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ORIGINAL RESEARCH

Retinal Arterial Vasospasm in Retinal Vein Occlusion and Its Association with Aqueous Humor Endothelin-1

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ABSTRACT

Introduction: To determine the incidence, clinical characteristics, and spatial associations of retinal arterial vasospasm in retinal vein occlusion (RVO), and to explore its relationship with aqueous humor endothelin-1 (ET-1) concentration.

Methods: This retrospective cohort study included 58 eyes with RVO that underwent wide-field fluorescein angiography (FA) within 1 month of presentation. In addition, aqueous humor samples were prospectively collected from a subset of 18 treatment-naïve RVO eyes. Arterial vasospasm was defined as a focal narrowing of the arterial lumen on early-phase FA. Cotton wool spots (CWS) and retinal hemorrhage were evaluated using color fundus photography and electronic medical records. Topographic concordance was assessed using quadrant-based, horizontal, and vertical hemifield classifications. Aqueous humor samples were analyzed for ET-1 concentration using enzyme-linked immunosorbent assay (ELISA).

Results: Arterial vasospasm was identified in 21 eyes (36.2%), including six eyes with central RVO and 15 eyes with branch RVO. Vasospasm was most commonly observed in the superotemporal quadrant and predominantly on second-order arteriolar branches (78.6%). CWS were more frequent in eyes with vasospasm compared with those without (81.0% vs. 54.1%; $p = 0.050$). Significant spatial concordance between vasospasm and CWS was observed in the vertical hemifield ($p = 0.049$), with no concordance observed with retinal hemorrhage location or severity. Exploratory aqueous humor analysis showed higher ET-1 concentrations in eyes with vasospasm (8.37 ± 4.59 vs. 5.74 ± 1.88 pg/mL), although statistical interpretation was limited by the sample size.

Conclusion: Retinal arterial vasospasm is a relatively common but under-recognized feature of RVO. Its association with CWS and higher ET-1

SolAh Han and Chau Thi Ngoc Tran have contributed equally to this study.

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levels suggests localized arterial endothelial dysfunction. Vasospasm may represent an arterial component of RVO pathophysiology and warrants further investigation.

Keywords: Cotton wool spot; Endothelial dysfunction; Endothelin-1; Retinal vein occlusion; Vasospasm

Key Summary Points

Why carry out this study?

Retinal vein occlusion (RVO) produces hypoxic damage and macular edema, but the contribution of arterial involvement to its pathophysiology remains poorly understood.

We investigated whether retinal arterial vasospasm is a measurable clinical feature in RVO and whether it is spatially linked to hypoxic signs and associated with aqueous humor endothelin-1 levels.

What was learned from the study?

Retinal arterial vasospasm was identified in over one-third of RVO eyes, showed topographic concordance with cotton wool spots, and was accompanied by higher aqueous endothelin-1 concentrations.

These findings indicated that arterial vasospasm represents a previously under-recognized component of RVO-related hypoxia, suggesting an endothelin-1-mediated endothelial dysfunction that may influence disease behavior and prognosis.

Recognizing arterial vasospasm may support new mechanistic insights and guide future studies targeting arterial endothelial dysfunction in retinal vascular disease.

INTRODUCTION

Arterial vasospasm is characterized by a transient or sustained narrowing of arterial segments, resulting in a subsequent impairment of downstream blood flow [1]. This localized narrowing can have variable clinical consequences depending on the vascular territory involved [2]. Substantial evidence has demonstrated that cerebral vasospasm following subarachnoid hemorrhage (SAH) is a major contributor to the high rates of mortality and morbidity associated with this condition [3–5]. After SAH, the extravasated blood breaks down, producing free radicals that trigger vascular injury. This activates inflammatory responses involving leukocytes and platelets, leading to the release of inflammatory mediators. Endothelin-1 (ET-1) is a key vasoconstrictor implicated in this microvascular dysregulation. As a result, cerebral arteries undergo phenotypic changes: endothelial cells have impaired nitric oxide and prostacyclin production, while smooth muscle cells activate signaling pathways that enhance contractility and upregulate contractile receptors [6, 7]. Given its profound impact on neurological outcomes, considerable research efforts have been directed toward the treatment and prevention of cerebral vasospasm after SAH [8, 9].

In contrast, much less is known about vasospastic phenomena in the retina. Although retinal arterioles, venules, and capillaries are enveloped by contractile pericytes or smooth muscle cells [10], retinal arterial vasospasm has been described only in limited case reports and small series, typically in association with transient reductions in visual acuity or visual field defects [11–16]. Furthermore, while arterial vasospasm has been reported in relation to central retinal vein occlusion (CRVO) [17] and retinal artery occlusion (RAO) [18], the relationship between these retinal vascular disorders and arterial vasospasm remains unclear, and its role in their pathogenesis or visual prognosis has not yet been systematically evaluated.

To date, no cohort study has systematically evaluated the incidence or clinical characteristics of retinal arterial vasospasm or its relationship with ET-1. The present study is the first to investigate the incidence, clinical features, and associated factors of arterial vasospasm in the context of retinal vein occlusion (RVO) and to demonstrate its potential association with the vasoconstrictive biomarker ET-1.

METHODS

Study Participants

For the investigation of the incidence, clinical characteristics, and associated factors of retinal arterial vasospasm in RVO, the retrospective observational study was conducted in accordance with the tenets of the Declaration of Helsinki and received approval from the Institutional Review Board of Asan Medical Center, Seoul, South Korea (approval number: 2025-1125). Consecutive patients diagnosed with RVO who underwent fluorescein angiography (FA) within 1 month of initial presentation were included.

Exclusion criteria were as follows: (1) less than 12 months of follow-up; (2) history of intraocular surgery other than uncomplicated cataract surgery, ocular laser therapy, or intravitreal injection; (3) presence of other retinal vascular disorders, including age-related macular degeneration, diabetic retinopathy, and uveitis; (4) significant media opacity precluding adequate image analysis.

A general medical assessment and a thorough ophthalmologic examination were performed for all patients. Best-corrected visual acuity (BCVA) was measured at baseline and at 12 months to assess visual outcomes.

Image Acquisition and Analysis

Wide-field FA images (Optos California; Optos PLC, Dunfermline, Scotland, UK) were acquired after informed consent was obtained from all patients. For each patient, the early arteriovenous phase image providing the clearest delineation of the retinal arterial structure was selected for analysis (Fig. 1b, Fig. 2c and d). The presence of arterial vasospasm was independently assessed by two retinal specialists (J.L. and S.H.). Inter-grader agreement for the diagnosis of arterial vasospasm was excellent, with a Cohen's kappa coefficient of 0.92. Arterial vasospasm was defined as a localized constriction of the retinal arterial lumen, consistent with the definition of prior reports [11–13, 15, 17, 18]. Vessel caliber reduction was qualitatively assessed by comparing the focal narrowing with adjacent unaffected segments of the same artery. Vasospasm was defined only when the estimated luminal constriction exceeded approximately 50% relative to the adjacent reference segment. To exclude leukostasis as a differential diagnosis, vasospasm was not considered present if angiographic findings demonstrated intraluminal plugging, vessel wall staining, or late-phase leakage [19]. To minimize the risk of misinterpretation, vasospasm was diagnosed only when both specialists reached unanimous agreement after detailed image evaluation.

Cotton Wool Spots and Vasospasm

The presence of cotton wool spots (CWS) was assessed using data extracted from the electronic medical records (EMR) and wide-field fundus photographs obtained within 2 months of the initial presentation (Figs. 1a and 2a). CWS were defined as whitish-gray, fluffy lesions with indistinct, frayed edges [20]. In eyes with branch retinal vein occlusion (BRVO), the concordance between the location of CWS and arterial vasospasm was evaluated using three classification schemes: (1) quadrant-based analysis, with four quadrants centered on the optic disc (superotemporal [ST], inferotemporal [IT], superonasal [SN] and inferonasal [IN]) [21], (2) horizontal hemifield, classified as nasal (SN and IN) versus temporal (ST and IT), and (3) vertical hemifield, as superior (SN and ST) versus inferior (IT and IN). For study eyes with more than one vasospasm, concordance was considered present only if all vasospasm regions aligned with the CWS locations.

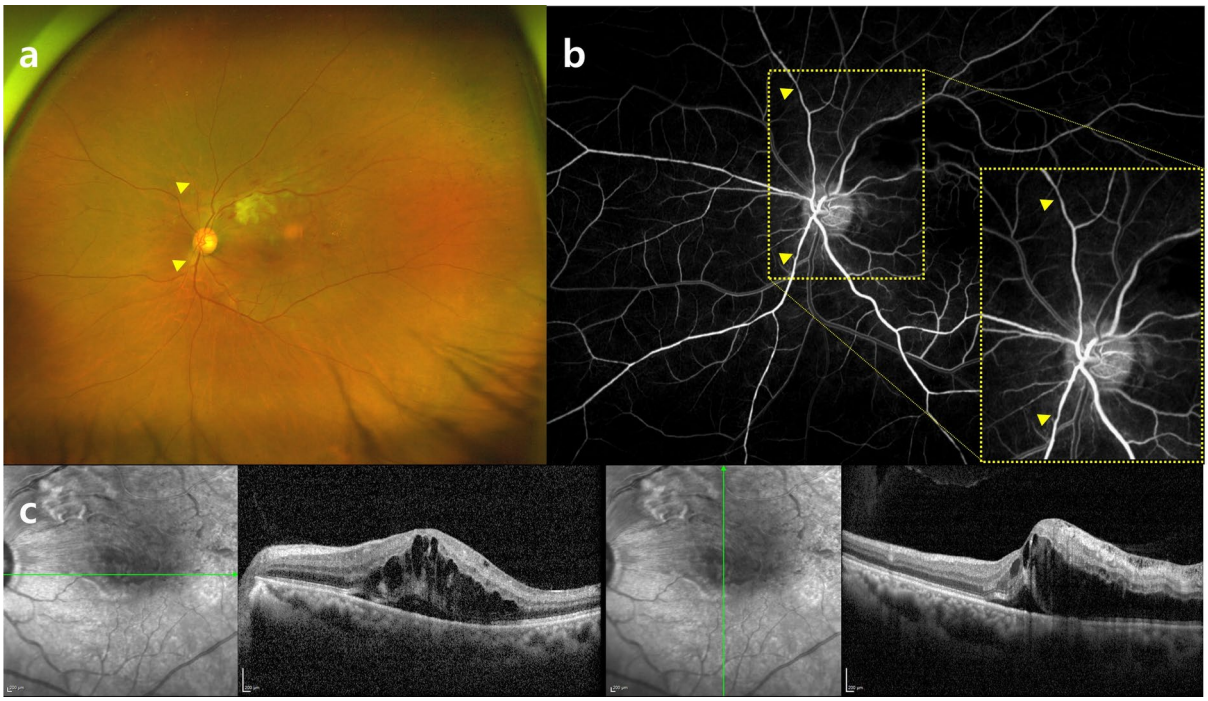

Fig. 1 Multimodal imaging of retinal arterial vasospasm in branch retinal vein occlusion (BRVO). **a** Wide-field color fundus photography of a 57-year-old male with hypertension and dyslipidemia, showing arterial vasospasm (yellow arrows) in an eye with BRVO. **b** Corresponding wide-field fluorescein angiography image at 18 s demonstrating more clearly delineated arterial vasospasm (yellow arrows). **c** Spectral-domain optical coherence tomography (SD-OCT) image of the same patient showing significant macular edema

Retinal Hemorrhage and Vasospasm

The presence of retinal hemorrhage was determined from the EMR and wide-field fundus photographs obtained at the time of FA. In eyes with BRVO, concordance between the location of retinal hemorrhage and arterial vasospasm was analyzed using the same quadrant-based method described for CWS. If more than one vasospasm was present, concordance was defined only when all vasospasm regions matched the retinal hemorrhage locations.

In eyes with CRVO, the severity of retinal hemorrhage was assessed using a modified grading system adapted from a previous report [22]: grade 0 = no hemorrhages; grade 1 = uncertain or questionable hemorrhages; grade 2 = minimal, small or isolated hemorrhages; grade 3 = moderate hemorrhages; grade 4 = extensive hemorrhages. Grading was performed independently by two retinal specialists (J.L. and S.H.), and a final grade was assigned only when both examiners reached unanimous agreement.

Aqueous Humor Collection

Aqueous humor (AH) samples were obtained from a subset of patients enrolled in a separate prospective observational study. Treatment-naïve patients aged over 40 years with RVO who were scheduled to undergo standard-of-care intravitreal injections were recruited at the Department of Ophthalmology, Asan Medical Center, between May 2025 and October 2025. The study did not involve any investigational intervention or deviation from routine clinical management. Ethical approval was obtained

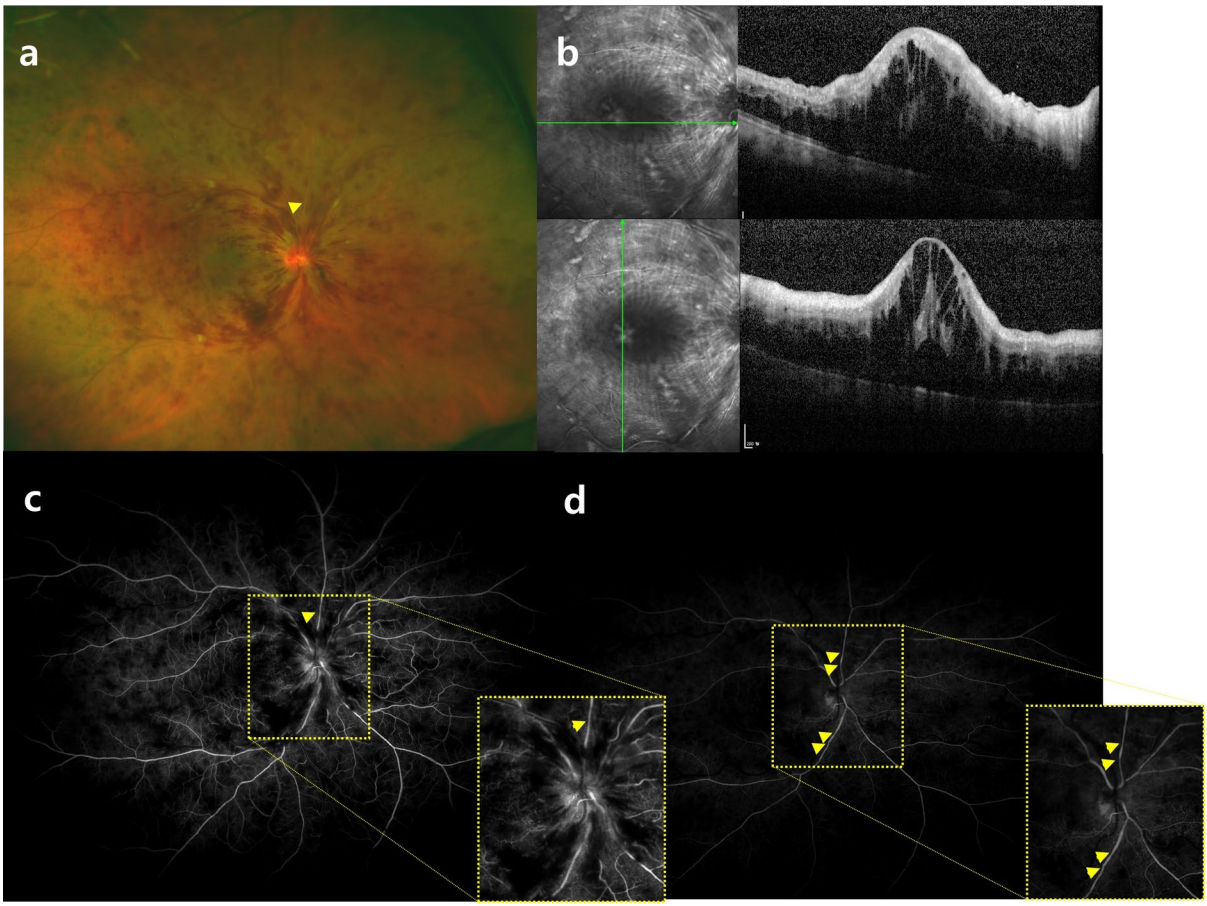

Fig. 2 Progression of retinal arterial vasospasm in central retinal vein occlusion (CRVO): baseline and follow-up imaging. **a** Wide-field color fundus photography of a 59-year-old patient with CRVO and hypertension showing arterial vasospasm (yellow arrow). **b** Spectral-domain optical coherence tomography (SD-OCT) image of the same patient demonstrating macular edema. **c** Wide-field fluorescein angiography (FA) image at 22 s demonstrating more clearly delineated arterial vasospasm (yellow arrows). **d** Wide-field FA image at 18 s obtained 5 months after four intravitreal injections (two bevacizumab [Avastin®; Genentech, Inc., San Francisco, CA] and two dexamethasone implants [Ozurdex®; Allergan Inc., Irvine, CA]), showing progression of arterial vasospasm (yellow arrows)

from the Institutional Review Board of Asan Medical Center (approval number 2025-0575), and written informed consent was secured from all participants or their legal guardians prior to enrollment. All patients included in this prospective cohort underwent FA within 1 month of initial presentation, and retinal arterial vasospasm was assessed using the same predefined criteria applied in the retrospective cohort. Patients were excluded if they had a history of intraocular surgery other than uncomplicated cataract surgery, ocular laser therapy, or prior intravitreal injections, or if they had significant retinal pathology other than RVO. AH samples (0.1 mL) were collected as ancillary biospecimens immediately before intravitreal anti-vascular endothelial growth factor (VEGF) injection, using a standardized aseptic technique, without influencing treatment decisions or clinical outcomes. All samples were obtained by a single retinal specialist (J.L.). A total of 18 AH samples were collected for biochemical analysis.

Endothelin-1 Level Assessment

Immediately after collection, AH samples were stored at –55 °C until analysis. Frozen samples were thawed on ice for approximately 1 h to allow gradual and uniform thawing. Each sample was then clarified by filtration through a 4-mm regenerated cellulose (RC) membrane syringe filter (Corning, #431212; USA) and transferred into sterile microcentrifuge tubes (Eppendorf, #022431081; Germany). Filtered samples were processed for ET-1 quantification using a commercial enzyme-linked immunosorbent assay (ELISA) kit (R&D Systems, #DET100; MN, USA), following the manufacturer's instructions. Prior to plate loading, each sample was diluted 1:3 with the provided diluent. A total volume of 75 µL of diluted sample was added to each well, and all assays were performed in duplicate. Final ET-1 concentrations were calculated by multiplying the measured values by a factor of 3 to account for the dilution, yielding the ET-1 levels in the original AH sample.

Statistical Analysis

IBM SPSS Statistics software version 21.0 (IBM Corporation, Armonk, NY, USA) was used for all statistical analyses. Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables as counts (*n*) and percentages (%). Comparisons of continuous variables were performed using the Mann–Whitney *U* test, and categorical variables using Fisher's exact test. Exact binomial tests were performed to assess the concordance of lesion location between vasospasm and CWS, as well as between vasospasm and retinal hemorrhage in eyes with BRVO. A two-sided *p*-value of < 0.05 was considered statistically significant.

RESULTS

A total of 58 patients with RVO were included in this study, of whom 21 (36.2%) demonstrated arterial vasospasm (Table 1). There were no significant differences in the baseline demographics between the vasospasm and no-vasospasm groups. The mean age was 60.9 ± 10.6 years in the vasospasm group and 61.8 ± 10.9 years in the no-vasospasm group ($p = 0.704$). The proportion of male patients was 23.8% (5/21) and 48.6% (18/37), respectively ($p = 0.094$). Hypertension was the most prevalent comorbidity, followed by dyslipidemia, diabetes mellitus, cardiovascular disease, and cerebrovascular disease, with no significant differences between the groups.

Table 1 Demographics and clinical characteristics of patients with and without arterial vasospasm in retinal vein occlusion (RVO)

	Total RVO ($n = 58$)	Vasospasm ($n = 21$)	No vasospasm ($n = 37$)	*p*-value[a]
Age (mean ± SD)	61.5 ± 10.7	60.9 ± 10.6	61.8 ± 10.9	0.704
Gender (male)	23 (39.7%)	5 (23.8%)	18 (48.6%)	0.094
Hypertension (%)	33 (56.9%)	12 (57.1%)	21 (56.8%)	1.000
Dyslipidemia (%)	22 (37.9%)	8 (38.1%)	14 (37.8%)	1.000
Diabetes mellitus (%)	9 (15.5%)	3 (14.3%)	6 (16.2%)	1.000
Cerebrovascular disease (%)	2 (3.4%)	0	2 (5.4%)	0.530
Cardiovascular disease (%)	5 (8.6%)	1 (4.8%)	4 (10.8%)	0.644
Change in LogMAR BCVA	−0.30 ± 0.65	−0.39 ± 0.69	−0.24 ± 0.63	0.227
CRVO (%)	24 (41.4%)	6 (28.6%)	18 (48.6%)	0.171

[a]Continuous variables were compared using the Mann–Whitney U test, and categorical variables using Fisher's exact test

Changes in BCVA from baseline to 12 months were not statistically different between groups (–0.39 ± 0.69 vs. –0.24 ± 0.63; $p = 0.227$).

Among the study population, 24 eyes (41.4%) had CRVO, and six (28.6%) of these presented with vasospasm (Table 1 and Fig. 2). Regarding the topographic distribution of vasospasm, the ST quadrant was most frequently involved (10/28, 35.7%), followed by the IT (7/28, 25.0%), SN (6/28, 21.4%), and IN (5/28, 17.9%) quadrants (Fig. 3). In eyes with multiple vasospasms, all sites were included in the analysis; seven eyes (33.3%) exhibited more than one vasospasm. Most vasospasms (78.6%) were located on second-order arteriolar branches, while the remainder involved third-order or lower branches of arterioles. Notably, no vasospasms were identified on the first-order branches arising directly from the central retinal artery.

CWS were observed in 37 eyes (63.8%), including 17 eyes (81.0%) in the vasospasm group and 20 eyes (54.1%) in the no-vasospasm group (Table 2). The association between the presence of vasospasm and CWS approached statistical significance ($p = 0.050$). Concordance between CWS and vasospasm locations

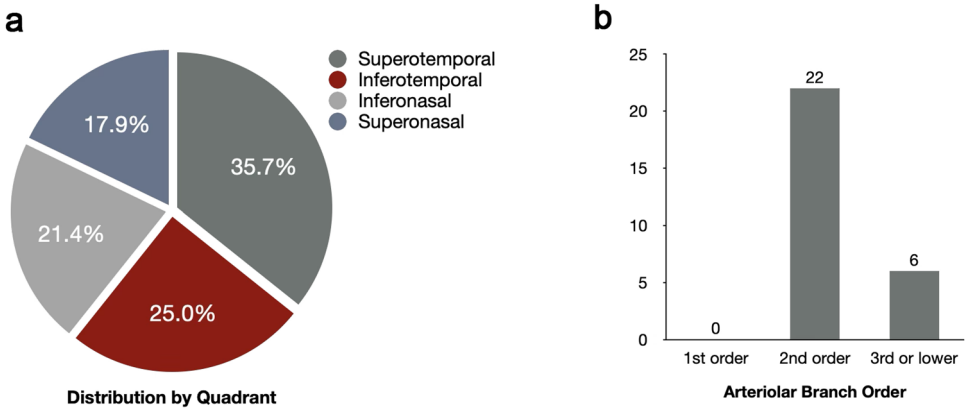

Fig. 3 Distribution of retinal arterial vasospasm in retinal vein occlusion (RVO). **a** Distribution of retinal arterial vasospasm by quadrant. **b** Distribution of retinal arterial vasospasm by arteriolar branch order. In eyes with multiple vasospasms, all locations were included in the analysis; seven eyes demonstrated more than one vasospasm

Table 2 Prevalence of cotton wool spots (CWS) and concordance of their location with arterial vasospasm in retinal vein occlusion

	Vasospasm ($n = 21$)	No vasospasm ($n = 37$)	p-value[a]
Prevalence of CWS (%)	17 (81.0%)	20 (54.1%)	**0.050**
Concordance between the location of CWS and vasospasm ($n = 17$)			
	Concordant	**Discordant**	p-value[b]
Quadrant-based[c]	12 (70.6%)	5 (29.4%)	0.143
Horizontal hemifield[d]	12 (70.6%)	5 (29.4%)	0.143
Vertical hemifield[e]	13 (76.5%)	4 (23.5%)	**0.049**

[a]Fisher's exact test; values approaching statistical significance are shown in bold

[b] Exact binomial test: values significantly higher than 50% are shown in bold

[c]Quadrant-based analysis: superotemporal (ST), inferotemporal (IT), superonasal (SN), inferonasal (IN)

[d]Horizontal hemifield: nasal (SN + IN) vs. temporal (ST + IT)

[e]Vertical hemifield: superior (ST + SN) vs. inferior (IT + IN)

was analyzed using quadrant-based, horizontal hemifield, and vertical hemifield classifications. Quadrant-based and horizontal hemifield analyses showed no significant concordance; however, vertical hemifield analysis (superior vs. inferior) revealed a significant concordance between CWS and vasospasm locations ($p = 0.049$).

In eyes with BRVO, concordance between the location of retinal hemorrhage and vasospasm was assessed using the classification applied for CWS (Table 3 and Fig. 1). No significant concordance was observed in any sub-analysis. In CRVO eyes, the relationship between retinal hemorrhage severity and vasospasm was also evaluated. Sixteen patients (66.7%) had retinal hemorrhage graded 3 or worse, of whom four also exhibited vasospasm; this association was not statistically significant.

A total of 18 AH samples were obtained from patients with RVO for ET-1 analysis (Fig. 4). Among these, nine eyes (50%) demonstrated retinal arterial vasospasm, of which five (55.6%) had CRVO. As shown in Table 4, the mean ET-1 concentration was higher in the vasospasm group (8.37 ± 4.59 pg/mL) than in the no-vasospasm group (5.74 ± 1.88 pg/mL). Formal statistical testing was not performed due to the limited sample size; however, the observed trend suggests a potential association between elevated ET-1 levels and the presence of retinal arterial vasospasm.

DISCUSSION

In this study, we demonstrated that arterial vasospasm occurred in over one-third of eyes with RVO and was most commonly located on second-order arteriolar branches. The presence of vasospasm was associated with a higher prevalence of CWS, with significant topographic concordance noted in the vertical hemifield. These findings provide novel insight into changes in the arterial circulation associated with RVO, a condition typically regarded as a venous disorder, and suggest a potential pathophysiological link between vasospasm and retinal hypoxic injury that has not been systematically examined before.

CWS represent acute retinal vascular injury and are histopathologically characterized by localized accumulations of axoplasmic debris within ganglion cell axons following interruption of axoplasmic flow after arteriolar occlusion [23]. Ashton and Harry suggested that arteriolar spasm may precipitate arteriolar occlusion; however, they also noted that CWS can occur

Table 3 Retinal hemorrhage and arterial vasospasm in retinal vein occlusion (RVO)

Concordance between the location of retinal hemorrhage and vasospasm in branch RVO ($n = 15$)			
	Concordant	**Discordant**	***p*-value[a]**
Quadrant-based[c]	9 (60.0%)	6 (40.0%)	0.607
Horizontal hemifield[d]	11 (73.3%)	4 (26.7%)	0.118
Vertical hemifield[e]	11 (73.3%)	4 (26.7%)	0.118

Correlation of retinal hemorrhage severity and arterial vasospasm in central RVO				
	CRVO ($n = 24$)	**Vasospasm ($n = 6$)**	**No vasospasm ($n = 18$)**	***p*-value[b]**
Retinal hemorrhage grading ≥ 3	16 (66.7%)	4 (66.7%)	12 (66.7%)	1.000

[a]Exact binomial test

[b]Fisher's exact test

[c]Quadrant-based analysis: superotemporal (ST), inferotemporal (IT), superonasal (SN), inferonasal (IN)

[d]Horizontal hemifield: nasal (SN + IN) vs. temporal (ST + IT)

[e]Vertical hemifield: superior (ST + SN) vs. inferior (IT + IN)

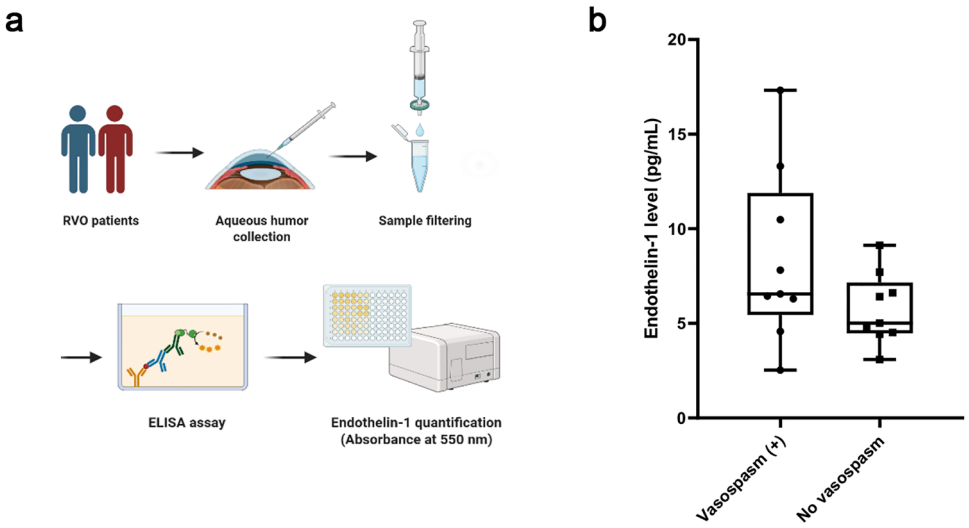

Fig. 4 Workflow for aqueous endothelin-1 (ET-1) measurement and comparison between vasospasm and no-vasospasm eyes. **a** Schematic workflow illustrating the process of ET-1 quantification in aqueous humor from patients with retinal vein occlusion (RVO) using an ELISA-based assay. **b** Comparison of ET-1 levels in the vasospasm and no-vasospasm groups

Table 4 Endothelin-1 (ET-1) levels in patients with and without retinal arterial vasospasm

	Vasospasm ($n=9$)	No vasospasm ($n=9$)
Age (mean ± SD)	68.56 ± 9.74	60.44 ± 7.75
Male (%)	3 (33.3%)	5 (55.6%)
CRVO (%)	5 (55.6%)	3 (33.3%)
ET-1 (pg/mL) (mean ± SD)	8.37 ± 4.59	5.74 ± 1.88

independently of occlusion, arising from altered endothelial permeability in arterial hypertension [24]. This implies that vasospasm and CWS may share a common underlying substrate of circulatory dysfunction rather than a strictly causal relationship. Our observation of significant spatial concordance supports this concept, suggesting that both lesions may reflect endothelial dysfunction within the same vascular territory.

Endothelial injury in RVO may result from several mechanisms, including hemodynamic stress, inflammatory cytokines, and systemic vascular risk factors [25]. At arteriovenous crossings, the retinal vein and artery share a common adventitial sheath. Atherosclerotic changes in the artery can compress the vein, producing turbulent flow and shear stress that elevate venous pressure and damage the venous endothelium. Hypoxia further induces upregulation of inflammatory mediators, such as vascular endothelial growth factor (VEGF), interleukin-6 (IL-6) and IL-8, and intercellular adhesion molecule 1 (ICAM-1), which perpetuate vascular permeability and endothelial dysfunction [26]. Although systemic comorbidities such as hypertension, diabetes mellitus, and smoking are known contributors to chronic endothelial damage and remodeling [27, 28], no significant differences in comorbidities were observed in our cohort, possibly due to the limited sample size.

The role of endothelial injury in cerebral vasospasm has been extensively studied in SAH, where disruption of nitric oxide (NO) production by endothelial NO synthase is a

key mechanism [3, 6]. Similar processes may occur in the retina: reduced NO bioavailability in BRVO has been reported to contribute to arteriolar constriction in areas of non-perfusion [29]. In this animal model, such vasoconstriction aggravated hypoxia and neuronal swelling, resulting in irreversible inner retinal damage. Our findings are consistent with these reports, supporting a potential role for impaired NO signaling in retinal vasospasm.

Paques et al. analyzed retinal and choroidal circulation in patients with recent-onset CRVO using indocyanine green videoangiography and demonstrated evidence of retinal arterial dysfunction, including delayed and pulsatile arterial filling [30]. Notably, their observations suggest that impaired arterial flow preceded the development of macular edema in some patients, highlighting a primary arterial component in the early pathophysiology of RVO. Although videoangiographic assessment was not performed in the present study due to the lack of appropriate instrumentation, our findings are consistent with this concept, supporting the presence of early arterial endothelial dysfunction and vasomotor instability in RVO. Together, these observations suggest that retinal arterial vasospasm may reflect underlying endothelial dysfunction, and its potential relationship with disease progression warrants further investigation. Other vasoactive mediators may also contribute. Elevated ET-1 levels have been reported in the AH of patients with RVO and were reduced following intravitreal bevacizumab injection [31]. ET-1 is a potent vasoconstrictor acting on smooth muscle and endothelial cell receptors [3], and experimental studies have shown that intravitreal and systemic administration of ET-1 reduces retinal arterial caliber and impairs retinal function [32–34]. In the present study, we conducted an additional prospective exploratory analysis of AH samples to quantify ET-1 concentrations. Although the sample size was limited and formal statistical testing was not performed, the mean ET-1 level was higher in eyes exhibiting vasospasm than in those without vasospasm. This preliminary observation aligns with the known biological role of ET-1 as a potent vasoconstrictive mediator and suggests that ET-1 may contribute to the arterial changes observed in RVO. Larger, adequately powered studies are needed to confirm this association and to further elucidate the mechanistic involvement of ET-1 in retinal arterial vasospasm.

Similarly, monocyte chemoattractant protein (MCP-1), a chemokine upregulated by ischemia and oxidative stress, has been implicated in cerebral vasospasm following SAH [35–37]. In vitreous samples from untreated CRVO eyes, MCP-1 levels were significantly elevated and correlated with structural damage to the outer retina and subfoveal fluid accumulation [38]. Together, these findings suggest that both ET-1 and MCP-1 may play a role in promoting arterial vasospasm in RVO through exacerbation of vascular inflammation and endothelial dysfunction. Endothelial injury in RVO has also been linked to the development of telangiectatic capillaries (TelCaps), which have been reported to be associated with disease recurrence and vascular instability [39]. Although the presence or progression of TelCaps was not specifically evaluated in the present study, these observations suggest that retinal arterial vasospasm and TelCap formation may represent related manifestations of underlying endothelial dysfunction in RVO. Future studies investigating the relationship between vasospasm and TelCap development may provide further insight into the vascular remodeling processes underlying RVO. The ST quadrant was the most frequent site of vasospasm in our study, paralleling the predilection of BRVO for this region [28]. Prior studies have attributed the higher frequency of BRVO in the ST quadrant to the greater number of arteriovenous crossings and the anatomical tendency for arterioles to cross anterior to veins in this quadrant [28, 40]. The predominance of vasospasm in the ST quadrant may reflect its higher density of arteriovenous crossings and greater susceptibility to hemodynamic shear stress, making this region intrinsically more vulnerable to microvascular dysregulation in RVO. Although change in visual acuity over 12 months did not differ significantly between eyes with and without vasospasm, it is possible that vasospasm at specific locations may affect visual function in ways not fully captured by visual acuity measurements alone. In particular, localized effects on the visual field may be more relevant, highlighting the

need for future studies incorporating perimetric assessment to better characterize the functional impact of vasospasm.

Vasospasm was not observed in first-order arteriolar branches, which may be attributable to the unique structure of retinal arteries. Unlike arteries of similar caliber in other organs, retinal arteries near the optic disc have five to seven layers of smooth muscle cells, decreasing to two or three layers near the equator and further to one or two in the periphery [41]. This structural stability likely confers greater resistance to vasospasm in larger arteries, while smaller branches remain more vulnerable to local hemodynamic stress and endothelial dysregulation. In addition, ET-1 and other endothelium-derived vasoactive mediators exert a greater effect on smaller-caliber vessels, consistent with the distribution of vasospasm observed in our study [34, 42].

The significant concordance between CWS and vasospasm in the vertical hemifield may reflect the natural organization of the retinal vasculature. The superior and inferior hemiretina are supplied by distinct vascular arcades, which rarely cross the horizontal raphe, resulting in a relatively compartmentalized blood supply and venous drainage [43]. This anatomic arrangement likely underlies the stronger spatial association observed in the vertical analysis compared with quadrant-based or horizontal divisions. We did not find a significant relationship between hemorrhage severity and vasospasm in eyes with CRVO. This may be due in part to the small sample size, but also reflects the fact that retinal hemorrhage primarily indicates venous stasis rather than the degree of hypoxia. Because capillary obliteration progresses over several weeks, a prospective design with serial FA imaging may be necessary to clarify the relationship between hypoxia and vasospasm [44]. Although causality cannot be established based on current data, the presence of retinal arterial vasospasm may represent an early indicator of localized hypoxia, potentially preceding FA-detectable nonperfusion or optical coherence tomography (OCT)-based perfusion abnormalities. Thus, vasospasm may warrant closer clinical surveillance as a marker of possible hypoxic progression.

This study has several limitations. The relatively small sample size limited statistical power, and the 12-month follow-up period may not fully capture the long-term visual consequences of retinal vasospasm. In addition, the study did not include other imaging modalities such as OCT or videoangiography. Because our analysis was based on static wide-field fluorescein angiographic images, transient vasospastic events may have been missed; continuous videoangiography could offer improved temporal resolution for evaluating dynamic arterial changes and provide complementary structural or functional information regarding hypoxia-related retinal findings. The retrospective, cross-sectional design precludes the establishment of potential causality between vasospasm and RVO. Future larger, prospective studies with longer follow-up and additional biochemical analyses are needed to clarify whether vasospasm predicts arterial occlusion, recurrent RVO, visual outcomes, or treatment response.

Future investigations incorporating serial FA will be essential to determine whether retinal arterial vasospasm precedes or predicts subsequent hypoxic progression and to define its impact on clinical outcomes. In addition, functional assessments such as automated perimetry may help clarify whether localized vasospasm produces corresponding visual field deficits that are not reflected in visual acuity measures, thereby providing a more comprehensive understanding of its clinical significance.

CONCLUSION

To our knowledge, this cohort study provides one of the first systematic evaluations of the incidence and distribution of retinal arterial vasospasm in RVO and its association with CWS. Our study demonstrates that arterial vasospasm is a relatively frequent finding in eyes with RVO and is associated with CWS, particularly within the superior–inferior hemifield distribution. In addition, exploratory analysis of aqueous humor analysis suggests a potential association between elevated ET-1 levels and retinal arterial vasospasm. Together, these

findings suggest that vasospasm reflects underlying arterial endothelial dysfunction rather than an isolated vascular event. Early detection of such arterial circulatory abnormalities may provide opportunities to mitigate hypoxic sequelae in RVO. Further prospective investigations are warranted to clarify the pathophysiological mechanisms, prognostic significance, and therapeutic implications of retinal arterial vasospasm in RVO.

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Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. SolAh Han, Chau Thi Ngoc Tran, Junyeop Lee, Young Hee Yoon, June-Gone Kim, Yoon Jeon Kim and Jee Myung Yang declare no competing interests.

Ethics/Ethical Approval. This study included both a retrospective observational component and a separate prospective clinical component. The retrospective analysis was conducted in accordance with the tenets of the Declaration of Helsinki and received approval from the Institutional Review Board of Asan Medical Center, Seoul, South Korea (IRB No. 2025-1125). For the prospective arm, participants were enrolled at the Department of Ophthalmology, Asan Medical Center, as part of an independent study approved by the Institutional Review Board (IRB No. 2025-0575). Written informed consent was obtained from all participants or their legal guardians prior to enrollment. No identifying personal information is included in this manuscript.

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