Collateral Vessel Development in Central and Branch Retinal Vein Occlusions Are Associated With Worse Visual and Anatomic Outcomes

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Purpose. The purpose of this study was to investigate the effects of the extension of collateral vessels on the outcomes of eyes affected by central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO).

Methods. The study was designed as a cross-sectional case series. Patients affected by CRVO and BRVO were progressively recruited, along with an age- and sex-matched control group of healthy subjects. Structural optical coherence tomography (OCT) and OCT angiography (OCTA; 4.5 × 4.5 mm and 9.0 × 9.0 mm acquisitions) were performed on all participants in order to assess the relationship between the presence of collateral vessels and final anatomical outcomes – central macular thickness (CMT), foveal avascular zone – and functional outcomes – best corrected visual acuity (BCVA).

Results. Fifty-six eyes affected by CRVO and 47 eyes affected by BRVO were included. Baseline LogMAR BCVA was 0.41 ± 0.33 LogMAR in CRVO, and 0.39 ± 0.25 LogMAR in BRVO ($P < 0.01$), improving to 0.20 ± 0.26 LogMAR in CRVO ($P < 0.01$), and 0.19 ± 0.22 LogMAR in BRVO ($P < 0.01$). Baseline CMT was 511 ± 214 µm in CRVO and 482 ± 178 µm in BRVO ($P > 0.05$), decreasing to 328 ± 105 µm ($P < 0.01$) and 321 ± 78 µm in CRVO and BRVO, respectively ($P < 0.01$). Collateral vessels were detected in 16 of 56 eyes (29%) in CRVO and in 47 of 47 eyes (100%) in BRVO. Their extension was correlated with worse anatomic and visual outcomes. Remarkably, no correlation was found with peripheral capillary nonperfusion and vessel density impairment.

Conclusions. The present study demonstrates that collateral vessel extension is associated with worse anatomic and functional outcomes in patients affected by CRVO and BRVO.

Keywords: central retinal vein occlusion (CRVO), branch retinal vein occlusion (BRVO), optical coherence tomography (OCT), optical coherence tomography angiography (OCTA). collateral vessels

Retinal vein occlusion (RVO) is the second most common retinal vascular pathology after diabetic retinopathy and an important cause of vision deterioration.[1,2] The prevalence of RVO in the overall world population has been estimated to be about 0.5%, corresponding to 5.2 per 1000 for RVO in general: 0.8 per 1000 for central retinal vein occlusion (CRVO) and 4.42 per 1000 for branch retinal vein occlusion (BRVO).[3] RVO has been shown to have a remarkable impact on health care utilization and expenditure, especially during the first year following the diagnosis,[4] with modestly cost-effective treatment outcomes.[5] The better knowledge of modifications of the vascular routes occurring after RVO may have a direct impact on the management of the condition and its prognosis.

Collateral vessels gradually develop within the optic disc or in the retina as a consequence of the hemodynamic overload and hydrostatic alterations due to RVO, constituting an attempt to favor the blood outflow.[6–9] Collateral vessels are biomicroscopically visible within the first 6 months, achieving their complete development within 24 months.[6–9] There is scant information in general regarding the relationship between collateral vessel development and structural and functional outcomes in RVO eyes.

Thanks to its characteristics, optical coherent tomography angiography (OCTA) can significantly improve the chances of identifying collateral vessels. Previous investigations have pointed out that collateral vessel development is negatively correlated with the vessel density (VD) of the retinal capillary plexa after the RVO occurrence,[10–13] and that collateral vessels – those in BRVO in particular – are located within the deep vascular complex.[14] However, these studies focused on qualitative analyses of the collateral vessels within the central macula; no study has specifically analyzed the extension of collateral vessels over the whole posterior pole.

In the present study, we used optical coherence tomography (OCT) and OCTA to investigate the quantitative characteristics of collateral vessels in a cohort of patients affected by CRVO and BRVO, exploring their correlation with anatomic and functional outcomes.

Methods

The study was designed as a cross-sectional case series with a planned follow-up of 2 years. Consecutive patients with CRVO and BRVO and a corresponding control group of healthy subjects were recruited at the Ophthalmology Department of San Raffaele Hospital in Milan from January 2016 to January 2018. Signed informed consent was obtained from all patients. The whole study was conducted in accordance with the Declaration of Helsinki and approved by the Ethical Committee. The inclusion criterion was the clinical diagnosis of CRVO or BRVO. The exclusion criteria were: high media opacity, any other type of retinal or optic nerve diseases (including glaucoma), ophthalmologic surgery within the last 6 months before OCTA acquisition, and any systemic condition potentially affecting the analyses. Ophthalmologic examination included best corrected visual acuity (BCVA) measurement using standard Early Treatment Diabetic Retinopathy Study (ETDRS) charts, slit-lamp biomicroscopy of anterior and posterior segments, fluorescein angiography (FA), Goldmann applanation tonometry, OCT, and OCTA. Structural OCT images were acquired by means of spectral-domain optical coherence tomography (Spectralis HRA+OCT; Heidelberg Engineering, Heidelberg, Germany). The structural OCT acquisition protocol included raster, radial, and dense scans with a high number of frames (ART > 25), and enhanced depth imaging (EDI). Structural OCT scans were used to measure central macular thickness (CMT) over the follow-up. In order to ensure a complete development of the collateral vessels, we collected OCTA images at the end of the 2-year follow-up, using a swept-source DRI OCT Triton (Topcon Corporation, Tokyo, Japan), with high-resolution 4.5 × 4.5 mm and 9.0 × 9.0 mm acquisitions, centered both at the level of the macula and the optic nerve head. Only high-quality images were considered for the analysis (Topcon's quality index > 80). Automatic segmentation into superficial capillary plexa (SCP), deep capillary plexa (DCP), and choriocapillaris (CC) was obtained from 4.5 × 4.5 mm OCTA acquisitions. We considered both macular (m) and optic nerve head (n) vascular plexa acquisitions. For optic nerve head reconstructions, we also considered radial peripapillary capillary (RPC) segmentation. We loaded all reconstructions in ImageJ software (https://imagej.net/Welcome) to calculate VD. We adopted the "Adjust threshold" ImageJ tool to highlight the blood vessels and reduce the noise. After automatic "mean threshold" image binarization, we calculated the ratio between white and black pixels (i.e. the VD parameter). The foveal avascular zone was manually segmented and excluded. We compared OCTA quantitative findings in both patients with CRVO and patients with BRVO with an age- and sex-matched control group of healthy subjects. The foveal avascular zone (FAZ) was manually segmented both in the SCP and DCP, and excluded for VD calculation. Furthermore, we used the segmentation tool provided by IMAGEnet 6 to measure the FAZ area of SCP and DCP.

We assessed the presence of optic disc collateral vessels in CRVO, and retina-retina collateral vessels in BRVO, detected on 9.0 × 9.0 mm OCTA reconstructions, quantifying their global extension at the level of both SCP and DCP by means of a segmentation tool provided by Topcon IMAGEnet 6 software. We started from the automatic reconstructions of retinal vascular plexa, placing the segmentation lines between the inner border of the retinal nerve fiber layer and the outer border of the outer plexiform layer in BRVO eyes in order to include the collaterals mainly developed at the level of the DCP, while also considering a possible extension at the level of the SCP. In CRVO, we started from the automatic segmentation of the optic nerve head provided by IMAGEnet 6 and included the space between the RPC and the upper portion of the DCP. Collateral vessels in CRVO with a thick and loopy aspect, located within or close to the optic disc, were identified as retino-choroidal shunt vessels.[15] Collateral vessels in BRVO were identified as dilated and tortuous capillaries connecting the occluded vein to an adjacent patent vein.[14]

All the measurements were performed at least twice by two expert ophthalmologists (authors A.A. and E.A.) in order to test repeatability and reproducibility. We also calculated the interclass correlation coefficient (ICC) to assess the intergrader agreement.

CRVO was described as ischemic when peripheral capillary nonperfusion was greater than a 10 disc areas, as determined by FA.[16] BRVO was considered ischemic when peripheral capillary nonperfusion was greater than 5 disc diameters on FA.[17]

RVO eyes presenting macular edema underwent intravitreal ranibizumab injection therapy with a loading phase of three monthly injections, followed by a pro re nata treatment regimen with monthly examination, and further injections administered on the basis of OCT evidence of macular edema.

The main outcome measure was the quantification of the global extension of collateral vessels in eyes affected by CRVO and BRVO, as well as the relationship with BCVA and CMT outcomes. Secondary outcome measures included VD values of mSCP, mDCP, mCC, RPC, nSCP, nDCP, and nCC.

All statistical analyses were performed by means of SPSS package software (SPSS, Chicago, IL, USA). Age and sex were considered as fixed factors. Continuous variables were analyzed by unpaired *t*-test. Moreover, ANOVA analysis was performed to compare different subgroups of eyes, both for patients with BRVO and patients with CRVO, depending on the presence or absence of peripheral capillary nonperfusion and/or collateral vessels. Post hoc analyses were conducted through a Tukey's test to assess the effect of the presence of these features on the final anatomic and visual outcomes. Bonferroni correction was adopted to correct for multiple comparisons. Tau-Kendall correlation analysis was used to assess the relationship between the variables considered. Statistical significance was set at $P < 0.05$.

Results

Sixty-two patients affected by CRVO and 51 patients with BRVO were considered for the study. Overall, 56 eyes (56 patients) with CRVO (30 male patients; 60 ± 13 years) and 47 eyes (47 patients) with BRVO (24 male patients; 67 ± 10 years) were included in the study. Seven patients were excluded because they were affected by glaucoma, whereas another two patients were ruled out because of cataract.

Fifty eyes of 50 healthy age- and sex-matched control subjects (25 male subjects; 61 ± 10 years; LogMAR BCVA 0.0 ± 0.0) were also analyzed. All the patients revealed macular edema, which was treated with a mean of 8.1 ± 3.5 ranibizumab injections over the 24-month follow-up.

Baseline LogMAR BCVA was 0.41 ± 0.33 LogMAR in CRVO, and 0.39 ± 0.25 LogMAR in BRVO ($P < 0.01$),

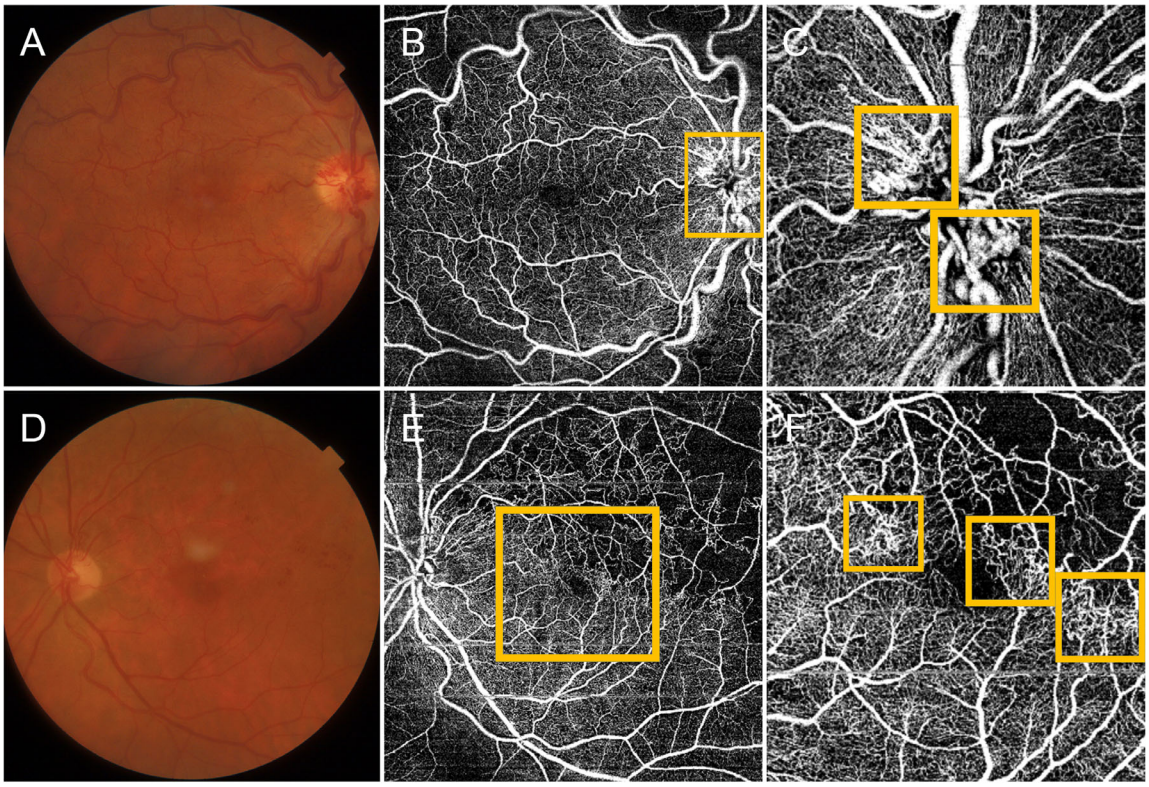

Figure. Illustrative case of central retinal vein occlusion (**A**). OCTA discloses collateral vessels developed at the level of the optic nerve head (**B**). The magnified image of the optic nerve head vascular network clearly shows the presence of optic disc collateral vessels (*orange squares*) (**C**). Illustrative case of branch retinal vein occlusion (**D**). OCTA shows retinal ischemia and diffused collateral vessels over the entire posterior pole (**E**). Retina-retina collateral vessels are clearly visualized in the magnified image of the macular region (*orange square*) (**F**). Both OCTA reconstructions are obtained through a full retina segmentation.

improving to 0.20 ± 0.26 LogMAR in CRVO ($P < 0.01$), and 0.19 ± 0.22 LogMAR in BRVO ($P < 0.01$) at the end of the study. Baseline CMT was 511 ± 214 µm in CRVO and 482 ± 178 µm in BRVO ($P > 0.05$), decreasing to 328 ± 105 µm ($P < 0.01$) and 321 ± 78 µm in CRVO and BRVO, respectively ($P < 0.01$).

All clinical and imaging data are reported in Supplementary Table S1. Both CRVO and BRVO eyes revealed worse BCVA, CMT, and VD values compared with control eyes (all $P < 0.01$). CRVO eyes revealed worse VD values than BRVO eyes, on mSCP ($P = 0.007$), mDCP ($P = 0.04$), and nCC ($P = 0.04$) examinations.

Capillary nonperfusion greater than 10 disc areas was identified in 18 of 56 (32%) CRVO eyes, whereas capillary nonperfusion greater than 5 disc diameters was detected in 14 of 47 (30%) BRVO eyes. Ocular neovascularization occurred in two CRVO eyes (angle neovascularization), and in three BRVO eyes (retinal neovascularization), which underwent peripheral laser treatment.

Overall, collateral vessels turned out to be visible in 16 of 56 eyes (29%) in CRVO and in 47 of 47 eyes (100%) in BRVO (Fig.). Mean global extension of collateral vessels was 68.32 ± 13.01 µm^2 in the 16 CRVO eyes showing collateral vessels, and 113.91 ± 50.34 µm^2 in BRVO eyes.

Interestingly, CRVO eyes developing optic disc collateral vessels were characterized by statistically significantly worse final BCVA ($P < 0.01$) and final CMT values ($P < 0.04$) in comparison with CRVO eyes in which these vessels were not detected. Complete data are listed in Supplementary Table S2.

The FAZ area of the SCP turned out to be 0.38 ± 0.18 mm^2 in CRVO and 0.35 ± 0.15 mm^2 in BRVO ($P < 0.05$) at the level of the SCP, and 1.85 ± 0.46 mm^2 in CRVO and 1.39 ± 0.55 mm^2 in BRVO ($P < 0.01$) in the DCP, showing a statistically significant larger FAZ area compared to control eyes (0.25 ± 0.09 mm^2 and 0.48 ± 0.12 mm^2, respectively, all $P < 0.01$).

Correlation analyses showed a negative statistically significant correlation between global collateral vessel extension and final BCVA, both in CRVO (Tau coeff. = 0.355; $P = 0.004$) and in BRVO (Tau coeff. - 0.383; $P = 0.003$) eyes. The global extension of collateral vessels also correlated with higher final CMT values, both in CRVO (Tau coeff. = 0.286; $P = 0.003$) and in BRVO (Tau coeff. = 0.275; $P = 0.004$).

The global collateral vessel extension correlated with FAZ area enlargement both at the level of both SCP (Tau coeff. = 0.425; $P < 0.001$ for CRVO; Tau coeff. = 0.433; $P < 0.001$ for BRVO), and DCP (Tau coeff. = 0.555; $P < 0.001$ for CRVO; and Tau coeff. = 0.466; $P < 0.001$ for BRVO).

Remarkably, a statistically significant correlation linked FAZ area and peripheral retinal capillary nonperfusion (Tau coeff. = 0.258; $P = 0.02$ for SCP and 0.411; $P = 0.003$ for DCP in CRVO; Tau coeff. = 0.336; $P = 0.004$ for SCP and 0.421; $P = 0.002$ for DCP in BRVO). In contrast, no correlation between global collateral vessel extension and peripheral capillary non-perfusion was found, either in CRVO or in BRVO eyes ($P > 0.05$). Similarly, no statistically

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Table 1. Quantitative Data of Eyes Affected by Central Retinal Vein Occlusion With or Without Peripheral Capillary Nonperfusion and Collateral Vessels

	CRVO					
Parameter	**No Peripheral Capillary Nonperfusion, No Collateral Vessels**	**No Peripheral Capillary Nonperfusion, Yes Collateral Vessels**	**Yes Peripheral Capillary Nonperfusion, No Collateral Vessels**	**Yes Peripheral Capillary Nonperfusion, Yes Collateral Vessels**		
Group number	1	2	3	4		
No. of patients	29	9	11	7		
Age	62 ± 14	61 ± 9	67 ± 10	65 ± 13		
Collateral vessels extension (μm²)	0.0 ± 0.0	21.11 ± 18.37	0.0 ± 0.0	20.51 ± 16.54		
Baseline LogMAR BCVA	0.37 ± 0.28	0.42 ± 0.35	0.46 ± 0.29	0.46 ± 0.53		
Final LogMAR BCVA	0.09 ± 0.12	0.33 ± 0.33	0.21 ± 0.25	0.44 ± 0.42		
Baseline CMT	474 ± 204	515 ± 185	643 ± 256	457 ± 164		
Final CMT	309 ± 79	371 ± 156	316 ± 90	368 ± 139		
mDCP VD	0.35 ± 0.03	0.35 ± 0.04	0.36 ± 0.02	0.32 ± 0.03		
P values	1 vs 2	1 vs 3	1 vs 4	2 vs 3	2 vs 4	3 vs 4
Age	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05
Collateral vessels extension (μm²)	N/A	N/A	N/A	N/A	>0.05	N/A
LogMAR BCVA baseline	>0.05	<0.01*	<0.01*	>0.05	>0.05	>0.05
LogMAR BCVA final	<0.01*	<0.01*	<0.01*	<0.01*	= 0.03*	<0.01*
CMT baseline	>0.05	<0.01*	>0.05	>0.05	>0.05	<0.01*
CMT final	<0.01*	>0.05	<0.01*	<0.01*	>0.05	<0.01*
mDCP VD	>0.05	>0.05	<0.01*	>0.05	<0.01*	<0.01*

Legend: CRVO, central retinal vein occlusion; BCVA, best-corrected visual acuity; CMT, central macular thickness; mDCP, macular deep capillary plexus.

Statistically significant differences are marked by asterisks (*). Only corrected *P* values are reported. The extended version of the table is provided in the Supplementary Materials (Supplementary Table S3).

Table 2. Quantitative Data in Eyes Affected by Branch Retinal Vein Occlusion With or Without Peripheral Capillary Nonperfusion

	BRVO	
Parameter	**No Peripheral Capillary Nonperfusion**	**Yes Peripheral Capillary Nonperfusion**
Group number	**1**	**2**
Age	65 ± 10	62 ± 8
	P = 0.23	
Collateral vessels extension (μm²)	113.27 ± 107.85	115.43 ± 82.02
	P = 0.94	
Baseline LogMAR BCVA	0.37 ± 0.25	0.43 ± 0.25
	P = 0.03*	
Final LogMAR BCVA	0.17 ± 0.22	0.23 ± 0.22
	P = 0.02*	
Baseline CMT	486 ± 189	475 ± 155
	P > 0.05	
Final CMT	320 ± 87	321 ± 54
	P > 0.05	
mDCP VD	0.37 ± 0.05	0.34 ± 0.02
	P = 0.02*	
RPC VD	0.42 ± 0.02	0.40 ± 0.02
	P = 0.01*	
nDCP VD	0.31 ± 0.01	0.30 ± 0.01
	P = 0.04*	

Legend: BRVO, branch retinal vein occlusion; BCVA, best-corrected visual acuity; CMT, central macular thickness; DCP, deep capillary plexus; RCP, radial peripapillary capillaries; VD, vessel density; macular plexa are indicated by "m", whereas optic nerve head plexa are indicated by "n." Statistically significant differences are marked by asterisks (*). The extended version of the table is provided in the Supplementary Materials (Supplementary Table S4).

significant correlation was identified between global collateral vessel extension and VD values (all $P > 0.05$). Overall, the presence of peripheral capillary nonperfusion in both CRVO and BRVO was associated with worse final BCVA and mDCP density. In particular, the extension of optic disc collateral vessels and the presence of peripheral capillary nonperfusion were associated with both baseline and final CMT values, and, in addition, with final BCVA. Moreover, collateral vessels and peripheral capillary nonperfusion were associated with significantly higher impairment in mDCP (Table 1, Supplementary Table S3).

Looking at BRVO, the presence of peripheral capillary nonperfusion was associated with worse baseline and final BCVA, and with worse VD values, measured in RPC and in both macular and nerve DCP (Table 2, Supplementary Table S4).

Our data showed high reliability in terms of reproducibility (overall = 0.94, range = 0.88–0.97) and repeatability

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(overall = 0.95, range = 0.89–0.98). Intergrader agreement also proved to be high (ICC = 0.92).

Discussion

Collateral vessels represent a frequently observed sequela after RVO. The development of collateral vessels is currently interpreted as the result of hemodynamic factors and hydrostatic pressure, leading to the opening of collateral channels that originate from the pre-existing capillary network and provide vein-to-vein drainage.[6–9]

Together with FA, fundus biomicroscopic examination provides a partial identification of collateral vessels, because deep capillaries and intraretinal communications are not usually visualized. In contrast, thanks to its distinctive features, OCTA can characterize both the presence and location of collateral vessels more precisely. Previous OCTA-based investigations have located the collateral vessels secondary to BRVO within the DCP,[14] and have found a correlation with lower VD at the level of SCP and DCP in RVO in general.[10–13] However, no study has thoroughly analyzed the effects of collateral vessel extension on anatomic and functional outcomes.

In the present study, OCTA was able to identify collateral vessels in about one third of CRVO eyes and in the totality of BRVO eyes. The rate of collateral vessel identification is quite variable across the different existing studies,[6–14] probably owing to discrepancies in the examination used, the RVO subtype, the extension of the retinal area analyzed, the size of the patient sample, and the duration of the follow-up. It is remarkable that our investigation based on a wider OCTA examination found collateral vessels in all BRVO eyes.

The second aim of the study was to address the association of collateral vessel development and final worse BCVA and anatomical conditions (CMT and FAZ). The alleged effects of collateral vessel formation in RVO are quite controversial, with contradictory results being published, once again probably related to the variable inclusion criteria and methods used in the detection of microvascular abnormalities, as mentioned above. In particular, there are conflicting data regarding the development and course of macular edema, as well as the final visual outcome.[9,11,12,18–20]

The present study was based on quite a large number of patients and included a 2-year follow-up that allowed the complete development of collateral vessels identified by means of OCTA.[6–9] Our data showed that overall, collateral vessel development represents a negative prognostic factor in patients affected by CRVO and BRVO, because collateral vessel extension correlated negatively with final BCVA, while correlating positively with higher CMT and larger FAZ.

Although not associated with the development and extension of collateral vessels, the presence of peripheral capillary nonperfusion turned out to be correlated with FAZ enlargement, and with worse final BCVA and mDCP density.

The previously described correlation between VD of SCP and DCP and collateral vessels was not completely confirmed by our results.[12] This finding may be related to the study design, based as it was on OCTA acquisition 2 years after the RVO onset, potentially allowing perfusion to be normalized in the retinal plexa, thus hampering the clear identification of a cause and effect relationship between OCTA-detected vascular damage and collateral vessel development. In view of this, future longitudinal prospective studies are warranted to assess the true relationship between VD damage and the emergence of collateral vessels in RVO.

Our data suggest that eyes affected by RVO tend to develop OCTA-detectable collateral vessels when the structural macular damage is more severe, as expressed by macular edema and macular ischemia.

We are aware that the present study has several limitations, especially related to the cross-sectional design of the investigation and the technique used. Indeed, the study design ruled out the possibility of a prospective follow-up detailing the timeframes of collateral vessel development. Moreover, we did not analyze the potential effects of intravitreal treatment for macular edema on the onset and extension of the collateral vessels, but previous studies have suggested that collateral vessel formation is not influenced by laser and anti-VEGF.[21–23] Other limitations concern technical issues related to the OCTA imaging, which can be affected by several artifacts,[24] and the intrinsic difficulty in detecting the full extension of collateral vessels.[14,25] The OCTA-detectable extension of collateral vessels may not correlate to blood flow volume and rate, so a more specific flow quantification might provide useful prognostic information. Last, the number of patients might be insufficient to achieve a statistically valid power, although both our CRVO and BRVO cohorts included more eyes than previous investigations.

In conclusion, our study demonstrated that collateral vessel extension is associated with worse anatomic and functional outcomes in patients affected by RVO. Further prospective studies are warranted to provide a thorough evaluation of the overall impact of collateral vessels on the final outcomes of RVO patients treated according to the current strategies.

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