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Comparative Quantitative Analysis of Retinal Superficial Capillary Plexus in Patients with Retinal Vein Occlusion and Unaffected Fellow Eyes

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Abstract

Purpose: To evaluate optical coherence tomography angiography (OCT-A) data obtained from the superficial retinal capillary plexus of patients with retinal vein occlusion and comparative analysis with data registered from unaffected fellow eyes. **Methods:** The examined patients were classified into 2 groups: group 1—eyes with established retinal vein occlusion (n = 29) and group 2—unaffected fellow eyes of patients with retinal vein occlusion (n = 24). The scanning protocol "Angiography 3 × 3 mm" of Zeiss Cirrus HD-OCT 6000, AngioPlex Metrix was used to evaluate the retinal superficial capillary plexus. The analyzed parameters were vascular density and perfusion density, as well as the area, perimeter, and circularity of the foveolar avascular zone (FAZ). **Results:** The comparative analysis of FAZ parameters at the superficial capillary plexus (SCP) between group 1 (eyes with retinal vein occlusion) and group 2 (unaffected fellow eyes) showed significant results for the three parameters, respectively area ($p = 0.003$), perimeter ($p \leq 0.001$), and circularity ($p = 0.011$) of FAZ. The comparative analysis of the vascular network at SCP in patients with diagnosed retinal vein occlusion and unaffected fellow eyes showed significant results for vascular density (VD) in the central ($p = 0.038$) and inner ($p \leq 0.001$) zones as well as total VD ($p \leq 0.001$) were statistically significant. Moreover, the results obtained in the study of vascular perfusion (VP) indicated significant results in the inner zone ($p \leq 0.001$) and total VP ($p = 0.001$). Vascular perfusion in the central zone ($p = 0.116$) was the only parameter not to meet significant results. **Conclusion:** The current study observed a significant enlargement of the FAZ and loss of its circularity, along with a reduction in vascular network parameters at the superficial retinal capillary plexus level.

Keywords

Retinal Vein Occlusion, Optical Coherence Tomography Angiography, Superficial Retinal Capillary Plexus

1. Introduction

Retinal vein occlusion (RVO) is the second most common vascular disease of the retina after diabetic retinopathy, and it is one of the most common causes of unilateral vision loss [1]. Retinal venous occlusion occurs as a result of partial or complete obstruction of a retinal venous vessel, which is classified based on the location of the obstruction [2]. The loss of vision is usually caused by macular edema or retinal ischemia and in the later stages by complications such as vitreous hemorrhage, epiretinal membrane formation, rubeosis of the iris, or neovascular glaucoma [2] [3].

The diagnosis is made by ophthalmoscopy, and fluorescein angiography (FA) determines the degree of retinal ischemia. It is known that FA is an invasive method with contraindications, as well as the possibility of severe complications, which makes its performance contraindicated. In recent years, to better understand the changes in the different retinal vascular plexuses, angio-optical coherence tomography has been introduced into ophthalmology practice.

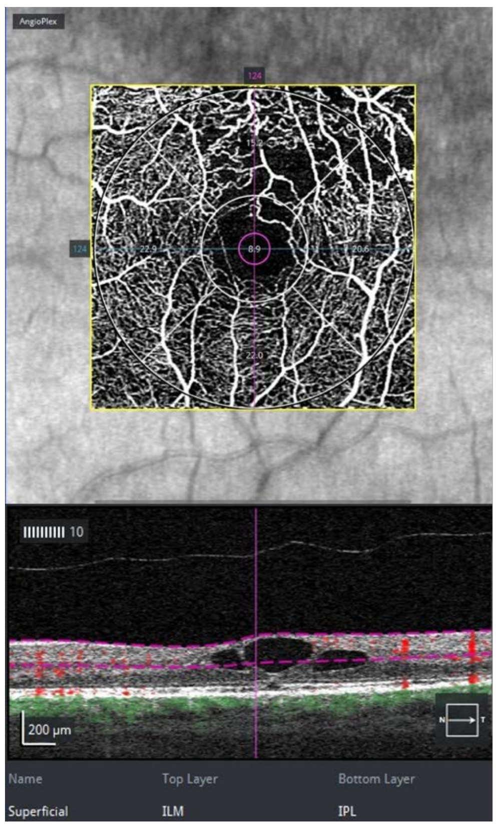

Figure 1. Angiography 3 × 3 of a RVO patient.

Optical Coherence Tomography (OCT) is a non-invasive, non-contact, and relatively new method for visualizing high-resolution retinal layers, based on the cross-sectional structure [4]. Angio-OCT is a functional addition to OCT, enabling visualization of the retinal vascular network without a contrast agent. The method is based on a split-spectrum amplitude decorrelation algorithm (SS-ADA), which analyzes two OCT scans performed on the same area of the retina and differentiates static from non-static tissue, allowing us to image retinal blood flow by calculating the decorrelation signal between the two scans [5]. As well as providing detailed information on the retina's superficial and deep capillary plexus, OCT-A allows the measurement of vascular density and vascular perfusion in the macular region and the determination of the size of the foveolar avascular zone (FAZ) [6] [7] (See **Figure 1** and **Figure 2**).

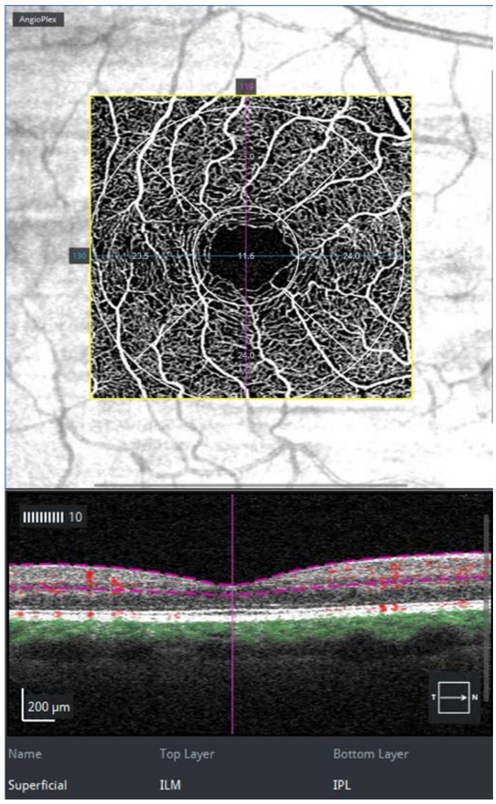

Figure 2. Angiography 3 × 3 of unaffected fellow eye of the same patient.

This study aims to evaluate OCT-A data obtained from the superficial retinal capillary plexus of patients with retinal vein occlusion and compare them to unaffected fellow eyes.

2. Materials and Methods

An initial prospective study was conducted on twenty-nine patients with established RVO enrolled at the University Eye Clinic, St. George University Hospital throughout a one-year period. The diagnosis of RVO was made following an ophthalmological examination that included indirect ophthalmoscopy. The examined eyes were systematized into 2 groups: group 1—eyes with established retinal vein occlusion (n = 29) and group 2—unaffected fellow eyes of patients with retinal vein occlusion (n = 24). Among the exclusion criteria were diabetic retinopathy, age-related macular degeneration, excessive myopia, and ocular trauma. OCT-A images with poor quality (signal strength below 6) were excluded from the study because of blinking, eye movements, and insufficiently transparent ocular media. Twenty-nine patients were studied during the time interval, of whom five had unaffected eyes excluded from the study because of the exclusion criteria described above. The mean age of group 1 was 62.52 ± 13.38 and the mean age of group 2 was 60.21 ± 13.43. The first group consisted of twenty men (69%) and nine women (31%), while seventeen men (70.8%) and seven women (29.2%) made up the second group (Table 1).

Table 1. Demographic characteristics and types of RVO.

	Eyes with RVO (group 1) n = 29	**Unaffected fellow eye** (group 2) n = 24
age (y)		
mean age	62.52 ± 13.38	60.21 ± 13.43
CI 95%	57.43 - 67.60	54.54 - 65.88
sex (%)	20 men (69), 9 women (31)	17 men (70.8) 7 women (29.2)
type (%)	RVO (total) = 29 eyes CRVO = 18 eyes (62.1) BRVO = 11 eyes (37.9)	

Mean age ± standard deviation (SD); CI 95% - 95% confidence interval; RVO—retinal vein occlusion; CRVO—central retinal vein occlusion, BRVO—branch retinal vein occlusion; n—number of eyes.

A summary of the risk factors encountered in the group of patients with RVO is presented in Table 2.

Table 2. Cardiovascular risk factors and diseases in the study sample.

		subtypes	
	RVO **(n = 29)**	***CRVO*** **(n = 18)**	***BRVO*** **(n = 11)**
Comorbidity (%)			
Systemic hypertension	79.3	72	91
Diabetes mellitus	13.8	11	18
Cardiovascular diseases	34.5	33	36
Dyslipidemia	20.7	22	18
Ocular hypertension/Glaucoma	20.7	22	18
Malignant neoplasms	10.3	17	0
Smoking (%)	20.7	11	36

RVO—retinal vein occlusion, CRVO—central retinal vein occlusion, BRVO—branch retinal vein occlusion, n—number of patients.

A complete ophthalmic examination involving best corrected visual acuity (BCVA), biomicroscopy, ophthalmoscopy, tonometry, SD-OCT, and OCT-A were conducted in all subjects, and fluorescein angiography was performed in patients except for those with contraindications. All study participants were examined with a Zeiss Cirrus HD-OCT 6000, AngioPlex Metrix. The device uses a superluminescent diode light source with a wavelength of 840 nm and a scanning speed of 100 kHz, 100,000 A-scans per second. The resolution of the current method is 5 μm (in tissue) for axial resolution and 15 μm (in tissue) for transverse resolution. The scanning protocol "Angiography 3 × 3 mm" is based on the amplitude-decorrelation signal from two consecutive B-scans. With this protocol, a scan of 3 × 3 mm of the macula is performed without needing contrast injections and provides information about the vasculature in the relevant field. This allows visualization of blood flow, and therefore of the retinal capillary network. Among the patients selected with established RVO, no other eye disease was present that could impede the results of the study. To correctly calculate the variables from different fields, the ETDRS field was strictly centered on the FAZ area when registering the results obtained from OCT-A.

Segmentation and analysis of the retinal layers were performed using an automatic segmentation program of Zeiss Cirrus HD-OCT 6000 software (AngioPlex Metrix). Segmentation of the retinal layers provides information about the capillary plexuses of the retina. The software program AngioPlex Metrix automatically segments retinal layers without allowing manual correction. The software marks the inner limiting membrane (ILM) for the inner boundary and the inner plexiform layer (IPL) for the outer boundary of the superficial capillary plexus (SCP). In regards to the deep capillary plexus, the inner plexiform layer (IPL) is assumed to be the inner boundary, and the outer plexiform layer (OPL) is assumed to be the outer boundary [8]. A possible bias could be caused by the automatic segmentation of layers by the software, which could lead to inaccurate variable measurement and affect the results of the study. The software uses specific formulas to calculate the exact boundaries of these layers. In addition, the latest Zeiss Cirrus HD-OCT 6000 software, AngioPlex Metrix, provides a quantitative assessment of the superficial capillary plexus only. Therefore, the current study compares values obtained by evaluating only the superficial capillary plexus of the retina.

To evaluate the superficial capillary plexus, several parameters were obtained by conducting OCT-A, including vascular density (VD) and perfusion density (PD), as well as the area, perimeter, and circularity of the foveolar avascular zone (FAZ). The topographic image obtained during the "Angiography 3 × 3" protocol is separated into several ETDRS zones, central, inner, and total, to investigate vascular density and vascular perfusion. For each zone, the Zeiss Cirrus HD-OCT 6000 AngioPlex Metrix software registers a value by calculating the area occupied by blood vessels. A blood vessel is defined as a pixel whose decorrelation value is higher than a threshold value [9]. A statistical analysis was performed on all data collected from OCT-A using SPSS 19.0 (SPSS Inc., IBM).

Kolmogorov-Smirnov tests and Q-Q plots were used to confirm the normal distribution of data, and the parametric Independent Samples T-test was used on those variables with a normal distribution. On variables without a normal distribution, the nonparametric Mann-Whitney U test is used. All statistical analyses were considered significant for a p-value < 0.05.

3. Results

Neither the mean age nor the proportion of males to females differed significantly between the two groups. The comparative analysis of FAZ parameters at the SCP between group 1 (eyes with retinal vein occlusion) and group 2 (unaffected fellow eyes) is presented in Table 3. Significant results were found for the three parameters, respectively area (p = 0.003), perimeter (p ≤ 0.001), and circularity (p = 0.011) of FAZ.

Table 3. Comparison of FAZ parameters at SCP in patients with RVO and unaffected fellow eyes.

	RVO eye (group 1) n = 29	**Fellow eye** (group 2) n = 24	**p Value**
FAZ (area)			**0.003[a]**
mean ± *SD*	0.35 ± 0.21	0.22 ± 0.10	
95% CI	0.27 - 0.43	0.17 - 0.26	
median	0.34	0.23	
FAZ (perimeter)			**<0.001[a]**
mean ± *SD*	2.84 ± 0.85	2.07 ± 0.50	
95% CI	2.52 - 3.17	1.86 - 2.28	
median	2.80	2.06	
FAZ (circularity)			**0.011[a]**
mean ± *SD*	0.52 ± 0.10	0.60 ± 0.11	
95% CI	0.48 - 0.56	0.55 - 0.65	
median	0.51	0.60	

FAZ—foveolar avascular zone; Mean ± standard deviation; CI—confidence interval, n—number of eyes; Independent Samples T-test[a]. **significant result**.

On the other hand, the comparative analysis of the vascular network at SCP in patients with diagnosed RVO and unaffected fellow eyes is presented in Table 4. The analysis showed significant results for every parameter except vascular perfusion in the central zone (p = 0.116). The results for vascular density (VD) in the central (p = 0.038) and inner (p ≤ 0.001) zones as well as total VD (p ≤ 0.001) were statistically significant. Furthermore, the results reached in the study of vascular perfusion (VP) have shown significant results in the inner zone (p ≤ 0.001) and the total VP (p = 0.001).

Table 4. Comparison of the vascular network at SCP in patients with RVO and unaffected fellow eyes.

	RVO eye (group 1) n = 29	Unaffected eye (group 2) n = 24	p Value
VD (central)			**0.038[a]**
mean ± SD	9.49 ± 3.78	11.58 ± 3.24	
CI 95%	8.05 - 10.92	10.21 - 12.95	
median	9.90	11.70	
VD (inner)			**<0.001[b]**
mean ± SD	18.38 ± 3.21	21.83 ± 1.86	
CI 95%	17.16 - 19.60	21.04 - 21.62	
median	19.40	22.25	
VD (full)			**<0.001[b]**
mean ± SD	17.37 ± 3.19	20.67 ± 1.82	
CI 95%	16.15 - 18.58	19.90 - 21.44	
median	18.20	20.90	
VP (central)			0.116[a]
mean ± SD	17.62 ± 6.99	20.47 ± 5.73	
CI 95%	14.97 - 20.28	18.05 - 22.89	
median	18.70	20.45	
VP (inner)			**<0.001[b]**
mean ± SD	35.88 ± 5.39	40.02 ± 3.07	
CI 95%	33.82 - 37.93	38.72 - 41.32	
median	37.20	40.75	
VP (full)			**0.001[b]**
mean ± SD	33.80 ± 5.39	37.79 ± 3.06	
CI 95%	31.75 - 35.85	36.50 - 39.08	
median	35.20	38.70	

VD—vascular density; VP—vascular perfusion; mean ± standard deviation; CI—confidence interval; n—number of eyes; Independent Samples T-test[a]; Mann-Whitney U test[b]. **significant result**.

4. Discussion

This study evaluated and compared quantitative data obtained by performing OCT-A on superficial capillaries in patients with established retinal vein occlusion with data from their unaffected fellow eyes. Accordingly, retinal vein occlusion was associated with decreased vascular density and vascular perfusion in specific ETDRS areas, as well as changes in FAZ parameters.

Samara *et al.* 2016, analyzed the OCT-A parameters of the foveolar avascular zone (FAZ) of superficial and deep capillary plexus in 17 patients with established branch retinal vein occlusion and concluded that the changes occurred only at the level of the deep capillary plexus [9]. Furthermore, Suzuki *et al.* 2016 reported that FAZ is significantly larger at the DCP level when compared to SCP values [10]. In addition, Chen *et al.* found that BRVO patients had abnormal FAZ circularity [11]. There are statistically significant results for the three FAZ parameters (area, perimeter, and circularity) at the level of superficial capillary plexus in the current study. The present study, however, did not investigate parameters related to the deep capillary plexus due to software limitations.

Koulisis *et al.* 2017 examined 34 eyes with retinal vein occlusion and compared the obtained quantitative data from OCT-A with data from 24 unaffected fellow eyes, and 26 healthy eyes (control group) [12]. Their study reported statistically significant results when comparing the vascular density of eyes with retinal vein occlusion and healthy eyes at the level of the superficial and deep capillary plexus. The changes are described as decreased values of vascular density in eyes with established retinal vein occlusion. In a study similar to that of Koulisis, Dave *et al.* 2019 retinal vasculature of patients with established retinal vein occlusion was significantly reduced at the superficial and deep capillary plexuses level [13]. Their study revealed that vascular reduction was more pronounced in the DCP. In the present study, the "Angiography 3 × 3" protocol, covering a 3 mm × 3 mm field, concluded that patients with established retinal vein occlusion have reduced vascular density at the superficial capillary plexus in every ETDRS zone.

In a study performed by Khodabandeh *et al.*, significant differences were reported in the vascular density and flow measurements of the superficial and deep capillary plexi between eyes with established retinal vein occlusions and unaffected fellow eyes [14]. A similar finding was reported by Adhi *et al.* regarding decreased blood flow in the affected eyes of patients with retinal vein occlusion [15]. Additionally, eyes with established RVO had a significantly larger FAZ than unaffected fellow eyes. In the present study, vascular perfusion was significantly reduced in all ETDRS zones except for the central zone of Angiography 3 × 3.

In a study performed by Wang *et al.*, 48 eyes with established RVO were compared to 48 unaffected eyes, and vascular density was reported to be lower at both the SCP and DCP levels, except for the foveal area [16]. A similar result was reported by Chen *et al.* [11]. Additionally, these patients had a significant enlargement of their FAZ. The results from the present study showed that there was a significant decrease in vascular density in all zones as well as in vascular perfusion, except for vascular perfusion in the central zone. In their study, Khodabandeh *et al.* reported that existing retinal edema and internal layer disorganization could account for the higher values of foveolar vascular density [14]. Possibly, this is the reason behind the lack of a significant result in this area.

Using OCT-A results, these patients' macular vasculature can be assessed for the severity of microvascular involvement, and visual outcome predictions can be made. As a non-invasive and easy-to-conduct technique, angio-OCT provides detailed information about the retinal vessels without the need for external contrast. Due to this, it is possible to use it frequently without experiencing any adverse effects. As a result of its non-invasive nature, this method is beneficial for monitoring patients with RVO to observe non-perfused areas as well as to assess the effectiveness of treatment.

Several limitations have been identified in the present study. Since Zeiss Cirrus HD-OCT 6000, AngioPlex Metrix software does not provide a numerical assessment of the deep capillary plexus, DCP data have not been analyzed. This shortcoming of the software limits the ability to analyze the entire retina in patients with RVO more thoroughly, which could be useful for gaining a deeper understanding of microcirculatory changes occurring in the retina as well as identifying which plexus has been severely affected. Therefore, only superficial retinal vascular plexus parameters were compared in the present study. During the scanning process, it was ensured that there would not be any artifacts caused by blinking or head movements. Artifacts have a significant impact on what the software calculates, so it is essential to identify them. Despite efforts to minimize artifacts and exclude low-quality scans, OCT-A parameters may have been influenced by low image quality in some of the studied eyes.

5. Conclusion

With OCT-A, the current study evaluated changes in vascular density and vascular perfusion of the retinal superficial capillary plexus and changes in the FAZ in patients with retinal vein occlusion. A noticeable enlargement of the FAZ and loss of its circularity were observed, as well as a decrease in the parameters of the vascular network at the level of SCP. In patients with vascular occlusive diseases, OCT-A could become the preferred method for diagnosis and follow-up as it provides detailed qualitative and quantitative information about retinal vessels. It may be possible to analyze microvascular changes in peripheral retinal areas, rather than only in the macula, in future studies using wide-field OCT-A scanning. Furthermore, DCP analysis can provide a more accurate assessment of the severity of the occlusive process. By introducing wide-field OCT-A and assessing DCP quantitatively, it will be possible to get a more complete picture of the changes that have occurred. It is necessary to conduct further studies to better understand the vascular changes detected by OCT-A.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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