellow eyes (unpaired student's t test); Pb: RVO eyes compared to control group (unpaired student's t test); Pc: fellow eyes compared to control group (unpaired student's t test); Pd: multiple group analysis (One-Way ANOVA test)

Discussion

This study analyzed OCTA parameters, including quantitative data such as the area, perimeter, and circularity from the FAZ. Measurements from the macular vascular network, including VD, PD, and VLD at the level of both capillary plexuses, were also quantified. The data from RVO eyes, their unaffected eyes, and the control group were compared.

OCTA is recognized as an efficient and noninvasive technique for evaluating the retinal microvascular network, enabling segmental analysis of the FAZ and capillary vascular network in eyes affected by RVO.[13] This study identified both a disruption in the FAZ capillary arcade and a decrease in the macular microvascular network. These alterations are comparable to findings from other research.

The present study, using OCTA, identified a notable enlargement of both superficial and deep FAZ in eyes with RVO compared to their fellow eyes and the control group, with the DCP showing a more marked enlargement. These results are similar to the research performed by Rispoli et al. and other authors who report that the enlargement in FAZ is seen in both capillary plexuses.[14,15] In contrast, some authors have pointed out that only the FAZ in the DCP level of RVO-affected eyes was significantly larger compared to their unaffected fellow eyes and the control group.[7,16] This could indicate that the DCP is more prone to ischemic changes than the SCP.[17] The present study found greater impairment in the DCP than in the SCP, occurring not only in RVO-affected eyes but also in the fellow eyes. Moreover, the current study found that FAZ circularity was impacted in both capillary plexuses. Similarly, Chen et al. noted irregularities in the FAZ circularity in patients with BRVO, resulting in a shape that differs from a perfect circle.[18]

The capillary network within the 3×3 mm area of the macula was quantified by evaluating both plexuses for VD, PD, and VLD. In the present study comparing the control group with eyes affected by RVO, a notable reduction was observed in the vascular density, perfusion density, and vascular length density in the SCP and DCP of eyes with RVO. Furthermore, all parameters, except for the VD and PD in the macula's central zone, showed significant differences between eyes with RVO and their unaffected fellow eyes. Previous studies have similarly found comparable results when examining eyes with RVO against their fellow eyes or control group.[6,19,20] A study of 102 eyes with CRVO revealed that the reduction in vascular density at the DCP was greater than that at the SCP compared to their unaffected eyes.[21] Comparable findings were reported by Dave et al., showing a reduction in vessel density, more pronounced in the DCP.[22]

In a study comparing eyes affected by RVO with their unaffected eyes, Fan et al. similarly found no significant results regarding the vascular density parameter in the foveal zone at the SCP level.[23] The present study also found a lack of significant findings in the central foveolar area of the macula when comparing RVO eyes to their fellow eyes. This may be due to central densities being less impacted by ischemic alterations. However, further investigations are needed to prove this theory.

Statistical differences were observed in the vascular and perfusion density of specific macular regions between fellow eyes and the control group at the SCP level. The reduction in vascular density was more significantly observed at the DCP level. It could be a result of altered vascular structures in the macula of RVO patients' fellow eyes, particularly in their DCPs. Other researchers have reported comparable findings showing a decrease in blood vessel density in the unaffected eyes of RVO patients compared to the control group.[9] These findings indicate the participation of the macular vascular network in the fellow eyes of RVO patients, with the DCP showing a greater impact. The implications of these changes require further exploration.

This study has a few limitations. Some of the RVO patients presented with cystoid macular edema (CME) at the onset of the occlusion. The presence of CME might affect the automatic segmentation of the retinal layers and, respectively, the capillary plexuses, and that may affect the quantified values. The presence of other systemic comorbidities, which are frequently observed in patients with RVO, such as systemic hypertension, cardiovascular disorders, and atherosclerosis, has the potential to influence the macular vascular network densities. This, in turn, may result in an impact on the recorded values. Artifacts were avoided when performing OCTA since they have a major impact on calculated values. Nevertheless, minor artifacts caused by blinking and head movement could have influenced the outcomes.

Conclusion

The current study measured OCTA parameters to evaluate the microvascular network of the macula in patients with diagnosed RVO. RVO eyes, when compared to the control group and unaffected fellow eyes, exhibited an expanded FAZ area, an increased perimeter, and a loss of circularity at the superficial and deep capillary plexuses. VD, PD, and VLD are significantly reduced in eyes with RVO, with similar reductions observed in fellow eyes of RVO patients, when compared to the control group.

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Competing Interests

The authors have declared that no competing interests exist

Author contributions

Sinan Aptikadir: conceptualization, design of the study, data curation and interpretation, writing – original draft, review and editing, visualization, supervision, final approval of the manuscript;

Nelly Sivkova: conceptualization, design of the study, data curation and interpretation, writing – original draft and editing, supervision, final approval of the manuscript.

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