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Deep Capillary Plexus as Biomarker of Peripheral Capillary Nonperfusion in Central Retinal Vein Occlusion

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Purpose: To identify the vascular biomarkers of peripheral capillary nonperfusion in patients affected by naive central retinal vein occlusion (CRVO), and to analyze their changes over the follow-up.

Study Design: Consecutive prospective case series with a planned follow-up of 2 years.

Participants: Thirty-five patients affected by CRVO and 35 healthy gender- and age-matched subjects were enrolled in the study.

Methods: Ophthalmic examination included best corrected visual acuity (BCVA), ultrawidefield fluorescein angiography (UWFFA), OCT, and OCT angiography (OCTA).

Main Outcome Measures: Vessel density (VD) at the superficial capillary plexus and deep capillary plexus (DCP) were calculated on OCTA images. The ischemic index (ISI) was calculated on UWFFA.

Results: The mean baseline ISI was 37%, increasing to 40% at the end of the follow-up, whereas it was 4.9% in the patients' fellow eyes and 4.5% in the control group with no change over the follow-up. OCT angiography revealed VD reduction in the DCP, considering both 3 × 3 mm and 12 × 12 mm scans. The correlation analyses revealed that DCP VD was the only parameter showing a statistically significant correlation with the foveal avascular zone (FAZ) area, BCVA, and ISI.

Conclusions: Deep capillary plexus VD impairment is detectable in all CRVO cases, variably involving both the central retina (with enlarged FAZ) and the periphery (with VD reduction in the peripheral retina). The severity of DCP VD reduction has correlates with various clinical markers. Deep capillary plexus VD may represent a crucial biomarker to characterize CRVO, and further studies are necessary to identify the cutoff thresholds for the different clinical manifestations.

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Capillary nonperfusion (CNP) is a well-known manifestation of central retinal vein occlusion (CRVO), which may involve both the peripheral retina and the macular region.[1,2]

The extent of CNP varies according to the CRVO subtype and severity, and may also directly influence the development of ocular neovascularization and macular edema.[1–7]

The most commonly used tool to identify both presence and extension of CNP is conventional fluorescein angiography (FA).[1,8–10] However, the advent of ultrawidefield FA (UWFFA) has revolutionized CNP assessment, since it provides a 200° field of view, enabling larger areas of the peripheral retina to be analyzed.[1–7]

The data currently available regarding the correlation of peripheral CNP assessed by UWFFA and vascular impairment assessed by OCT angiography (OCTA) in eyes affected by CRVO are limited.[11–14]

The aim of the study was the identification of vascular biomarkers of peripheral CNP in patients affected by naive CRVO and to analyze their changes over the follow-up.

Methods

The study was designed as a consecutive prospective series of patients affected by CRVO, along with a control group of healthy gender- and age-matched subjects, with a planned follow-up of 2 years. The 2 groups were recruited at the Ophthalmology Department of San Raffaele Hospital in Milan from January 2017 to January 2019. All patients gave signed, informed consent. The study followed the tenets of the Declaration of Helsinki and was approved by the local Ethical Committee.

The inclusion criterion was high quality imaging diagnosis of naive CRVO, with a duration of < 12 months since the onset of symptoms.

In order to be able to rely upon solid data, exclusion criteria needed to be very strict and comprised unsatisfactory quality imaging, media opacity, any concomitant retinal or optic nerve disease, ophthalmic surgery within 6 months prior to OCTA acquisition, and any systemic condition potentially affecting the analyses (especially diabetes mellitus and ocular ischemic syndrome).

Ophthalmic examination of patients affected by CRVO included best corrected visual acuity (BCVA) measurement, using

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standard ETDRS charts, slit-lamp biomicroscopy of anterior and posterior segments, Goldmann applanation tonometry, UWFFA on Optos Silverstone (Optos Inc), OCT, and OCTA.

Structural OCT images were acquired by means of spectral-domain OCT (Spectralis HRA+OCT; Heidelberg Engineering). The structural OCT acquisition protocol included raster, radial and dense scans with a high number of frames (automatic real time [ART] > 25), and enhanced depth imaging. Structural OCT scans were used to measure central macular thickness (CMT) over the follow-up. We defined OCTA slabs as follows: superficial capillary plexus (SCP) was included between the inner limiting membrane and the slab 15.6 μm below the inner plexiform layer/inner nuclear layer junction; deep capillary plexus (DCP) was between 2 slabs 15.6 μm and 70.2 μm below the inner plexiform layer/inner nuclear layer junction, respectively; choriocapillaris was from the Bruch's membrane to the slab 20.8 μm below. Full inner retina was the slab that included both SCP and DCP.

OCT angiography was performed at baseline using a swept-source DRI OCT Triton (Topcon Corporation) centered on the fovea. Only high-quality images were considered for the analysis (Topcon's quality index > 80). Automatic segmentation into the SCP, DCP, and choriocapillaris was obtained from 3 × 3 mm and 12 × 12 mm OCTA acquisitions.

We loaded all reconstructions in ImageJ software (https://imagej.net/Welcome) to calculate vessel density (VD). We adopted the "Adjust threshold" ImageJ tool to highlight the blood vessels and reduce the noise. The foveal avascular zone (FAZ) was calculated throughout the inner retina using the 3 × 3 mm acquisition. Vessel density was calculated as the ratio of white to total pixels, after automatic "mean threshold" image binarization and FAZ exclusion. In the 12 × 12 mm reconstructions, both the overall VD and the VD values within and outside a 6 mm diameter ring were calculated in order to assess vascular impairment in central and peripheral areas.

Collateral vessel extension in both SCP and DCP on 12 × 12 mm OCTA reconstructions was quantified by means of a segmentation tool provided by Topcon IMAGEnet 6 software, as previously described.[15]

Ultrawidefield fluorescein angiography was performed after intravenous injection of fluorescein dye, and central images (centered on the fovea) were obtained during the midphase (2 minutes and 30 seconds) of the examination to better identify CNP.[16] Moreover, the regions of peripheral CNP detected on UWFFA were further subclassified as partial CNP, complete CNP, and total CNP.[17] Partial CNP was characterized by the presence of a cluster of small fragmented areas of hypofluorescence, with dilation and irregular patterns in the capillary network; complete CNP was defined as a contiguous area of hypofluorescence due to retinal capillary loss and the obstruction of the precapillary arterioles and postcapillary venules, with the remaining precapillary arterioles and postcapillary venules being dilated and tortuous.[17] Total CNP was the sum of the 2 previous categories. Graders (A.A. and L.B.) manually outlined the border of the nonperfusion areas and the peripheral extent of the total visible retinal area, using OptosAdvance software (Optos Inc). Grading results were expressed (in mm^2) directly by the software, and their values were used to calculate the extent of complete and partial ischemic areas and the ischemic index (ISI).[17] This method was used for each area to calculate the partial ISI (pISI), complete ISI (cISI), and total ISI (tISI), with the last representing the sum of the partial and complete ischemic areas. Ischemic index assessment was performed at baseline and at the end of the 2-year follow-up.

Capillary non-perfusion was also assessed in the fellow eye of the retinal vein occlusion (RVO) patients so as to obtain intra-patient comparison.

Two masked retinal specialists (A.A. and L.B.) independently analyzed the images. The average values from the 2 independent graders were used for all analyses. Interclass correlation coefficient has been calculated for all the collected parameters.

Retinal vein occlusion eyes presenting with macular edema underwent intravitreal ranibizumab injections, with a loading phase of 3 monthly injections, followed by a pro re nata treatment regimen, with monthly examination over a 2-year follow-up and further injections based on OCT evidence of macular edema.

All statistical analyses were performed by means of SPSS package software (SPSS). For all the parameters collected, we considered baseline and last follow-up examinations. Age and sex were considered fixed factors. Pearson's correlation coefficient was used to analyze data, whereas continuous variables were analyzed by unpaired *t* test. Moreover, analysis of variance was performed to compare different subgroups of eyes, depending on the presence or absence of peripheral CNP and collateral vessels.

Posthoc analyses were conducted through a Tukey's test to assess the effect of the presence of these features on the final anatomical and visual outcomes. Tau-Kendall correlation analysis was used to assess the relationship between the variables considered. Statistical significance was set at $P < 0.05$. The multivariate analysis was conducted considering age, sex, and systemic conditions as fixed factors, and including as variables the number of injections, CMT, BCVA, RVO duration, peripheral CNP, and OCTA VD values. Bonferroni correction was adopted to correct for multiple comparisons.

Results

Sixty-one patients were originally considered for the study, but 26 patients were excluded (10 patients because they were affected by diabetic retinopathy, 7 because of previous intraocular treatments, 6 because of bad quality imaging, and 3 because they were suffering from open-angle glaucoma). Overall, 35 patients were enrolled in the study (Table 1). Mean age was 58 ± 2 years (range: 22−78 years, with 25 males (69%), and 26 patients were affected by systemic hypertension). Our statistical evaluation did not reveal significant effects associated with age, gender, and the systemic status of the patients ($P > 0.05$).

Twenty-two of 35 patients (63%) had macular edema and underwent a planned pro re nata strategy with intravitreal ranibizumab injections.

Table 1. Demographic and Clinical Data of Patients Affected by CRVO and Control Subjects

	CRVO	Controls	*P* Value
Number of Patients	35	35	
Age (years)	58 ± 2	58 ± 1	> 0.05
Baseline BCVA (logMAR)	0.5 ± 0.3	0.0 ± 0.0	< 0.05
Final BCVA (logMAR)	0.1 ± 0.3	0.0 ± 0.0	< 0.05
P Value	< 0.05		
Baseline CMT	467 ± 184	253 ± 25	< 0.05
Final CMT	309 ± 70	250 ± 31	< 0.05
P Value	< 0.05		

BCVA = best corrected visual acuity; CMT = central macular thickness; CRVO = central retinal vein occlusion; logMAR = logarithm of the minimum angle of resolution.

The control group consisted of 35 healthy gender- and age-matched subjects, with BCVA of 0.0 ± 0.0 logarithm of the minimum angle of resolution (LogMAR) (approximately corresponding to 20/20 Snellen equivalent) and CMT of 253 ± 25.

Overall, the mean CRVO duration was 9 months (range: 4−12 months), whereas the mean macular edema duration was 4 months (range: 0−7 months).

Central retinal vein occlusion patients had a mean baseline BCVA of 0.5 ± 0.3 LogMAR (approximately corresponding to 20/63 Snellen equivalent), with a baseline CMT of 467 ± 184 μm, improving to 0.1 ± 0.3 LogMAR (approximately corresponding to 20/25 Snellen equivalent) and 309 ± 70 μm at the end of the 2-year follow-up.

Ocular neovascularization was detected in just a single case of CRVO, showing 1-hour angle neovascularization.

Mean baseline cISI, pISI, and tISI were 27 ± 18%, 11 ± 10%, and 37 ± 15% in CRVO, respectively, and peripheral CNP mainly involved the temporal sector in 28 CRVO eyes (80%). Mean final cISI, pISI, and tISI proved to be 29 ± 17%, 13 ± 9%, and 40 ± 16% in CRVO eyes, respectively. Mean tISI was 4.9 ± 1% in the fellow eye of the patients, and 4.5 ± 1% in the control group, with no change over the follow-up (Table 2). Interestingly, tISI was below 5% in 6 CRVO cases (17%).

OCT angiography examination revealed a reduced VD in the DCP, considering both 3 × 3 mm and 12 × 12 mm scans (Table 2). The mean FAZ area was significantly wider in CRVO (419 μm^2) than in fellow eyes (245 μm^2) and control eyes (238 μm^2).

We found OCTA and UWFFA parameters to be basically stable over the 2-year follow-up. A significant reduction of the FAZ was registered at the end of the follow-up (415−388 mm^2; $P < 0.05$), although the FAZ proved significantly larger than in control eyes (230 mm^2) ($P < 0.05$). The UWFFA follow-up examination recorded no statistically significant change over the 2-year follow-up ($P > 0.05$) with regard to cISI, pISI, and tISI.

Collateral vessels were detected in 12 out of 35 eyes (34%) at the end of the follow-up, and their mean global extension was 62.6 ± 10 μm^2 in the 12 eyes in which they could be identified.

The correlation analyses revealed that DCP was the only parameter which disclosed a statistically significant correlation with the FAZ area, BCVA, and ISI (Table 3). No correlation was identified between any ISI and collateral vessel extension. The overall agreement of the reviewers was interclass correlation coefficient 0.89 (0.85−0.92).

Discussion

Peripheral CNP is an important feature characterizing the RVO subtype. In the past decades, the identification of peripheral CNP was generally based on the imaging provided by standard FA, according to the classification used in the CRVO and branch retinal vein occlusion (BRVO) studies, which defined peripheral CNP as ≥ 10 disc areas in CRVO, and ≥ 5 disc diameters in BRVO.[8−10] But the recent introduction of UWFFA has refined the assessment of peripheral CNP, introducing the concept of ISI, which is calculated by dividing the area of peripheral CNP by the total visible fundus area.[2−7] Interestingly, a physiological peripheral CNP is also found in normal subjects, making it more difficult to interpret the results in RVO.[18]

Previous studies have demonstrated the superiority of UWFFA in the detection of CNP, especially central CNP, which is more closely associated with the development of ocular neovascularizations.[5−7] The capacity of OCTA to identify macular microvascular alterations in RVO has been confirmed by several authors.[11−14,19−21]

Our study was designed to investigate vascular biomarkers related to peripheral CNP in a consecutive series of carefully selected patients affected by naive CRVO, in order to rule out the effects of ocular and systemic conditions potentially leading to CNP, basing the assessment on high quality imaging alone. Furthermore, we used Ryu et al. CNP classification to investigate the effects of varying severity levels of CNP on the OCTA parameters.

Our data indicated that contralateral and control eyes showed a comparable tISI, which proved similar to that registered in 17% of CRVO eyes (< 5%). A variable extension of peripheral CNP was detected in the remaining cases. Two previous studies investigated the correlation between ISI and OCTA parameters in eyes affected by CRVO[13,14] and BRVO.[14] However, our cohort of patients consisted of highly selected naive CRVO patients showing high-quality imaging and no local and systemic conditions potentially causing CNP, who were followed up for 24 months in order to detect possible changes in ISI and OCTA parameters.

The assessment over the follow-up revealed that peripheral CNP progressed only slightly in our case series, maybe as a result of the anti-VEGF treatment adopted in two-thirds of CRVO cases.

The salient OCTA result was the decreased VD in the DCP, which was found in both the central region (3 × 3 mm) and the peripheral area (12 × 12 mm) and was the only parameter correlating with the FAZ, BCVA, and ISI.

The FAZ was the only OCTA parameter showing significant changes over the 2-year follow-up. This may be related to the intravitreal treatment-induced macular edema's regression, determining a progressive reduction of the displacement effect caused by the intraretinal edema. Conversely, VD values turned out to be stable over the follow-up, as did the peripheral CNP, suggesting that a valid correlation may be achieved after the baseline examination, providing useful prognostic information. Interestingly, we need to underline that the ISI classification into pISI and cISI proved not to be useful, because the same data could be obtained using the tISI, corresponding to the more commonly standardized ISI.[17]

The interpretation of the results is challenging, owing to the complexity of the cellular and non-cellular interactions secondary to retinal ischemia, but we suggest that the CNP should be analyzed on the basis of 2 different features: extension and severity.

Capillary non-perfusion extension may involve the complete retina, as suggested by the reduced DCP VD registered using wide-field OCTA (12 × 12 mm), also involving retinal areas not specifically classifiable as

Table 2. OCT Angiography Parameters and Peripheral CNP at Baseline on Ultrawidefield Fluorescein Angiography

		CRVO Eye	Fellow Eye	Controls	*P* Value (CRVO vs. Controls)
VD SCP 3 × 3mm		0.38 ± 0.02	0.40 ± 0.02	0.41 ± 0.01	< 0.001
VD DCP 3 × 3mm		0.35 ± 0.05	0.42 ± 0.03	0.43 ± 0.01	< 0.001
VD CC 3 × 3mm		0.49 ± 0.01	0.50 ± 0.02	0.50 ± 0.01	0.15
FAZ area		419 ± 159	245 ± 114	238 ± 89	< 0.001
Total peripheral CNP (%)		37%	4.9%	4.5%	< 0.001
Complete peripheral CNP (%)		27%	4.9%	4.5%	< 0.001
Partial peripheral CNP (%)		11%	0%	0%	< 0.001
			CRVO	**Controls**	***P* Value**
Overall 12 × 12mm	VD SCP		0.37 ± 0.02	0.38 ± 0.01	0.34
	VD DCP		0.28 ± 0.05	0.39 ± 0.01	< 0.001
	VD CC		0.48 ± 0.03	0.48 ± 0.01	0.23
Inner ring	VD SCP		0.38 ± 0.04	0.39 ± 0.01	0.37
	VD DCP		0.30 ± 0.04	0.40 ± 0.01	< 0.001
	VD CC		0.49 ± 0.02	0.49 ± 0.01	0.24
Outer ring	VD SCP		0.36 ± 0.04	0.38 ± 0.01	0.09
	VD DCP		0.22 ± 0.05	0.39 ± 0.01	< 0.001
	VD CC		0.48 ± 0.04	0.48 ± 0.01	0.12

CC = choriocapillaris; CNP = capillary non-perfusion; CRVO = central retinal vein occlusion; DCP = deep capillary plexus; FAZ = foveal avascular zone; SCP = superficial capillary plexus; VD = vessel density.

affected by CNP on UWWFA but detected by OCTA on the basis of the reduced DCP VD.

Conversely, FA may more easily identify CNP severity in the peripheral retina and in the macula by visualizing retinal nonperfusion with capillary dropout. Nevertheless, the actual severity of CNP consistent with the whole metabolic changes due to retinal ischemia,[22] which lead to the final anatomical and functional outcomes, cannot be fully assessed by angiography alone. Indeed, the interaction of several biochemical factors may contribute to the final clinical manifestation, many of them still eluding our appraisal. Approaches other than angiographic evaluation should be considered so as to attain a more precise assessment of CNP severity. In this respect, some promising experiences have been published regarding oxygen saturation and flow measurement in RVOs.[23–26]

The most important vascular alteration in CRVO occurs in the DCP, as demonstrated by the whole VD reduction. Deep capillary plexus VD impairment is detectable in all CRVO cases, variably involving both the central retina (with enlarged FAZ) and the periphery (with VD reduction in the peripheral retina). The severity of DCP VD reduction is correlated with the clinical findings concerning FAZ area, BCVA, and ISI. Deep capillary plexus VD may thus represent a crucial biomarker in characterizing CRVO. Further studies are necessary to identify the cutoff thresholds for the different clinical manifestations (especially involving visual field and visual acuity), culminating with the development of ocular neovascularization.

We are aware that our investigation is burdened by several limitations. First of all, the number of patients analyzed is limited, owing to the strict exclusion criteria adopted so as to focus specifically on the CNP secondary to the CRVO occurrence. Even though the present analysis is based on high-quality imaging, calculating the ISI can prove difficult because the exact dividing line between the different ISI

Table 3. Correlations Between Peripheral CNP and Clinical Parameters

	Parameter	Total Peripheral CNP (%)	Complete Peripheral CNP (%)	Partial Peripheral CNP (%)	FAZ Area DCP	CMT Baseline	CMT Final
DCP VD 12 × 12 mm	Pearson coeff.	0.668	0.598	0.555	0.467	0.521	0.489
	P Value	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
	Parameter	**Total Peripheral CNP (%)**	**Complete Peripheral CNP (%)**	**Partial Peripheral CNP (%)**	**FAZ Area DCP**		**CMT Final**
LogMAR BCVA Final	Pearson coeff.	0.563	0.525	0.532	0.554		0.552
	P Value	< 0.01	< 0.01	< 0.01	< 0.01		< 0.01

BCVA = best corrected visual acuity; CMT = central macular thickness; CNP = capillary non-perfusion; DCP = deep capillary plexus; FAZ = foveal avascular zone; logMAR = logarithm of the minimum angle of resolution; VD = vessel density.

parameters is often a matter of subjective interpretation. Moreover, OCTA parameters are prone to artifacts and their applicability on eyes affected by CRVO is not yet standardized. More specifically, the presence of intraretinal hemorrhages and macular edema at baseline may have affected the measurement of OCTA parameters, although our sample included patients with a CRVO mean duration of 9 months, allowing a good resolution of retinal hemorrhages, and the tISI corresponded to 37%, with no case with extensive CNP and extensive intraretinal hemorrhages. In addition, our data were limited to the analyses of the OCTA parameters within 12 × 12 mm scans, with no assessment of the far periphery of the retina owing to OCTA's technical shortcomings. Most of the patients included in the study were under treatment with anti-VEGF, which might have modified the CRVO's clinical manifestations, especially as regards CNP development and progression.

On the other hand, the study's strengths are the enrollment of carefully selected naive CRVO patients with high-quality imaging and without local and systemic conditions potentially causing CNP. This helped ensure reliable assessment and effective evaluation of the long-term effects of ranibizumab injection for macular edema, as happens in a clinical setting following a pro re nata (PRN) regimen.

In conclusion, DCP VD may be considered an important biomarker in characterizing the final anatomical and functional outcomes. Further studies are warranted both to confirm our preliminary results and to improve the OCTA techniques that ensure a precise calculation of the DCP. Future investigations will also need to identify the DCP cutoff thresholds related to the CRVO prognosis, especially regarding visual acuity and ocular neovascularization development.

Footnotes and Disclosures

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HUMAN SUBJECTS: Human subjects were used in this study. The study followed the tenets of the Declaration of Helsinki and was approved by the local Ethical Committee. All patients gave signed, informed consent.

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Abbreviations and Acronyms:
BCVA = best corrected visual acuity; **BRVO** = branch retinal vein occlusion; **cISI** = complete ischemic index; **CMT** = central macular thickness; **CNP** = capillary non-perfusion; **CRVO** = central retinal vein occlusion; **DCP** = deep capillary plexus; **FA** = fluorescein angiography; **FAZ** = foveal avascular zone; **ISI** = ischemic index; **OCTA** = OCT angiography; **pISI** = partial ischemic index; **RVO** = retinal vein occlusion; **SCP** = superficial capillary plexus; **tISI** = total ischemic index; **UWFFA** = ultrawidefield fluorescein angiography; **VD** = vessel density.

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