

Ultra Wide-Field Angiographic Characteristics of Branch Retinal and Hemicentral Retinal Vein Occlusion

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Purpose: To study the peripheral angiographic features of branch retinal vein occlusions (BRVO) and hemicentral retinal vein occlusions (HRVO) and explore associations with macular edema and neovascularization.

Design: Retrospective observational case series.

Participants: Seventy-eight outpatients.

Methods: An imaging database of angiograms performed at a single academic institution was searched for patients with a diagnosis of BRVO or HRVO. Images were graded for the presence of untreated nonperfusion (areas without evidence of laser photocoagulation), late peripheral vascular leakage (LPVL), neovascularization, macular edema, and prior laser treatment. Optical coherence tomography images were reviewed for all patients to confirm the presence of macular thickening and to exclude eyes with vitreomacular traction.

Main Outcome Measures: Angiographic evidence of nonperfusion, neovascularization, macular edema, LPVL, and prior laser treatment.

Results: Angiograms from 80 eyes of 78 patients were analyzed with a diagnosis of BRVO (86%) or HRVO (14%). Angiographic macular edema (80%), untreated nonperfusion (82%), neovascularization (21%), and LPVL (58%) were observed. Untreated nonperfusion at any location was significantly associated with macular edema ($P = 0.043$). Untreated nonperfusion anterior to the globe equator was significantly associated with macular edema ($P = 0.007$). Untreated nonperfusion was significantly associated with the presence of neovascularization ($P = 0.033$). Late peripheral vascular leakage was not associated with other angiographic or clinical findings studied.

Conclusions: Ultra wide-field angiography provides visualization of peripheral retinal pathology in BRVO and HRVO patients, which may be useful in their evaluation and treatment. Our findings support the hypothesis that areas of untreated retinal nonperfusion may be the source of production of biochemical mediators that promote neovascularization and macular edema.

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Retinal vein occlusion is the most common retinal vascular occlusion. Traditional angiographic techniques can be used to identify, monitor, and treat the potentially visually debilitating sequelae of retinal vein occlusion, such as neovascularization and macular edema. Indeed, angiographic findings played an integral role in the treatment protocols dictated by both the Branch Vein and Central Vein Occlusion Studies.^{1,2}

Although these clinical trials represent major breakthroughs in the clinical evaluation and management of retinal vascular occlusions, a number of clinical issues remain. Specifically, large subsets of eyes with branch (BRVO) and hemicentral retinal vein occlusion (HRVO) suffer macular edema recalcitrant to macular laser. Some eyes with macular edema seem to transiently respond to pharmacologic intervention (antivascular endothelial growth factor [VEGF] therapy or steroid therapy); however, recurrence of edema is common and continuous biochemical manipulation is often necessary, and can eventually fail.³ Similarly, a subset of eyes with retinal neovascularization can experience recur-

rent vitreous hemorrhage despite quadrant or hemispheric retinal photocoagulation guided by traditional angiography.

A shortcoming of previous studies was the lack of visualization of the retinal periphery, which was limited by the standard 30° images of traditional fluorescein angiography. Even with composite images, which can provide a 75° view of the retina, the majority of the retinal periphery is not visualized. Although the Branch Vein and Central Vein Occlusion Studies were able to base outcomes and recommendations on available angiographic data extrapolated to include the entire retina, it remains unknown what role peripheral retinal vascular pathology plays in the pathogenesis of vision loss in eyes with retinal vein occlusion.

Numerous successful attempts have been made to obtain wide-angle angiographic images of the retina; however, prior studies have been hampered by the need for a contact lens-based systems or the requirement of excellent patient cooperation or sedation.^{4–6} Ultra wide-field fluorescein angiography using the Optos C200 MA scanning laser ophthalmoscope (Optos PLC, Dunfermline, UK) provides a

new method to visualize up to 200° of the retina using a non-contact-lens-based system.⁷

We studied this new imaging modality in patients with a diagnosis of either BRVO or HRVO to determine whether or not peripheral retinal vascular pathology is associated with visually significant sequelae.

Methods

We conducted a retrospective review of all ultra wide-field fluorescein angiograms performed for the evaluation of a primary diagnosis of BRVO or HRVO at a single academic institution. All images were obtained with the Optos C200 MA (Optos, PLC) after standard intravenous infusion of 5 cc of sodium fluorescein 10%. Images were digitally archived and reviewed using the V2 Vantage Review Software (Optos, PLC) allowing high-resolution zoom functionality for the review of all images.

A single, masked reviewer (PP) graded the angiograms for the presence or absence of nonperfusion of ≥ 1 disc area, neovascularization (defined as focal leakage ≥ 2 disc diameters), macular edema (defined as late hyperfluorescence ≥ 500 μm diameter), late peripheral vascular leakage (LPVL, defined as late venous or arterial hyperfluorescence), prior evidence of focal macular laser (focal hypofluorescence with hyperfluorescent borders within the macula), and prior evidence of panretinal photocoagulation (focal hypofluorescence with hyperfluorescent borders outside the macula). All patients referred for evaluation and management of venous occlusion who had undergone laser photocoagulation before referral seemed to have undergone laser treatment aided only with traditional angiographic techniques. Nonperfusion, neovascularization, and LPVL were further graded as to their presence anterior or posterior to the equator. The equator was identified using the vortex veins as landmarks. In cases where multiple angiograms were performed for a single patient, we included only the earliest angiogram in the analysis.

Optical coherence tomography (OCT) images were reviewed for all patients to confirm the presence of macular thickening and to detect evidence of vitreomacular traction or serous macular detachment. Only eyes with evidence of angiographic macular edema and macular thickening documented on OCT were considered to have macular edema. Eyes with vitreomacular traction were excluded from statistical analyses concerning macular edema.

A chart review was performed for all patients for the following data: gender, age, duration of vein occlusion, the presence of cardiovascular risk factors (hypertension, diabetes, and hyperlip-

Table 1. Patient Demographics at the Time of Angiography

Gender (n)	
Male	46
Female	28
Average age (yrs) [range]	66 [16–90]
Average duration (mos) of vascular occlusion [range]	24.5 [0–216]
Cardiovascular risk factor history	
Hypertension	51
Diabetes	14
Hyperlipidemia	31
Prior intravitreal injection	
Anti-VEGF agent	10
Triamcinolone	5

VEGF = vascular endothelial growth factor.

Table 2. Summary of Ultra Wide-Field Fluorescein Angiographic Characteristics

Angiographic Characteristic	No. of Eyes	Percentage of Eyes (%)
Nonperfusion	62	82
Anterior*	59	78
Posterior*	38	50
Neovascularization	16	21
Anterior	8	11
Posterior	13	17
Late peripheral vessel leakage	44	58
Anterior	34	45
Posterior	39	51
Angiographic macular edema	61	80

*Anterior and posterior refer to the location of angiographic characteristics with respect to the globe equator.

idemia), prior intravitreal injections (pegaptanib, bevacizumab, ranibizumab, or triamcinolone acetonide), and the presence of rubeosis iridis at the time of, or before, the wide-field angiography study.

Statistical analyses were performed using the SAS 9.1 software package (SAS Inc., Cary, NC) utilizing the chi-square test. $P < 0.05$ were considered significant.

Retrospective review of all patient records was conducted with approval of the Institutional Review Board of the University of California, Los Angeles.

Results

A total of 80 ultra wide-field fluorescein angiograms from 78 patients were reviewed. Four angiograms could not be interpreted owing to poor quality and were not included in the analysis. Of the 76 angiograms analyzed, BRVO was the primary diagnosis in 65 eyes (86%) and HRVO was the primary diagnosis in 11 eyes (14%). The demographic data for patients in this analysis are summarized in Table 1. Of note, a total of 15 patients had prior intravitreal injection with ≥ 1 anti-VEGF agent ($n = 10$) or triamcinolone acetonide ($n = 5$), but none underwent injection of both. Angiographic macular edema was identified in 61 eyes (80%). Of these cases, 2 demonstrated evidence of vitreomacular traction and 56 demonstrated macular thickening on OCT. Seven patients demonstrated evidence of serous macular detachment on OCT without evidence vitreomacular traction. Untreated retinal vascular nonperfusion, neovascularization and LPVL were noted in 62 (82%), 16 (21%), and 44 (58%) of eyes, respectively. The results of the statistical analysis are summarized in Table 2.

Untreated nonperfusion at any location was associated with neovascularization at any location ($P = 0.033$). All eyes of patients with evidence of neovascularization (16/16 eyes) demonstrated areas of untreated nonperfusion (Table 3). Similarly, nonperfusion posterior to the equator was associated with both neovascularization at any location ($P = 0.047$) and neovascularization posterior to the equator ($P = 0.013$). Neovascularization anterior to the equator without evidence of neovascularization posterior to the equator was seen in 3 eyes. One patient with neovascularization anterior to the equator also developed rubeosis iridis.

Untreated nonperfusion was associated with macular edema ($P = 0.043$; Table 4). More than 85% of eyes with macular edema on angiography and OCT demonstrated areas of untreated nonperfusion. Similarly, nonperfusion anterior to the equator was strongly

Table 3. Association between Nonperfusion at Any Location and Neovascularization

	Nonperfusion Present	Nonperfusion Absent	Total	%
NV present	16	0	16	100
NV absent	46	14	60	77
Total	62	14	76	$P = 0.033$

NV = neovascularization.

associated with macular edema ($P = 0.007$). Of eyes with macular edema, 48 of 56 (86%) demonstrated areas of untreated nonperfusion anterior to the equator (Table 5). Nonperfusion isolated to areas posterior to the equator was not significantly associated with macular edema ($P = 0.341$).

Late peripheral vessel leakage was not significantly associated with macular edema, nonperfusion, or neovascularization. A subset of eyes studied showed angiographic evidence of photocoagulation; 11 of 76 eyes (14%) demonstrated evidence of prior grid macular laser and 20 of 76 eyes (26%) demonstrated angiographic evidence of prior peripheral scatter photocoagulation. Significant associations between angiographic characteristics are summarized in Table 6.

Discussion

To our knowledge, this is the first study utilizing ultra wide-field fluorescein angiography to analyze peripheral retinal vascular pathology in patients with retinal vascular occlusive disorders. Although the pathogenic sites of HRVO and BRVO are different,⁸ we chose to include both retinal vascular occlusive disorders in this study because the evaluation and management of BRVO and HRVO are often similar. We opted to include eyes with evidence of prior laser photocoagulation for 2 reasons. First, a central, routine observation noted early in our experience with ultra wide-field angiography was the significant areas of untreated peripheral retinal pathology even in eyes that had undergone laser photocoagulation. Second, because of the retrospective, noninterventive nature of this study, we felt inclusion of eyes with previous photocoagulation better represented the group we sought to study.

This study demonstrates the value of peripheral fluorescein angiography in visualizing peripheral retinal pathology. Delineation of retinal vascular nonperfusion in the far retinal periphery and detection of subtle areas of early peripheral neovascularization may be of particular clinical value (Fig 1). The association between retinal vascular nonperfusion and retinal neovascularization demonstrated

Table 4. Association between Nonperfusion at Any Location and Macular Edema

	Nonperfusion Present	Nonperfusion Absent	Total	%
Macular edema present	49	7	56	88
Macular edema absent	12	6	18	67
Total	61	13	74	$P = 0.043$

Table 5. Association between Nonperfusion Anterior to the Globe Equator and Macular Edema

	Anterior Nonperfusion Present	Anterior Nonperfusion Absent	Total	%
Macular edema present	48	8	56	86
Macular edema absent	10	8	18	56
Total	58	16	74	$P = 0.007$

in this study supports the hypothesis that zones of retinal nonperfusion may stimulate production of biochemical mediators leading to neovascularization.⁹ Ultra wide-field fluorescein angiography, therefore, may be a powerful tool to identify therapeutic target areas for photocoagulation, allowing for efficient treatment of ischemic retina and potentially minimizing collateral destruction of viable, perfused retina.

Human studies have demonstrated that elevated levels of VEGF and interleukin-6 correlate with the development and severity of macular edema in BRVO,¹⁰⁻¹² suggesting that the same areas of nonperfusion leading to neovascularization may also promote the development of macular edema. This hypothesis is supported by our study, which demonstrates a significant association between untreated nonperfusion and macular edema. This hypothesis does not explain the presence of macular edema in all patients with retinal vein occlusion, but may apply to a large subset of eyes with this condition. Seven out of 56 patients (12.5%) in our study demonstrated evidence of macular edema but did not have angiographic evidence of untreated nonperfusion. Eight of 56 patients (14%) developed macular edema without untreated anterior nonperfusion. Some of these cases were distal macular BRVO that resulted in clinical and angiographic changes limited to the macula. Other patients had persistent macular edema despite laser photocoagulation to areas of posterior and anterior nonperfusion. In these cases, photocoagulation therapy may have been insufficient to diminish the production of chemical mediators leading to macular edema. Intravitreal anti-VEGF or triamcinolone therapies may be of value in treating macular edema in these patients.

The hypothesis that untreated retinal vascular nonperfusion may be associated with macular edema seems to be supported by the observed results that 88% of patients with macular edema demonstrated evidence of untreated nonperfusion at any location and 86% demonstrated untreated nonperfusion anterior to the equator. As expected, not all patients with angiographic evidence of untreated nonperfusion developed macular edema: 12 of 61 patients (20%) and 10 of 58 patients (17%) demonstrated evidence of untreated

Table 6. Statistically Significant Angiographic Associations

Associated Angiographic Characteristics	P-Value
Any nonperfusion and any neovascularization	0.033
Posterior nonperfusion and any neovascularization	0.047
Posterior nonperfusion and posterior neovascularization	0.013
Any nonperfusion and macular edema	0.043
Anterior nonperfusion and macular edema	0.007

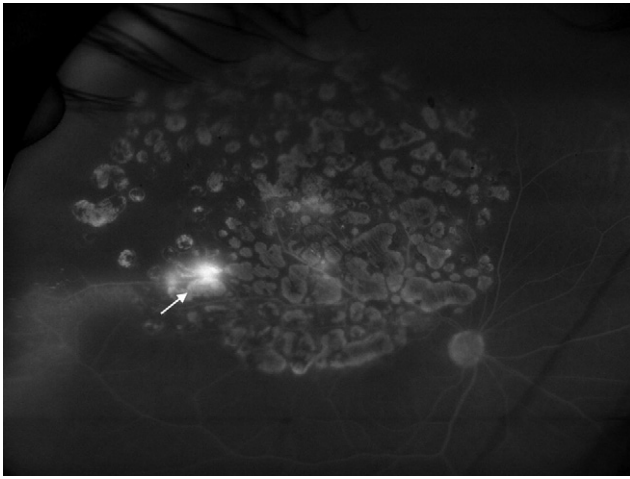


Figure 1. Angiogram demonstrating persistent neovascularization (arrow) at the border between perfused and non-perfused retina despite extensive scatter photocoagulation.

nonperfusion at any location and untreated nonperfusion anterior to the equator, respectively, without developing macular edema. There are a number of biologically plausible explanations for this observation. First, the duration of vein occlusion in our study population varied, some of whom underwent wide-field angiography studies within a few months of onset. Some of these patients, if left untreated, may have progressed to develop macular edema. Second, the total area of nonperfusion may directly correlate with the development of macular edema. Future studies quantifying the area of nonperfusion may be of particular utility to explain why some patients with retinal vein occlusion progress to develop macular edema whereas others remain stable. Third, systemic factors may decrease the threshold for the development of macular edema, such as microvascular damage from uncontrolled hypertension, diabetes, and hyperlipidemia.

A similar observation was made among patients who failed to develop neovascularization. Of 62 patients with evidence of untreated nonperfusion, 42 (74%) failed to develop neovascularization. The hypothetical explanations for this phenomenon are similar to those who failed to develop macular edema despite untreated nonperfusion. Objective measurements such as determining the total area of nonperfusion or the ratio of nonperfused to perfused retina may help to stratify patients who are at high risk for the development of neovascularization. Additionally, some patients with untreated nonperfusion may not have developed neovascularization due to prior injection with anti-VEGF agents or triamcinolone acetonide. Given time, these patients may remain quiescent or develop neovascularization in the future. Finally, although the hypoxia-induced upregulation of VEGF pathway seems to be the most reasonable explanation for the development of neovascularization, there may be other, unidentified pathways by which retinal damage from venous occlusion promotes neovascularization.

We noted a number of cases that demonstrated untreated nonperfusion with persistent macular edema despite treatment with grid macular laser (Fig 2). We hypothesize that

treatment of peripheral nonperfusion paired with grid macular laser may be a more efficacious approach in the management of BRVO and HRVO with recalcitrant macular edema. Similarly, combination targeted photocoagulation to nonperfused areas with intravitreal anti-VEGF or triamcinolone acetonide therapy may be beneficial in a subset of eyes. Further prospective study is certainly indicated before widespread clinical adoption of these proposed regimens.

We noted a much more robust association between nonperfusion anterior to the globe equator and macular edema than nonperfusion at any location and macular edema. Additionally, a significant association between posterior retinal vascular nonperfusion and macular edema was not demonstrated. One explanation for this finding is that it may be not only the presence of nonperfusion, but the extent of nonperfusion that promotes macular edema. We observed among our study patients that nonperfusion peripheral to the equator encompassed at least twice as much area as nonperfusion posterior to the equator. This is partly because of the wedge- or hemispheric-shaped area of pathology in BRVO and HRVO, wherein the area of involved retina increases with distance from the occlusive source. Another explanation centers on selection bias. Specifically, eyes with significant posterior nonperfusion may have been treated before referral. Our trial design did not allow for this question to be answered accurately.

Late peripheral vascular leakage is not an easily appreciated angiographic characteristic unless wide-field angiographic studies are performed (Fig 3). We observed this finding in a number of clinical cases. Associations with macular edema, nonperfusion, and retinal neovascularization and LPVL in eyes with diabetic retinopathy have been reported (Schwartz SD, Oliver SCN, Gonzales CR. Association of Peripheral Retinal Vascular Abnormalities Detected on Ultra Wide-Field Fluorescein Angiography With Diabetic Macular Edema and Neovascularization. Paper presented at: Association for Research in Vision and Ophthalmology, April 30, 2008, Fort Lauderdale, Florida). Thus, we hypothesize that LPVL may be a sign of retinal hypoxia despite angiographic perfusion. Alternatively, it may indicate other phenomena such as vitreoretinal

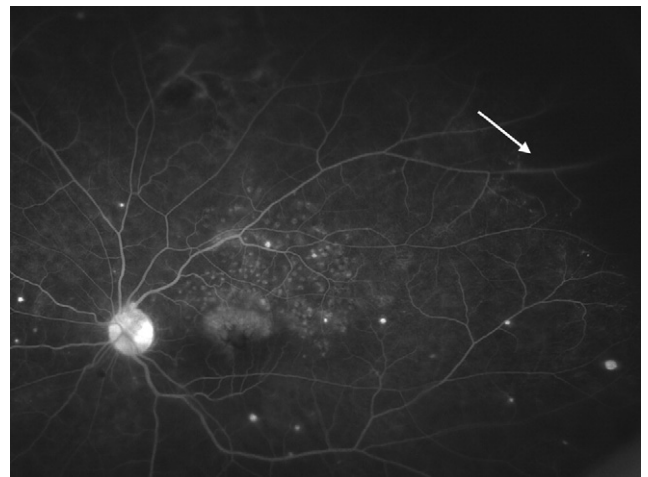


Figure 2. Angiogram demonstrating anterior nonperfusion (arrow) with persistent macular edema despite prior grid macular laser.



Figure 3. Angiogram demonstrating late peripheral vascular leakage (arrow) adjacent to an area of nonperfusion.

traction, evidence of reperfusion in a damaged vascular bed, or lack meaningful association. As such, we were compelled to quantify our observation to determine whether or not any meaningful clinical associations were present in this cohort. Although this finding was not significantly correlated with neovascularization or macular edema in this study, further research may be necessary to determine the role that this finding plays in the evaluation and treatment of retinal vascular disorders. Elucidation of a reliable, clinically significant sign of retinal hypoxia might greatly enhance our ability to time, select, and combine treatments for retinal vascular diseases.

There are limitations to the conclusions that can be drawn from this study. First, as a retrospective review, the selection bias for patients undergoing ultra wide-field fluorescein angiography is likely significant. A number of patients in our study were referred to our institution after failing treatment by community physicians. Furthermore, the patients in this study were not a traditionally homogenous group, and represented BRVO and HRVO in various stages of disease and treatment. However, the cohort studied does represent a “real-world” group of non-central retinal venous occlusion patients. Despite these limitations, this study represents an important first step in the evaluation of peripheral retinal vascular pathology in retinal venous occlusive disease.

Footnotes and Financial Disclosures

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Randomized, prospective studies are needed to confirm the findings of this study. Specifically, future studies are needed to determine the role that treatment of peripheral nonperfusion can play in both the management and prevention of neovascularization and macular edema.

References

1. Branch Vein Occlusion Study Group. Argon laser scatter photocoagulation for prevention of neovascularization and vitreous hemorrhage in branch vein occlusion: a randomized clinical trial. *Arch Ophthalmol* 1986;104:34–41.
2. Central Vein Occlusion Study Group. Natural history and clinical management of central retinal vein occlusion. *Arch Ophthalmol* 1997;115:486–91.
3. Rabena MD, Pieramici DJ, Castellarin AA, et al. Intravitreal bevacizumab (Avastin) in the treatment of macular edema secondary to branch retinal vein occlusion. *Retina* 2007;27:419–25.
4. Nyori KS, Chino K, Deguchi T. Wide field fluorescein angiography by use of contact lens. *Retina* 1983;3:131–4.
5. Staurengi G, Viola F, Mainster MA, et al. Scanning laser ophthalmoscopy and angiography with wide-field contact lens system. *Arch Ophthalmol* 2005;123:244–52.
6. Roth DB, Morales D, Feuer WJ, et al. Screening for retinopathy of prematurity employing the RetCam 120: sensitivity and specificity. *Arch Ophthalmol* 2001;119:268–72.
7. Manivannan A, Plskova J, Farrow A, et al. Ultra-wide-field fluorescein angiography of the ocular fundus. *Am J Ophthalmol* 2005;140:525–7.
8. Hayreh SS. Retinal vein occlusion. *Indian J Ophthalmol* 1994;42:109–32.
9. McIntosh RL, Mohamed Q, Saw SM, Wong TY. Interventions for branch retinal vein occlusion: an evidence-based systematic review. *Ophthalmology* 2007;114:835–46.
10. Noma H, Funatsu H, Yamasaki M, et al. Pathogenesis of macular edema with branch retinal vein occlusion and intraocular levels of vascular endothelial growth factor and interleukin-6. *Am J Ophthalmol* 2005;140:256–61.
11. Noma H, Funatsu H, Yamasaki M, et al. Aqueous humour levels of cytokines are correlated to vitreous levels and severity of macular oedema in branch retinal vein occlusion. *Eye* 2008;22:42–8.
12. Noma H, Funatsu H, Mimura T, et al. Vitreous levels of interleukin-6 and vascular endothelial growth factor in macular edema with central retinal vein occlusion. *Ophthalmology* 2009;116:87–93.

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