• Clinical Research •

Ranibizumab on optic disc perfusion in central retinal vein occlusion

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Received: 2025-05-10 Accepted: 2025-09-09

Abstract

● **AIM:** To evaluate the therapeutic effects of ranibizumab on optic disc and macular microvascular perfusion in central retinal vein occlusion (CRVO) with macular edema (ME).

● **METHODS:** Optical coherence tomography angiology (OCTA) parameters, including optic disc vessel density (VD; including whole-disc VD, intra-disc VD, and peripapillary VD), superficial/deep capillary plexus (SCP/DCP) VD, and central macular thickness (CMT) were analyzed. Additional assessments included best-corrected visual acuity (BCVA) *via* Early Treatment Diabetic Retinopathy Study (ETDRS) chart and hemorheological profiling. CRVO patients received monthly intravitreal ranibizumab injections for three consecutive months. Pre- and post-treatment parameters were statistically compared.

● **RESULTS:** The study comprised 60 CRVO-ME patients (28 males; 32 females), aged 50–78y (mean 63.3±7.6y) and 60 age-/sex-matched healthy controls. As compared with participants exhibiting normal funduscopic findings, CRVO patients demonstrated significantly elevated levels of low-shear-rate whole blood viscosity (LSR-WBV), high-shear-rate whole blood viscosity (HSR-WBV), and aggregation index (AI, all $P<0.05$). In CRVO-affected eyes, vertical cup-to-disc (C/D) ratio and optic cup volume were significantly smaller, whereas retinal nerve fiber layer (RNFL) thickness was significantly greater, compared to both unaffected contralateral eyes and normal control eyes (all $P<0.05$). Following treatment, VD of the entire optic disc ($P<0.05$), intra-disc VD ($P<0.05$), and peripapillary VD ($P<0.05$) all increased significantly relative to baseline. CMT decreased significantly ($P<0.05$), whereas macular SCP-VD and macular DCP-VD showed non-significant slight reductions ($P>0.05$). At baseline, BCVA of CRVO eyes correlated with whole-disc VD ($r=-0.276$, $P=0.033$), intra-disc VD ($r=-0.342$, $P=0.009$), and peripapillary VD ($r=-0.335$, $P=0.007$), with intra-disc VD demonstrating the strongest association. Besides, BCVA improvement, after the treatment, correlated positively with whole-disc VD ($r=0.342$, $P=0.008$) and intra-disc VD ($r=0.396$, $P=0.002$).

● **CONCLUSION:** Optic disc blood perfusion is more closely associated with visual acuity than macular perfusion, suggesting intra-disc VD may serve as a potential biomarker for monitoring visual acuity changes in CRVO. Multiple ranibizumab injections significantly improve optic disc perfusion but may have exerted detrimental effects on the macula. CRVO patients shows higher hemorheological parameters than those with normal fundi. Reduced vertical C/D ratio and optic cup volume may be linked to CRVO incidence, potentially acting as susceptibility factors.

● **KEYWORDS:** central retinal vein occlusion; macular edema; optic disc; ranibizumab; optical coherence tomography angiology

DOI:10.18240/ijo.2026.01.10

Citation: Li X, Hao XF, Xie LK, Luo JH, Zhang MJ. Ranibizumab on optic disc perfusion in central retinal vein occlusion. *Int J Ophthalmol* 2026;19(1):77-82

INTRODUCTION

Central retinal vein occlusion (CRVO) results from obstruction of the main retinal vein trunk, with retinal damage primarily stemming from microcirculatory disturbances manifested as venous tortuosity/dilation, pan retinal hemorrhages, structural alterations in the macular arch ring (including deformation or obliteration), expansion of macular non-perfusion zones, and marked reduction in blood flow density[1]. Given that the obstruction occurs at the optic disc through which the central retinal vein traverses, hemodynamic changes in this region have garnered significant research interest. Macular edema (ME), the most prevalent CRVO complication and principal contributor to visual morbidity, is managed per month[1]. European Association of Retinal Specialists guidelines recommend anti-

vascular endothelial growth factor (VEGF) therapy as first-line treatment based on its pathophysiological rationale[1]. However, emerging evidence suggests anti-VEGF agents may exert detrimental effects on macular microcirculation, raising clinical concerns given the necessity for repeated intravitreal administrations[2].

Emerging evidence demonstrated the detrimental effects of anti-VEGF agents on macular microcirculation in some retinal diseases, including vasoconstriction and capillary density reduction, choroidal thinning and blood flow reduction, short-term decreases in retinal blood flow, and geographic atrophy and long-term atrophy risk[2-3]. While anti-VEGF agents remain a mainstay in the management of CRVO, accumulating evidence underscores the importance of monitoring for adverse effects on macular microcirculation, particularly in patients with repeated use. Till now, the specific impact of anti-VEGF on optic disc perfusion in patients with ME secondary to CRVO remains elusive.

In this study, we aim to explore the quantitative impact of ranibizumab, a prototypical anti-VEGF agent, on both macular and optic disc vascular perfusion parameters in CRVO patients, seeking to elucidate the therapeutic implications of these microcirculatory changes.

PARTICIPANTS AND METHODS

Ethical Approval Ethical approval was obtained from the Ethics Committee of the Eye Hospital of China Academy of Chinese Medical Science (No.TKEC-KT-2022-024-P002), and written informed consent was acquired from all participants prior to enrollment.

Study Design And Participants This prospective randomized case-control trial was conducted at the Eye Hospital of China Academy of Chinese Medical Sciences. Sixty treatment-naïve patients diagnosed with ME secondary to CRVO within 30d of symptom onset were enrolled, along with 60 age- and sex-matched healthy controls with normal fundus examinations.

Diagnostic Criteria CRVO-ME diagnosis adhered to the *RETINA* (Fifth Edition) guidelines[4]: requiring: 1) acute-onset vision loss or visual field defects; 2) fundoscopic evidence of retinal venous tortuosity/dilation with diffuse superficial hemorrhages; 3) fluorescein angiography (FFA) demonstrating delayed venous filling, vascular leakage, capillary tortuosity, and/or optic disc edema; 4) optical coherence tomography angiography (OCTA)-confirmed central macular thickness (CMT) >250 μm.

Inclusion and Exclusion Criteria The inclusion criteria were as follows: 1) age between 35 and 90 years old; 2) BCVA (logMAR) ranged from 3 to 0.4. 3) diagnosed with CRVO-ME; 4) was able to cooperate to complete examinations; 5) agreed to participate in this clinical trial and signed the informed consent.

Participants were excluded for: 1) OCTA signal strength index <6 due to refractive media opacity; 2) concurrent ocular pathologies (retinal detachment, diabetic retinopathy, age-related macular degeneration, glaucoma, *etc*); 3) severe systemic comorbidities (malignancy, acute myocardial/cerebral infarction); 4) recent ocular trauma/surgery (≤3mo); 5) pregnancy, lactation, or planned conception; 6) participation in other clinical trials within the preceding 3mo.

Ocular Assessments Quantitative vascular parameters were evaluated using RTVue XR OCTA (Optovue Inc., USA). Optic disc perfusion metrics (4.5×4.5 mm^2 scans) included whole disc vessel density (VD), intra-disc VD, and peripapillary VD. Macular parameters (3×3 mm^2 scans) encompassed superficial/deep capillary plexus (SCP/DCP) VD and CMT. Functional assessments employed ETDRS charts to derive best-corrected visual acuity (BCVA) in logMAR units. Systemic hemodynamic profiling included whole blood viscosity (low/high shear rates: 5/s, 200/s), plasma viscosity (PV), hematocrit (HCT), erythrocyte aggregation/rigidity indices, and deformability index (DI).

OCTA was performed for preoperative assessment and postoperative follow-ups at baseline, and post each injection (0, 1, 2, 3mo). An experienced technician (with clinical experience >5y) was fixed for OCTA operation and data recording, and the operation was in accordance with the operation specification.

Intervention Protocol CRVO-ME eyes received standardized intravitreal ranibizumab (10 mg/mL, 0.05 mL, Novartis Pharma Schweiz AG) injections administered monthly for three consecutive cycles, adhering to aseptic surgical protocols.

Statistical Analysis Data analysis utilized IBM SPSS 23.0 with continuous variables expressed as mean±standard deviation (SD). Normally distributed data were analyzed *via* *t* tests, while non-normally distributed data were analyzed *via* Mann-Whitney *U* tests. Correlation analyses employed Spearman's rank coefficients. Statistical significance was defined as $P<0.05$ (two-tailed).

RESULTS

Demographic and Safety Profile The study cohort comprised 60 CRVO-ME patients (28 males, 32 females) aged 50–78y (mean 63.3±7.6y). No treatment-related ocular or systemic complications were observed throughout the study period.

Hemorheological Alterations CRVO patients demonstrated elevated hemorheological parameters compared to healthy controls, including low-shear-rate (5/s) and high-shear-rate (200/s) whole blood viscosity (LSR-WBV, HSR-WBV), PV, HCT, erythrocyte aggregation index (AI), rigidity index (IR), and DI. Statistically significant increases were identified in LSR-WBV, HSR-WBV, and AI (all $P<0.05$; Table 1).

Optic Disc Morphology and Vascular Changes CRVO-affected eyes exhibited significantly reduced vertical cup-to-disc (C/D) ratio, smaller optic cup volume, and thicker

Table 1 Comparisons of hemorheological parameters between CRVO patients and healthy controls

Parameters	*n*	LSR-WBV (5/s) (mPa·s)	HSR-WBV (200/s) (mPa·s)	PV (mPa·s)	HCT (L/L)	AI	IR	DI
CRVO patients	60	9.025±1.641	4.943±0.618	1.503±0.205	0.425±0.031	3.571±1.736	5.487±1.278	0.893±0.133
Healthy controls	60	8.470±1.167	4.557±0.616	1.461±0.190	0.413±0.062	2.910±1.511	5.145±1.449	0.910±0.285
P		0.035	0.001	0.251	0.168	0.028	0.173	0.673

CRVO: Central retinal vein occlusion; LSR-WBV: Low-shear-rate whole blood viscosity; HSR-WBV: High-shear-rate whole blood viscosity; PV: Plasma viscosity; HCT: Hematocrit; AI: Aggregation index; IR: Rigidity index; DI: Deformability index.

Table 2 Comparisons of optic disc structure and VD among CRVO-affected, contralateral, and normal eyes

Parameters	*n*	Vertical C/D	Optic disc area (mm^2)	Optic cup volume (mm^3)	RNFL thickness (μm)	Whole-disc VD (%)	Inside-disc VD (%)	Peripapillary VD (%)
CRVO-affected eyes	60	0.168±0.220	2.182±0.594	0.0257±0.0469	155.0±49.5	42.47±6.32	42.23±5.40	43.53±8.13
Contralateral eyes	60	0.276±0.206	2.095±0.365	0.0460±0.0566	114.0±12.0	49.93±2.65	49.62±5.14	52.67±3.17
Normal eyes	60	0.270±0.145	2.095±0.521	0.0517±0.0695	113.1±14.0	49.06±2.72	51.48±4.35	52.07±2.83
P_1		0.006	0.335	0.034	0.000	0.000	0.000	0.000
P_2		0.003	0.398	0.018	0.000	0.000	0.000	0.000
P_3		0.862	0.994	0.623	0.691	0.080	0.034	0.273

P_1: Comparisons between CRVO and unaffected eyes; P_2: Comparisons between CRVO and normal eyes; P_3: Comparisons between unaffected and normal eyes. C/D: Cup-to-disc; VD: Vessel density; RNFL: Retinal nerve fiber layer; CRVO: Central retinal vein occlusion.

Table 3 Comparison between before and after the treatment of BCVA and VD of the optic disc and macula in CRVO eyes

Parameters	*n*	BCVA (logMAR)	Whole-disc VD (%)	Intra-disc VD (%)	Peripapillary VD (%)	SCP-VD (%)	DCP-VD (%)	CMT (μm)
Before treatment	60	1.303±0.690	42.47±6.32	42.23±5.40	43.53±8.13	39.32±5.55	39.00±6.68	531.4±220.7
After treatment	60	0.030±0.070	49.94±2.75	48.98±4.94	52.65±3.36	39.00±3.82	38.98±3.80	236.3±13.6
P		0.000	0.000	0.000	0.000	0.386	0.581	0.000

CRVO: Central retinal vein occlusion; BCVA: Best-corrected visual acuity; VD: Vessel density; CMT: Central macular thickness; SCP/DCP: Superficial/deep capillary plexus.

retinal nerve fiber layer (RNFL) compared to both unaffected contralateral eyes and healthy controls (all $P<0.05$). Contralateral eyes showed nonsignificant decreases in vertical C/D and cup volume versus controls ($P>0.05$). Optic disc VD was markedly diminished in CRVO-affected eyes relative to contralateral and normal eyes ($P<0.05$). Notably, intra-disc VD in contralateral eyes was significantly lower than in healthy controls ($P<0.05$; Table 2).

Predictors of Visual Morbidity BCVA logMAR correlated inversely with whole-disc VD (r=-0.276, P=0.033), intra-disc VD (r=-0.342, P=0.009), and peripapillary VD (r=-0.335, P=0.007), with intra-disc VD demonstrating the strongest association, but no significant associations observed for other vascular parameters, including SCP-VD, DCP-VD, CMT or all the seven hemorheological parameters (Figure 1).

Therapeutic Outcomes Post-ranibizumab Following three monthly ranibizumab injections, edema of both optic disc and macula was relieved obviously. VD in optic disc increased but didn't in macula (Figures 2 and 3).

Significant improvements were observed in BCVA ($P<0.05$), whole-disc VD ($P<0.05$), intra-disc VD ($P<0.05$), peripapillary VD ($P<0.05$), and CMT ($P<0.05$). SCP-VD and DCP-VD densities showed nonsignificant downward trends ($P>0.05$; Table 3).

Determinants of Visual Recovery BCVA improvement correlated positively with changes of whole-disc VD (r=0.342, P=0.008) and intra-disc VD (r=0.396, P=0.002), with no significant associations observed for other vascular parameters changes, including peripaillary VD, SCP-VD, DCP-VD or CMT.

DISCUSSION

Hemorheological Abnormalities in CRVO While the precise pathogenesis of CRVO remains incompletely understood, thrombosis has been strongly implicated as a critical contributing factor[5-6]. Histopathological evidence from Green *et al*'s[7] landmark autopsy study of 29 CRVO eyes revealed fresh or recanalized thrombi localized within the lamina cribrosa in all specimens. Niu *et al*[8] considered that some serological parameters levels could predict the outcomes in RVO-ME patients. Our findings aligned with previous reports demonstrating significant elevations in hemorheological parameters, including HCT, WBV, and AI among RVO patients[9-10]. Notably, AI elevation appeared particularly relevant as it directly impacted the pathological cascade of venous occlusion through enhanced erythrocyte aggregation[9]. The marked differences observed in LSR-WBV, HSR-WBV, and AI between CRVO patients and controls suggested a

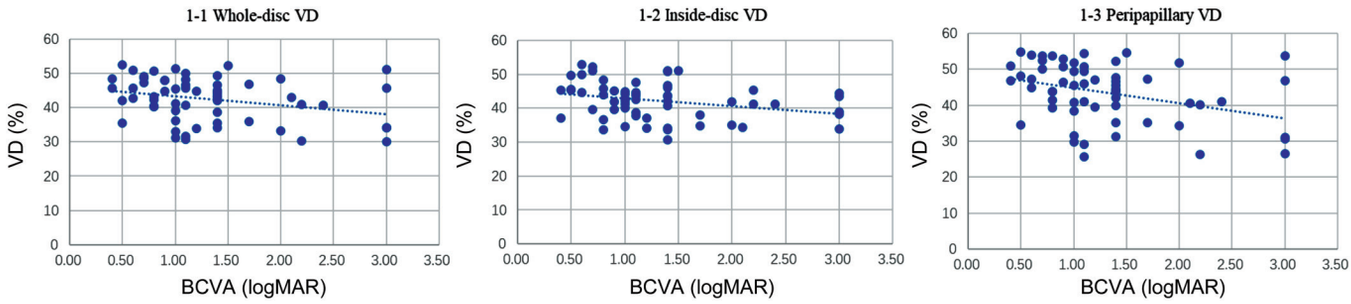

Figure 1 Risk factors of visual impairment in CRVO eyes VD: Vessel density; CRVO: Central retinal vein occlusion.

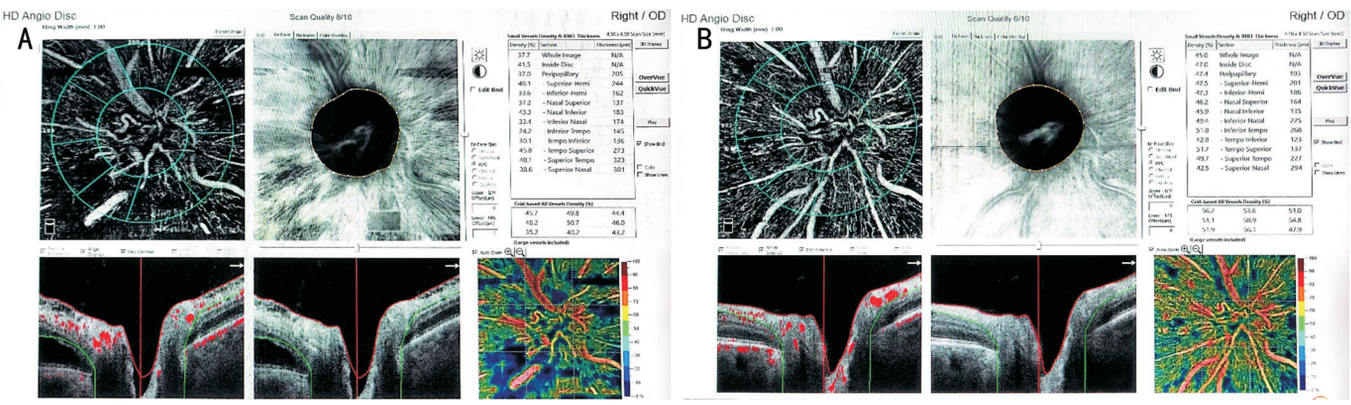

Figure 2 Optic disc perfusion before and after treatment in CRVO-affected eye OCTA images of optic disc before (A) and after (B) the treatment of CRVO-affected eye, showing obvious relief of edema and improvement of perfusion in optic disc. RNFL thickness decreased from 205 μm to 193 μm, and whole-disc VD improved from 37.7% to 45.0%. VD: Vessel density; CRVO: Central retinal vein occlusion; RNFL: Retinal nerve fiber layer; OCTA: Optical coherence tomography angiology.

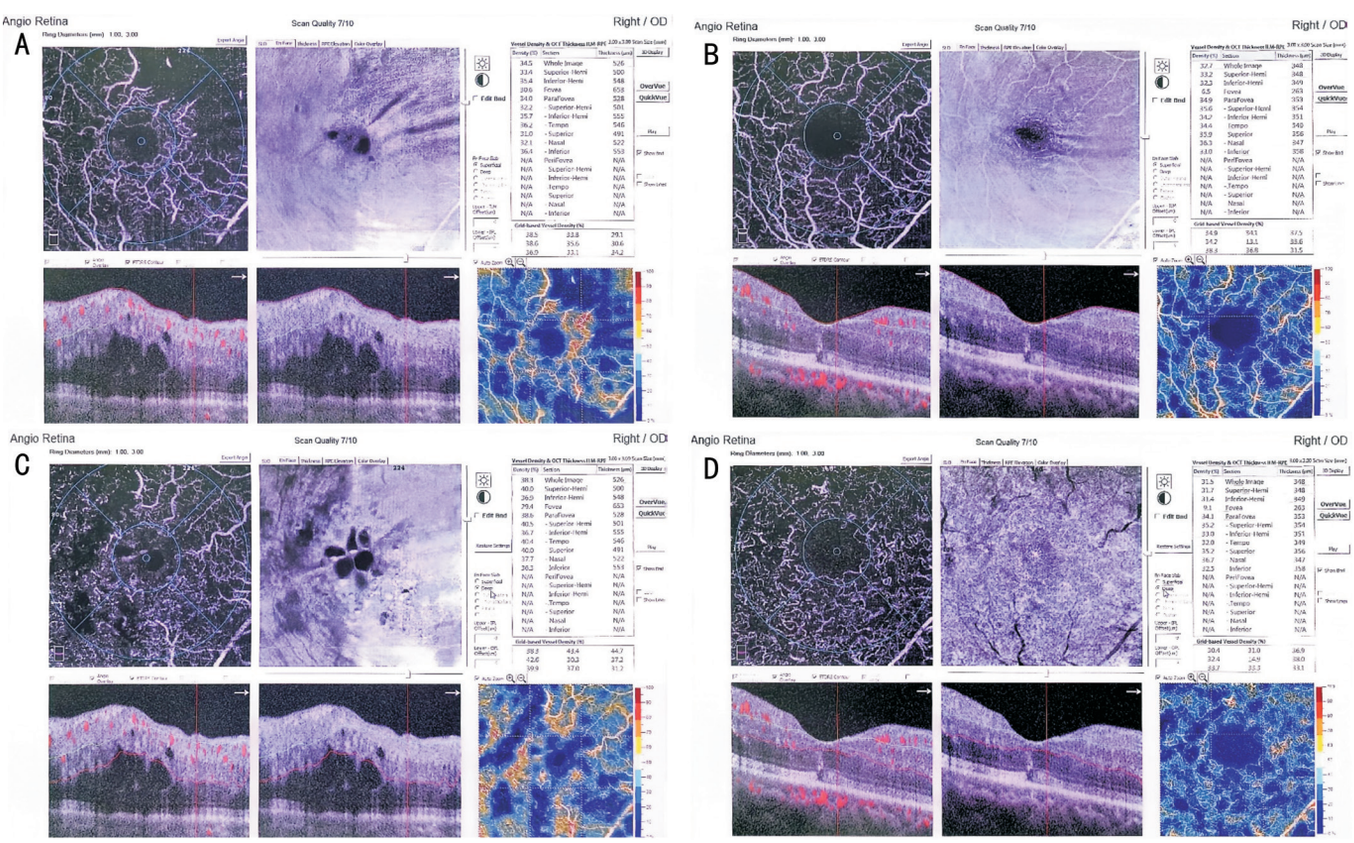

Figure 3 Macular perfusion before and after treatment in CRVO-affected eye OCTA images of macula before (A for SCP, C for DCP) and after (B for SCP, D for DCP) the treatment of CRVO-affected eye. Impressive relief of macular edema was found after the treatment, with CMT decreased from 526 μm to 348 μm. However, macular perfusion was not improved. Macular SCP-VD dropped from 34.5% to 32.7%, and macular DCP-VD dropped from 38.3% to 31.5%. OCTA: Optical coherence tomography angiology; VD: Vessel density; CRVO: Central retinal vein occlusion; CMT: Central macular thickness; SCP/DCP: Superficial/deep capillary plexus.

prothrombotic hematological profile characterized by increased blood viscosity and impaired microcirculatory flow.

Structural Predisposition of the Optic Disc Our data revealed significantly smaller C/D and reduced cup volumes in both affected and unaffected eyes of CRVO patients compared to normal controls, supporting Lei *et al*'s[11] hypothesis of a "high-risk disc" morphology defined as C/D≤0.2. This anatomical configuration might predispose to venous compression, particularly given the established correlation between optic disc size and retinal vessel diameters[12]. Longo *et al*'s[13] observation of disc size reduction in 25% of CRVO cases further supported the mechanical theory of CRVO pathogenesis, where confined scleral outlet spaces might exacerbate venous compression under elevated lamina cribrosa pressure. These collective findings suggested that inherent disc morphology constitutes an important anatomical risk factor for CRVO development.

Optic Disc Perfusion as a Novel Biomarker Contrary to conventional understanding of macular dominance in visual acuity determination[14-15], our analysis revealed stronger correlations between BCVA and optic disc perfusion parameters than with macular metrics. This parallels recent findings in diabetic retinopathy[16], suggesting a broader paradigm shift in our understanding of posterior pole perfusion-viability relationships. We identified that the at the baseline level, BCVA was correlated with intra-disc VD; three months after ranibizumab injection, the improvement of BCVA was also correlated with intra-disc VD. These findings indicated that intra-disc VD may be an independent predictor for visual improvement with a strong correlation to both baseline BCVA and post-treatment visual acuity. While we observed a significant reduction in CMT after ranibizumab treatment, this parameter was not selected as a primary biomarker because no significant correlation is found neither at baseline nor after the treatment. In fact, CMT reflects structural rather than functional changes, and VD provides a direct measurement of microvascular perfusion, which may be better correlated with visual function and long-term outcomes in CRVO. To our knowledge, this is the first report of the association between intra-disc VD dynamics with visual prognosis in CRVO, positioning it as a promising biomarker for therapeutic monitoring.

Differential Vascular Effects of Anti-VEGF Therapy Three consecutive monthly ranibizumab injections produced divergent vascular responses: while disc VD increased significantly, we observed paradoxical reductions in both macular SCP-VD and DCP-VD. Wang *et al*[17] conducted a retrospective and observational study with 50 RVO patients and also found SCP-VD reduced in CRVO eyes after intravitreal ranibizumab injections. These findings aligned with some reports in the literature[18-19], especially with Suzuki *et al*'s[20] documentation of progressive SCP deterioration following sustained treatment, yet contrast with Zhou *et al*'s[21] report of macular DCP-VD improvement post-anti-VEGF therapy. Mechanistically, we proposed that transient intraocular pressure spikes during injection (peaking at about 50 mm Hg)[22] induce ischemic injury to macular microvasculature through two mechanisms: 1) acute hypoperfusion preferentially affecting terminal vessels in the macula, 2) cumulative damage from repeated injections that overwhelms vascular repair capacity. This pressure-induced injury hypothesis was supported by the observed correlation between injection frequency and macular VD decline.

Regarding the macular VD, although there was a declining tendency of macular VD without reaching statistical significance before and after ranibizumab injections, their potential clinical relevance should not be disregarded. Even modest reductions in macular perfusion may contribute to subclinical dysfunction or delayed visual recovery, especially in patients with pre-existing macular ischemia or borderline perfusion status. As there is a lack of longitudinal studies with large researches about the influence of ranibizumab on optic disc and macular perfusion at the same time, we just draw a conclusion on our study and the underlying mechanism still remain unknown. Sample sizes and extended follow-up are warranted to determine whether these trends in macular VD decline carry prognostic value.

In the present study, we did not analyze the comparison between a fixed 3-month injection regimen and alternative approaches such as a single injection followed by *pro re nata* (PRN) dosing. The selected uniform 3-time loading protocol was based on the guideline of European Society of Retina Specialists (EURETINA), but also satisfied the clinical need to minimize confounding treatment variability in this initial investigation of VD change[23]. In fact, the 90-day investigation period is far from enough, which could possibly impact on the conclusion, and we believe that the macular VD decreases might become significant with longer follow-up. Future studies with larger subjects with longer follow-up are warranted to directly compare fixed versus individualized anti-VEGF strategies with both macular and optic disc vascular outcomes.

The essential role of edema resolution of anti-VEGF agents in CRVO has been largely proven, however, our study found that anti-VEGF therapy, such as ranibizumab may induce complex vascular remodeling effects on optic disc and macula beyond mere edema resolution. Recognizing the comprehensive effects of anti-VEGF therapy could help set the optimal strategy, aiming at balancing edema remission and perfusion preservation.

In conclusion, this study established optic disc perfusion parameters, particularly intra-disc VD, as superior predictors

of visual outcomes in CRVO compared to traditional macular metrics. While ranibizumab effectively improved disc perfusion, its potential iatrogenic effects on macular microvasculature warrant careful monitoring, especially in patients requiring multiple injections. The identified hemorheological abnormalities and characteristic disc morphology (reduced C/D ratio and cup volume) provided new insights into CRVO pathophysiology, suggesting multimodal risk stratification incorporating both hematological and anatomical factors. Further validation of intra-disc VD as a therapeutic biomarker through longitudinal studies was recommended.

ACKNOWLEDGEMENTS

Foundations: Central High-Level Traditional Chinese Medicine Hospital Project of Eye Hospital China Academy of Chinese Medical Science (No.GSP5-83; No.GSP4-02; No.GSP5-06); Supported by National Natural Science Foundation of China (General Program; No.82474582).

Conflicts of Interest: Li X, None; **Hao XF,** None; **Xie LK,** None; **Luo JH,** None; **Zhang MJ,** None.

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