

Peripapillary and Subfoveal Choroidal Thickness in Retinal Vein Occlusions

Ana Filipa Moleiro^{1,2}, Gonçalo Godinho³, Carolina Madeira⁴, Ana Faria Pereira¹, Elisete Brandão¹, Fernando Falcão-Reis^{1,2}, João Nuno Beato^{1,2}, Susana Penas^{1,2}

¹Department of Ophthalmology, Centro Hospitalar e Universitário de São João, Porto, Portugal; ²Department of Surgery and Physiology, Faculdade de Medicina da Universidade do Porto, Porto, Portugal; ³Department of Ophthalmology, Centro Hospitalar de Leiria, Leiria, Portugal; ⁴Department of Ophthalmology, Centro Hospitalar Gaia-Espinho, Gaia, Portugal

Correspondence: Ana Filipa Moleiro, Department of Ophthalmology, Centro Hospitalar e Universitário de São João, Alameda Hernani Monteiro, Porto, 4200-426, Portugal, Tel +351 915689259, Email anafomoleiro@gmail.com

Purpose: This work aimed to longitudinally assess the peripapillary (PPCT) and subfoveal (SFCT) choroidal thickness (CT), in patients diagnosed with central (CRVO) or branch retinal vein occlusions (BRVO), correlating SFCT with central macular thickness (CMT) and PPCT with peripapillary retinal nerve fiber layer thickness (pRNFL).

Patients and Methods: This was a retrospective longitudinal study of 71 eyes from 71 patients with treatment-naïve retinal vein occlusion (24 CRVO and 40 BRVO). Spectral-domain optical coherence tomography (SD-OCT, Spectralis HRA-OCT, Heidelberg) was used to measure PPCT, SFCT, pRNFL and CMT of the affected and fellow eyes at baseline (acute phase) and at 3 and 9 months post anti-VEGF treatment. IBM SPSS Statistics version 27.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. A p -value ≤ 0.05 was considered statistically significant.

Results: Affected eyes presented a thicker baseline PPCT and SFCT compared to their fellow eyes both in CRVO and BRVO ($p < 0.05$). Both groups presented a significant decrease of PPCT in the affected eyes at 3 months compared to baseline ($p < 0.05$). At 9 months, compared to 3 months, PPCT remained stable ($p > 0.05$). Similarly, affected eyes' SFCT significantly decreased at 3 months ($p < 0.05$) in both groups. At 9 months, compared to 3 months, SFCT decreased in the CRVO patients ($p = 0.047$) but remained stable in the BRVO patients ($p = 0.850$). No correlations between SFCT and CMT were seen at any timepoint in both groups ($p > 0.05$). PPCT correlates with pRNFL in CRVO at 3 months, although no other correlations were found during the follow-up. In BRVO, PPCT did not show any significant correlation with pRNFL.

Conclusion: Both in CRVO and BRVO eyes, PPCT and SFCT at diagnosis are significantly thicker compared to the fellow eye, suggesting a possible increase in CT immediately after the occlusion, which is followed by a decrease at an early follow-up stage.

Keywords: biomarkers, vascular retinal diseases, retinal vein occlusions, choroidal thickness, optical coherence tomography

Introduction

Retinal vein occlusions are the second most prevalent retinal vascular pathology, after diabetic retinopathy,^{1,2} with a prevalence of 0.1–0.2% in the active population.³ Cardiovascular risk factors increase their incidence, particularly arterial hypertension (AHT).⁴ A pro-coagulant state is usually associated with the younger population.⁵ They are classified as central (CRVO) or branch retinal vein occlusions (BRVO), according to the site of obstruction to the blood flow, and their findings include vascular engorgement and stasis, intraretinal hemorrhages, cotton wool spots, and lipid exudation.⁶ Visual acuity (VA) may be decreased if macular edema develops, but also due to vitreous hemorrhage or macular ischemia.

The choroid is responsible for the highest blood flow per unit weight of any tissue in the body⁷ and provides metabolic support and thermoregulation for the retinal pigment epithelium (RPE) and the outer retinal layers. Several studies have evaluated the subfoveal choroid in retinal venous occlusions, seeking to relate the hypoxic stimulus and increased levels of vascular endothelial growth factors (VEGF) with the morphological changes in the vascular layer. The results, however, were not consistent, with some authors reporting greater subfoveal choroidal thickness (SFCT),^{8,9} and

others finding no differences.¹⁰ Data on the peripapillary choroidal thickness (PPCT) in this pathology is scarce. A previous study reported no differences between the affected and the fellow-eyes in the acute phase, while showed a decrease in the affected eyes after 12 months.¹¹ There are a lot of unanswered questions about the role of the choroid in the retinal venous occlusion phenomenon, and little is known about the choroid correlation to retinal thickness, namely the development of macular edema.

This study aims to evaluate PPCT and SFCT over time in patients with BRVO and CRVO after treatment, correlating PPCT with peripapillary retinal nerve fiber layer (pRNFL) and SFCT with central macular thickness (CMT).

Materials and Methods

This was a retrospective longitudinal observational study, performed in the Ophthalmology Department of São João University Hospital Center, a tertiary referral hospital in Porto, Portugal, including treatment-naïve patients newly diagnosed with CRVO and BRVO. Patients were selected from a specifically created medical retinal outpatient clinic, targeted to study and treat vascular occlusions. All data were collected and reviewed at the center. A minimum follow-up of 3 months was required. This study was conducted under the tenets of the Declaration of Helsinki and was approved by the hospital Ethics Committee.

The following exclusion criteria were applied: prior retinal venous occlusion, intravitreal (IV) treatment with anti-VEGF, corticoid, or retinal laser; concomitant macular or choroidal pathologies; a history of uveitis; refractive error higher than 6 diopters of spherical equivalent in the affected or fellow-eye; poor image quality precluding the correct assignment of SD-OCT images.

Data were collected at three timelines: baseline (acute phase), 3, and 9 months of follow-up after treatment. Demographics and risk factors for RVO, such as AHT, dyslipidemia, diabetes mellitus (DM), and glaucoma were evaluated. Best-corrected VA (BCVA) was assessed using the ETDRS chart. Patients were all assessed by a retinal specialist (JB and SP), undergoing a treat-and-extend regimen with anti-angiogenic or corticosteroid agents according to their clinical findings.

All patients underwent a Spectral Domain – Optical Coherence Tomography (Spectralis; Heidelberg Engineering, Germany) examination with enhanced depth-imaging (EDI) technology, during the afternoon period (2 pm to 8 pm) during every visit. Both macular volume and peripapillary scans were performed. Images with poor quality were excluded. Two experienced masked observers reviewed the SD-OCT images. PPCT and SFCT were assessed in the affected and fellow eyes. SFCT was manually measured using the software caliper in a 6mm EDI horizontal scan, centered on the fovea (Figure 1). The PPCT measurement was performed based on previous descriptions,¹² using an EDI 3.4-mm diameter peripapillary circle scan (comprising 100 averaged scans and centered on the optic disc) that has also been used for measurement of the peripapillary retinal nerve fiber layer (RNFL) thickness. Manual segmentation was performed. The outer border of the choroid was defined as the hyperreflective line of the inner surface of the sclera. The intern border was automatically defined by the Heidelberg software. If a clear line could not be detected, the outer choroidal border was defined as a smoothing line connecting the outer limits of the large choroidal vascular spaces. Measurements of this layer thickness were performed on the upper, nasal, lower, and temporal quadrants (Figure 2). The measurements obtained at these four locations were averaged as pPPCT. Inter-observer correlation coefficient was calculated to be 0.931 (95% Confidence Interval 0.892–0.955). Data on pRNFL and CMT of the affected eye was evaluated, using the system's automatic software.

The statistical analysis was performed using IBM SPSS Statistics, version 27.0 (IBM Corp., Armonk, NY, USA). The Shapiro–Wilk test and kurtosis and skewness evaluation verified the normal distribution of continuous variables. Continuous variables were represented as mean \pm standard deviation when normally distributed or median and range for variables with non-normal distribution. Comparisons between independent groups were performed with the independent *t*-test when normality was confirmed, and with the Mann–Whitney test otherwise; comparisons over time and with the fellow-eye were performed using the paired sample *t*-test when normality was confirmed or the Wilcoxon test when normality was not present. Differences in the mean PPCT and SFCT between CRVO and BRVO patients were assessed by analysis of covariance (ANCOVA), adjusting for age. Categorical variables were reported as frequencies and percentages and the chi-square test was used for comparisons. Spearman's rank correlation coefficient was used to describe the strength of association between two variables. Pearson correlation coefficient was applied to study possible correlations of PPCT with pRNFL and SFCT with CMT. A *p*-value of 0.05 or less was considered statistically significant.

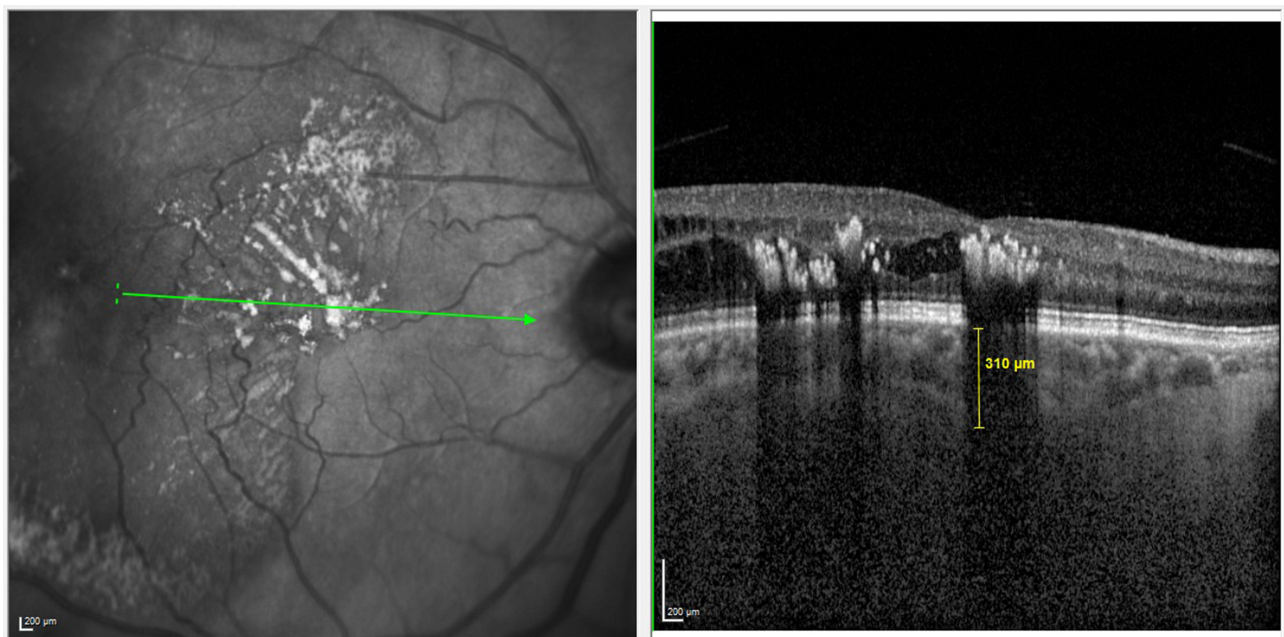


Figure 1 Schematic representation of macular choroidal thickness measurement. Choroidal Thickness was measured from the outer edge of the hyperreflective line, corresponding to the Retinal Pigment Epithelium, to the choroidal-scleral junction. Measurements were taken at the subfoveal level (yellow caliper).

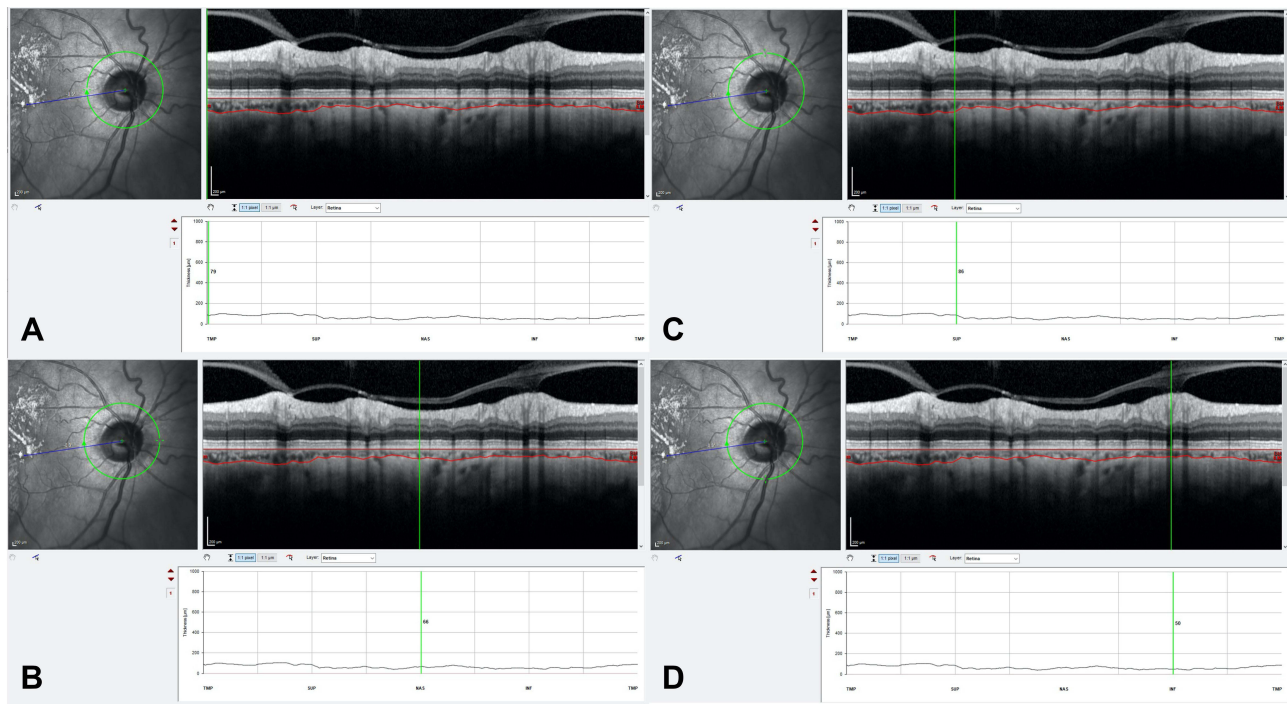


Figure 2 Measurement illustration of peripapillary choroidal thickness at 4 locations. Manual delineation of the inner (top red line) and outer choroidal (bottom red line) borders using eye-tracking software (Heidelberg Engineering). Measurement of choroidal thickness at 4 locations using image-processing software, illustrated with the green vertical lines. (A) Temporal choroidal thickness measurement; (B) Nasal choroidal thickness measurement; (C) Superior choroidal thickness measurement; (D) Inferior choroidal thickness measurement.

Results

Sixty-four patients were included; 64 affected-eyes and 64 fellow-eyes were analyzed. A total of 24 CRVO and 40 BRVO were evaluated. Age of the patients was statistically higher in BRVO patients (vs CRVO, $p=0.008$) (Table 1). No

Table 1 Demographic and Clinical Data Comparison Between CRVO and BRVO

	CRVO n=24	BRVO n=40	P
Age - years (mean±SD)	58.00±18.90	70.15±10.15	0.008*
Sex – Male/Female [n(%)]	12 (50.0) / 12 (50.0)	16 (40.0%) / 24 (62.0%)	0.278
AHT [n(%)]	12 (50.0%)	25 (62.5%)	0.063
DM [n(%)]	3 (12.5%)	10 (25.0%)	0.164
Dyslipidemia [n(%)]	10 (41.6%)	14 (35.0%)	0.535
Glaucoma [n(%)]	2 (8.3%)	7 (17.5%)	0.239
IOP – mmHg (mean±SD)	15.79±5.67	15.38±3.38	0.735
Time from symptoms to baseline – days (median[IQ range])	42 [30–60]	62 [30–90]	0.079
IVI at 3 months – n (mean±SD)	2.57±1.44	2.77±1.33	0.573
IVI at 9 months – n (mean±SD)	5.69±2.68	6.17±2.21	0.519

Notes: Comparisons between CRVO and BRVO evaluated through t-test (for age and number of injections) and with Chi-square for the remainders. * $p < 0.05$: statistically significant.

Abbreviations: AHT, Arterial hypertension; DM, diabetes mellitus; IOP, intraocular pressure; IVI, intravitreal injections; CRVO, central retinal vein occlusion; BRVO, branch retinal vein occlusion.

statistically significant differences were found related to sex ($p=0.278$) or different risk factors, namely AHT ($p=0.063$), DM ($p=0.164$), dyslipidemia ($p=0.535$), or the presence of glaucoma ($p=0.239$) between both groups (Table 1).

A mean of 6.00 ± 3.37 injections was performed during 9 months period - 98.1% anti-VEGF and 1.9% corticosteroid (Table 1). In the anti-VEGF sub-group of patients, more than 95% of the injections performed were from bevacizumab, the remaining from aflibercept.

Peripapillary Choroidal Thickness (PPCT)

In CRVO patients, affected eyes presented a significant thicker baseline PPCT compared to the fellow eyes ($155.38 \pm 48.23 \mu\text{m}$ vs $137.25 \pm 59.7 \mu\text{m}$, $p=0.041$), but no statistical differences were found at 3 and 9 months ($p=0.357$ and $p=0.152$, respectively). The PPCT in the affected eye presented a statistically significant decrease at 3 months compared to the baseline ($p=0.002$) but remained stable at 9 months ($p=0.945$). There were no statistically significant PPCT changes in the fellow-eye over time ($p>0.05$) (Table 2).

In BRVO patients, affected eyes presented a statistically significant thicker baseline PPCT compared to the fellow eyes ($116.84 \pm 51.29 \mu\text{m}$ vs $106.77 \pm 48.02 \mu\text{m}$, $p=0.003$), but no statistical differences were found at 3 and 9 months ($p=0.232$ and $p=0.206$, respectively). The PPCT in the affected eyes presented a statistically significant decrease at 3 months compared to baseline ($p=0.023$), but remained stable afterward, at 9 months ($p=0.244$). There were also no significant PPCT changes in the fellow-eye over time ($p>0.05$) (Table 2).

Subfoveal Choroidal Thickness (SFCT)

In CRVO patients, affected eyes presented a significantly thicker baseline SFCT compared to the fellow eyes ($273.16 \pm 60.98 \mu\text{m}$ vs $248.05 \pm 82.80 \mu\text{m}$, $p=0.004$), but no statistically significant differences were found at 3 and 9 months ($p=0.251$ and $p=0.724$, respectively). The SFCT in the affected eyes presented a significant decrease in the first 3 months ($p=0.002$), and afterward, from 3 to 9 months ($p=0.047$). There were no significant SFCT changes in the fellow-eye over time ($p>0.05$) (Table 2).

In BRVO patients, affected eyes presented a significantly thicker baseline SFCT compared to the fellow eyes ($232.00 \pm 77.45 \mu\text{m}$ vs $205.62 \pm 82.41 \mu\text{m}$, $p=0.002$), and although there is no statistically significant differences between the affected and the fellow eyes at 3 months ($p=0.321$), PPCT is significantly thicker in the affected eyes at 9 months of follow-up ($p=0.048$). The SFCT in the affected eyes presented a statistically significant decrease at 3 months compared to

Table 2 SD-OCT Thickness Measurements During the Follow-Up in Patients with CRVO and BRVO

		Baseline (n=64)	3 Months (n=64)		9 Months (n=50)	
				p^1		p^2
CRVO	PPCT (μm)	–	–	–	–	–
	Affected-eyes	155.38 \pm 48.23	132.43 \pm 52.64	0.002*	151.83 \pm 61.61	0.945
	Fellow-eyes	137.25 \pm 59.71	136.72 \pm 58.37	0.923	150.75 \pm 59.85	0.367
	p^3	0.041*	0.357	–	0.152	–
	SFCT (μm)	–	–	–	–	–
	Affected-eyes	273.16 \pm 60.98	251.65 \pm 74.50	0.002*	246.47 \pm 69.35	0.047*
	Fellow-eyes	248.05 \pm 82.80	236.39 \pm 86.23	0.330	259.75 \pm 85.09	0.154
	p^3	0.004*	0.251	–	0.724	–
	RNFL (μm)	187.00 \pm 53.33	130.75 \pm 39.89	0.004*	112.13 \pm 35.242	<0.001*
	CMT (μm)	709.00 \pm 231.57	317.80 \pm 142.84	0.002*	322 \pm 150.52	0.509
BRVO	PPCT (μm)	–	–	–	–	–
	Affected-eyes	116.84 \pm 51.29	110.50 \pm 52.34	0.023*	115.21 \pm 53.52	0.244
	Fellow-eyes	106.77 \pm 48.03	113.00 \pm 50.88	0.449	109.69 \pm 50.43	0.523
	p^3	0.003*	0.232	–	0.206	–
	SFCT (μm)	–	–	–	–	–
	Affected-eyes	232.00 \pm 77.45	220.62 \pm 77.51	<0.001*	222.93 \pm 82.17	0.850
	Fellow-eyes	205.62 \pm 82.41	210.00 \pm 87.67	0.194	201.74 \pm 84.86	0.578
	p^3	0.002*	0.321	–	0.048*	–
	RNFL (μm)	110.95 \pm 34.23	101.50 \pm 24.01	0.007*	94.63 \pm 18.20	<0.001*
	CMT (μm)	614.31 \pm 237.46	365.40 \pm 145.943	0.002*	300.06 \pm 97.04	0.311

Notes: Variables represented as mean \pm standard deviation or as median [range]; p^1 : comparison between baseline and 3 months; p^2 : comparison between 3 and 9 months; p^3 : comparison between the affected and the fellow-eyes at each time-point. * p <0.05: statistically significant.

Abbreviations: CRVO, central retinal vein occlusion; BRVO, branch retinal vein occlusion; PPCT, peripapillary choroidal thickness; SFCT, subfoveal choroidal thickness; pRNFL, peripapillary retinal nerve fiber layer; CMT, central macular thickness.

the baseline (p <0.001), with no additional statistical change at 9 months (p =0.850). There were no significant SFCT changes in the fellow-eye overtime (p >0.05) (Table 2).

Peripapillary Retinal Nerve Fiber Layer (pRNFL)

In CRVO patients, the pRNFL of the affected eye was 187.00 \pm 53.33 μm at baseline and it was found to significantly decrease at 3 months (p =0.004) and, again, at 9 months (p <0.001). PPCT correlates with pRNFL at the baseline (r =0.389; p =0.01, Pearson coefficient correlation). No correlations were found between PPCT and pRNFL at 3 or 9 months (p >0.05, Pearson coefficient correlation).

In BRVO patients, the pRNFL of the affected eye was 110.95 \pm 34.23 μm at baseline, and significantly decreased at 3 months (p =0.007) and, again, at 9 months (p <0.001). No correlations were found between PPCT and pRNFL at any timepoint in BRVO (p >0.05, Pearson coefficient correlation).

Central Macular Thickness (CMT)

In CRVO patients, the CMT of the affected eye was $709.00 \pm 231.57 \mu\text{m}$ at baseline, significantly decreased at 3 months ($p=0.002$), with no further statistical change between 3 and 9 months ($p=0.509$). No correlations were found between SFCT and CMT at any time point ($p>0.05$).

In BRVO patients, the CMT of the affected eye was $614.31 \pm 237.46 \mu\text{m}$ at baseline and significantly decreased at 3 months ($p=0.002$), remaining stable between 3 and 9 months ($p=0.311$). No correlations were found between SFCT and CMT at any time point ($p>0.05$, Pearson correlation).

CRVO versus BRVO

Baseline PPCT of CRVO patients was significantly greater than in the BRVO subset of patients in both the affected and fellow eye ($p=0.017$ and $p=0.014$, respectively) (Table 3). At 3 months of follow-up, no statistically significant differences in PPCT were seen between CRVO and BRVO both in the affected and the fellow eye. Nevertheless, at 9 months, PPCT was significantly thicker in CRVO patients both in the affected and fellow eye ($p=0.017$ and $p=0.001$, respectively).

No statistically significant differences were found between CRVO and BRVO patients concerning the SFCT of both the affected and the fellow eye at baseline ($p=0.129$ and $p=0.099$, respectively). No significant differences were registered at 3 months, but a significantly thicker SFCT was found at 9 months on the CRVO fellow eyes compared to the BRVO fellow eyes. (Table 3).

Table 3 Comparison of PPCT and SFCT Between CRVO and BRVO

	CRVO n=26	BRVO n=45	P
PPCT			
Affected-eye (μm)			
Baseline	155.38 \pm 48.23	116.84 \pm 51.30	0.017*
3 months	132.34 \pm 52.64	114.52 \pm 52.34	0.408
9 months	151.84 \pm 61.61	113.17 \pm 53.76	0.017*
Fellow-eye (μm)			
Baseline	144.50 \pm 59.71	106.77 \pm 48.03	0.014*
3 months	136.72 \pm 58.37	113.00 \pm 50.88	0.192
9 months	162.13 \pm 59.85	109.69 \pm 50.43	0.001*
SFCT			
Affected-eye (μm)			
Baseline	273.16 \pm 60.99	232.00 \pm 77.49	0.129
3 months	251.65 \pm 74.50	220.62 \pm 77.51	0.402
9 months	246.47 \pm 69.45	222.93 \pm 82.17	0.073
Fellow-eye (μm)			
Baseline	248.05 \pm 82.80	205.62 \pm 82.41	0.099
3 months	236.39 \pm 86.23	213.70 \pm 67.67	0.405
9 months	259.75 \pm 85.09	201.74 \pm 84.86	0.011*

Notes: Comparisons between CRVO and BRVO evaluated through ANCOVA (values presented were corrected for age). * $p < 0.05$: statistically significant.

Abbreviations: CRVO, central retinal vein occlusion; BRVO, branch retinal vein occlusion; PPCT, peripapillary choroidal thickness; SFCT, subfoveal choroidal thickness.

Discussion

In our study, we found a significantly increased baseline PPCT and SFCT in the eyes affected with CRVO and BRVO when compared to their fellow unaffected eyes. Nevertheless, the choroidal thickness in the peripapillary and subfoveal location decreased significantly in the first 3 months after treatment. We also found that CRVO patients presented a statistically significant thicker peripapillary choroid at baseline compared to BRVO patients, both in the affected and unaffected eyes, but no statistically significant differences were found for the subfoveal choroid between both groups.

Retinal vein occlusions create a hypoxic environment that could increase the expression of intraocular VEGF. Subsequently, vascular hyperpermeability and dilation of the choroid could occur.^{13–16} We found that PPCT and SFCT of the affected eyes were statistically higher than in the fellow eyes after CRVO and BRVO. These findings agree with other studies that evaluated the SFCT after occlusions.^{17–20}

Interestingly, in our study, after the acute event, there was a sudden statistically significant decrease in the PPCT and SFCT after anti-VEGF treatment, followed by a thickness stabilization in the remaining follow-up, both in CRVO and BRVO patients. These findings could be justified by a sudden decrease in the initial hypoxic stimulus, as well as by the repetitive use of anti-VEGF therapy throughout the time.^{18,19} Our findings corroborate previous data on the choroidal thickness variation after an occlusive event.^{11,20,21} On the contrary, PPCT and SFCT of the fellow eyes remained similar during the follow-up, and do not seem to be affected by the event. During the follow-up, the peripapillary and subfoveal choroidal responses were similar, strengthening the hypothesis of a generalized effect on the choroid due to the retinal occlusion event.

The CMT and pRNFL were higher after the acute event, as expected, in both groups due to the subsequent acute edema, decreasing along with the follow-up. pRNFL seems to correlate with PPCT at the baseline in BRVO, with a positive linear correlation. Nevertheless, no significant correlations were found during the following follow-up. Also, no correlations were found between PPCT and pRNFL or SFCT and CMT for CRVO eyes. As so, we believe that the retinal tissue's response is not directly related to the choroid's response. Similarly, we presume that the reduction of the hypoxic stimulus and the anti-VEGF therapy may act differently on the choroid and the retina during the follow-up, as they represent independent vascular structures.

CRVO patients presented a thicker PPCT at baseline than the BRVO group. Although we do not know the choroid status of the patients previous to the occlusion, we hypothesize that the thicker choroid in CRVO could indicate that CRVO leads to a higher ischemic insult, releasing more inflammatory mediators and VEGF and, consequently, promoting a higher increase in CT. However, during the follow-up period, no significant differences in PPCT were found between both groups, at least until 9 months post-treatment. Curiously, the SFCT, was similar in both groups throughout the entire follow-up, as previously described.²⁰ Interestingly, the fellow eyes of CRVO patients also present higher PPCT, which could solely mean that this group of patients had a physiologically thicker choroid and that the occlusion would not be the cause of the difference between both groups.

We found no differences related to sex, AHT, DM, dyslipidemia, or the presence of glaucoma in patients with CRVO or BRVO. Additionally, we found no differences for IOP at baseline, time from symptoms onset to the first evaluation, and the total number of IV injections between both groups. Though no significant differences were found concerning age, since CRVO patients were significantly younger than BRVO patients, we performed another analysis comparing groups and adjusting for this parameter.

To the best of our knowledge, this was the first study evaluating sequentially PPCT and SFCT in more than two time points, both in CRVO and BRVO patients. Nevertheless, our study has some limitations. The short sample size and its retrospective observational nature are its major drawbacks. We also did not consider the presence of macular edema or the severity of retinal ischemia in the analysis. Moreover, we only included patients with good-quality OCT images. This may induce a selection data bias excluding the more severe occlusions from our analysis. Furthermore, choroidal thickness tends to variate with age, refractive error, and even daytime of measurement.^{22–24} In order to minimize these biases, although no age-specific groups were created, the comparisons were adjusted for this parameter, patients with spherical equivalent higher than 6D were excluded and patients' assessment was performed between 2 pm and 8 pm.

Conclusion

In conclusion, in both CRVO and BRVO eyes, PPCT and SFCT are significantly thicker compared to the fellow eye, suggesting a possible increase in CT immediately after the occlusion, followed by a decrease at an early follow-up stage. Longer follow-up studies with larger samples could clarify the relation of choroidal thickness to the retinal vascular occlusive insult. However, this study shows that choroid may have a role in the pathophysiologic response of RVO. A further understanding of the relation between choroid thickness and retina response may provide an additional structural marker for predicting the prognosis of these patients.

Statements of Ethics

This research was done ethically and in accordance with the World Medical Association Declaration of Helsinki. Patients were treated according to the standard of care. No different approaches or treatments were performed. The Ethics Committee from São João Hospital approves retrospective review of the data when consented by the patients. Included data were anonymized. Patients were informed of the purpose of this study and agreed and consented to the use of their follow-up data for clinical research purposes.

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Disclosure

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