Ischemic Index and Distribution of Retinal Capillary Non-perfusion in Neovascular Glaucoma: a Retrospective Study

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Research Article

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Abstract

Purpose: To evaluate the pattern of retinal ischemia in newly diagnosed neovascular glaucoma (NVG).

Methods: This is a retrospective single-center cross-sectional study of patients seen at LAC+USC Medical Center from January 2015 to April 2020. Patients with newly diagnosed NVG and ultra-widefield fluorescein angiography (UWFA) without prior panretinal photocoagulation were included. A total of 11 eyes from 10 patients met inclusion criteria. Three zones centered on the fovea were defined: posterior pole (within 2 disc-fovea lengths), mid periphery (between 2 and 3 disc-fovea lengths), and far periphery (>3 disc-fovea lengths). Ischemic index was calculated in these zones using ImageJ software.

Results: The etiology of NVG was from proliferative diabetic retinopathy (n=9) and central retinal vein occlusion (n=2). Patients were aged between 48-74 years old. Ischemic index was found to be 91% in the far periphery, 77% in the mid periphery, and 42% at the posterior pole. The total average ischemic index was 76%. There was a statistically significant difference between the far periphery and posterior pole and mid periphery and posterior pole.

Conclusions: High levels of retinal ischemia were found with newly diagnosed NVG. The pattern of ischemia was more pronounced in the far periphery than posterior pole.

Background:

Neovascular Glaucoma (NVG) is a condition normally caused by hypoxic posterior ocular disease, which produces angiogenic factors that stimulate new vessel proliferation of the anterior segment and angle, eventually leading to closure of the angle and increased intraocular pressure. NVG is a common complication of central retinal vein occlusion (CRVO), diabetic retinopathy, and ocular ischemic syndrome. In longstanding proliferative diabetic retinopathy, the incidence of iris rubeosis was found to be between 43–64% [1, 2] and the incidence of NVG was 10% [2]. Postoperative NVG has been shown to be in 5.3% of patients with proliferative diabetic retinopathy (PDR) who were treated with vitrectomy and endolaser panretinal photocoagulation (PRP) [3]. NVG has also been shown to progress in a high proportion of patients with ischemic CRVO [4]. The Central Vein Occlusion Study (CVOS) determined who was at risk for neovascular glaucoma based on levels of retinal ischemia. In CVOS, standard 5-view or 7-view photographs were captured to evaluate the retina; however, only 70 to 120 degrees of retina could be visualized, only allowing a partial view of the peripheral retina [5].

The Optos ultra-widefield camera (Optos, PLC, Scotland) allows imaging of 200 degrees of the retina in a single image [6]. Ultra-widefield fluorescein angiography (UWFA) provides a larger view of the retina, including the anterior retina. Thus, further characterization of ischemia is possible than with prior imaging techniques.

UWFA has been used to evaluate the peripheral retina for central retinal vein occlusion [7–10], branch and hemicentral retinal vein occlusion [11–14], diabetic retinopathy [15–20], and recalcitrant diabetic macular

edema [21]. However, there is no prior study using UWFA to characterize newly diagnosed NVG. It is important to understand the pattern and level of ischemia in newly diagnosed NVG, especially in the far periphery. The purpose of this study was to address these issues by using UWFA on a series of newly diagnosed NVG patients.

Methods:

This is a retrospective study, conducted at Los Angeles County + University of Southern California (LAC + USC) Medical center from January 2015 to April 2020 under Institutional Review Board (IRB) approval and in accordance with the ethical standards of the Declaration of Helsinki. UWFA records were reviewed for patients with a diagnosis of NVG during this period of time. Meticulous chart review was conducted to ensure these patients had a chart recorded diagnosis of NVG with angle neovascularization and an IOP over 21 mmHg. Patients with UWFA after 2 weeks of diagnosis were excluded. Those with PRP prior to the UWFA were excluded from the study because it would make it difficult to properly assess the laser treated areas for non-perfusion and could alter the dynamics of NVG formation. Poor quality images such as images with media opacities were excluded. From a total of 77 NVG patients with UWFA, 11 eyes from 10 patients met inclusion and exclusion criteria.

In the study center, UWFA is performed using Optos 200 Tx after intravenous injection of 5ml sodium fluorescein 10%. The best image in terms of quality and field of view was chosen for analysis. Images were processed using ImageJ software (National Institutes of Health, Bethesda, MD). First, three perfusion zones were identified on the fluorescein angiogram. The distance from the optic nerve to the fovea was measured. Zone 1 was defined as the posterior pole, within 2 disc-fovea lengths from the foveal center. The mid periphery, Zone 2, consisted of an annulus between 2 and 3 disc-fovea lengths from the fovea. Zone 3, defined as the far periphery, was > 3 disc-fovea lengths from the fovea. The area of capillary perfusion was outlined on the image. Ischemic index (ISI) was calculated as a proportion of non-perfusion to total area. Portions of the image that were obscured were not included in analysis. Figure 1 shows an example of UWFA after obscured peripheral areas were cropped.

Statistical Analysis: The ISI in Zones 1, 2, and 3 were calculated along with 95% confidence intervals and compared using a one-way ANOVA with Bonferroni post-test, using a significance value of $p < 0.05$ with Microsoft Excel.

Results:

Patient demographics are shown in Table 1. Patient age ranged from 48 to 74 years old with a mean age of 58 years old. 6 patients were male. 8 of 10 patients had a history of hypertension. Etiology of NVG was PDR in 9 of 11 eyes and CRVO in 2 eyes. 3 eyes had anti-VEGF treatment prior to UWFA, one on the same day as UWFA, and 2 one day prior to UWFA. 4 of 11 eyes had NVE, and 10 of 11 eyes had NVD.

ISI for the total retina was 76% (CI 64.8% − 86.7%). The ISI increased when moving from the posterior pole (42%, CI 23.3% − 61.6%) to mid periphery (77%, CI 62.1%-91.6%) and far periphery (91% CI 85.7% − 97.2%) (Fig. 2). There was statistical significance between Zone 1 and Zone 2, and Zone 1 and Zone 3 ($p = 0.01$ and $p = 0.0001$ respectively). Zone 2 and Zone 3 did not meet criteria for statistical significance ($p = 0.087$).

For eyes with NVG due to PDR, average ISI was 72% (CI 60.1% − 84.7%) for the entire measured retina, 32% (CI 15.3% − 49.2%) in the posterior pole, 72% (CI 55.7% − 89.3%) in the mid-periphery, and 92% (CI 85.2% − 98.0%) in the far periphery. There was statistical significance between Zone 1 and Zone 2 as well as Zone 1 and Zone 3 ($p = 0.004$ and $p < 0.0001$ respectively). However, Zone 2 and Zone 3 did not meet criteria for statistical significance ($p = 0.053$).

Table 1
Patient demographics and Ischemic Index.

Age	Gender	Etiology	HTN	NVE	NVD	Ischemic Index			
						Zone 1	Zone 2	Zone 3	Total
50	M	PDR	+	+	+	16%	46%	78%	56%
74	M	CRVO	+	-	-	86%	100%	100%	95%
51 (OU)	M	PDR	+	+	+	59%	94%	100%	90%
				-	+	65%	99%	100%	93%
63	F	PDR	-	-	+	1%	60%	86%	50%
59	M	PDR	+	-	+	65%	100%	100%	92%
48	F	PDR	+	+	+	0%	32%	80%	49%
61	F	PDR	+	-	+	20%	70%	100%	79%
62	M	CRVO	+	-	+	90%	93%	81%	86%
66	F	PDR	-	-	+	38%	96%	98%	85%
53	M	PDR	+	+	+	27%	55%	82%	59%
Mean						42%	77%	91%	76%

Legend: Hypertension (HTN), neovascularization elsewhere (NVE), neovascularization of the disc (NVD).

Discussion:

This study is the first, to our knowledge, to use UWFA to measure ISI and pattern of ischemia in newly diagnosed NVG patients. The data in this study demonstrates the angiographic presence of extensive retinal ischemia in NVG, with predominance for the peripheral retina compared to the posterior pole. A comparison of our findings with studies performed on PDR and CRVO demonstrates a similar pattern of

capillary non-perfusion, i.e. more extensive involvement of the peripheral retina compared to the posterior pole. However, the extent of non-perfusion is much higher in NVG than PDR or CRVO.

In diabetic retinopathy, several authors have shown increasing ischemia in the periphery compared with the posterior pole. Fan et. al evaluated ISI for treatment naïve early stage PDR and found an ISI of 12% at the posterior pole, increasing to 38% in the far periphery [16]. Lange found ISI increasing from 20.5% in the posterior retina to 27.2% in the far periphery in patients with PDR [22].

In addition, higher levels of ischemia have been shown to be associated with more advanced diabetic retinopathy [18]. Silva demonstrated higher levels of ischemia associated with more severe retinopathy, which plateaued for proliferative diabetic retinopathy [18]. Ehlers found a similar trend, although with lower levels of ISI than prior authors [23]. Nicholson et. al used levels of ischemia to set a threshold of 118.3 disc diameters of ischemia for identification of proliferative diabetic retinopathy [19]. Speilburg found increasing levels of ischemia with worsening retinopathy, with mild non-proliferative diabetic retinopathy (NPDR) having an ISI of 2.2% and PDR having an ISI of 18.6% [20]. This trend held true in patients with recalcitrant macular edema. Eyes with NPDR had an ISI of 0%, moderate or severe PDR had an ISI of 34%, and active PDR without PRP had an ISI of 65% [21].

For patients with CRVO, studies have shown a predominance of peripheral over posterior ischemia. Kwon et. al evaluated eyes with RVO and recalcitrant macular edema including 12 eyes with CRVO and 12 eyes with BRVO. They found an overall baseline ISI of 30.5% with a trend of ischemia increasing in the periphery (17.7% at perimacular area increasing to 48.0% in the far peripheral area) [13]. Wang et. al used montaged images to measure ISI in eyes with ischemic RVO and persistent macular edema. They showed eyes with CRVO to have an average ISI of 26.4% and to have increasing ischemia in the periphery compared to posterior retina [14].

ISI has been used to differentiate ischemic from non-ischemic CRVO and has been related to macular edema. Thomas et. al used UWFA to calculate ISI for eyes with CRVO and found a mean ISI of 22.43% with a range of 0–63.9%. They used a cutoff ISI of 35% to differentiate ischemic versus non-ischemic CRVO [9]. For patients with CRVO and macular edema, Aghdam et. al found that non-perfusion in the far-periphery of greater than 5 disc diameters was related to an increased number of ranibizumab injections for macular edema, compared with less than 4 disc diameters of non-perfusion [24]. Singer et. al calculated ISI for RVO patients with refractory macular edema during treatment and found an average ISI for CRVO patients of 22.5% with macular edema and 16.1% once macular edema had resolved [10].

The findings in this study of overall ISI in NVG are comparable with the literature for patients with anterior segment neovascularization due to CRVO. Tsui et al evaluated the ISI in CRVO in a retrospective study using UWFA and found an average ISI of 78% for the 10 eyes with anterior segment neovascularization without glaucoma [7]. We comparably found an average ISI of 76% in our cohort of patients. However, unlike in Tsui's study, our patients had NVG, and in 9 out of 11 eyes, the etiology of NVG was PDR and only two eyes had CRVO.

Strengths of this study include the ability to find patients with newly diagnosed NVG with UWFA imaging prior to panretinal photocoagulation. In addition, no patient had anti-VEGF longer than 1 day prior to UWFA, allowing us to evaluate the UWFA for neovascularization of the retina and disc as well. Numbers of patients were limited, given meticulous screening of patients and logistical challenges obtaining UWFA in the acute setting of NVG, especially given corneal edema and media opacities.

We defined the mid-peripheral and peripheral retina using the disc to fovea distance. We chose this method because it allowed us to compare different sized eyes on a proportional scale.

Limitations to the study include the small sample size (n = 11 eyes) and retrospective nature of the study. We removed obscured areas of the UWFA, and the superior and inferior areas were more frequently obscured compared to nasal and temporal areas due to the patients' eyelashes and eyelids. If the non-perfusion was significantly different in these areas, this could skew the data.

Finally, there is an image warp in UWFA emanating from projection of a three-dimensional image on a two dimensional computer screen; this distortion is more pronounced in the far periphery. This could potentially affect studies measuring surface area. To overcome this, some authors have used stereographically projected images. However, prior work has shown that ISI calculated in the manner of our study correlates with stereographically projected images [12]. Even if there is any error from using ISI, it is less likely to skew our data for zone comparisons because both perfused and non-perfused areas would be affected.

Conclusions:

In conclusion, this is the first study in our knowledge to use UWFA in patients with newly diagnosed NVG. The data here demonstrates high levels of peripheral ISI in newly diagnosed NVG. Future directions and implications of this data may include directing panretinal photocoagulation to the far periphery to treat the areas of retina with the highest levels of ischemia for patients with NVG or concern for development of NVG. Further studies are needed to determine how UWFA findings and retinal ischemia may predict patients who are at high risk for developing NVG, not only in the setting of CRVO, but also in the setting of PDR.

Declarations:

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Conflict of Interest:

The authors declare that they have no conflict of interest.

Availability of data and materials:

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

Authors' contributions:

CD: data collection, data analysis, manuscript writing

BW: manuscript revision

HA: project conception, data analysis, manuscript revision

Ethics approval and consent to participate:

Approved by the Los Angeles County + University of Southern California (LAC + USC) Medical center Institutional Review Board (IRB) approval and in accordance with the ethical standards of the Declaration of Helsinki. This study was retrospective.

Informed consent:

This study was retrospective and does not include identifiable information. Individual informed consent was not collected.

Consent for publication:

All authors read and approved the final manuscript.

Competing interests:

None

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References:

1. Ohrt V (1971) The frequency of rubeosis iridis in diabetic patients. Acta Ophthalmol 49:301–307. https://doi.org/10.1111/j.1755-3768.1971.tb00954.x
2. Madsen PH (1971) Rubeosis of the iris and haemorrhagic glaucoma in patients with proliferative diabetic retinopathy. Br J Ophthalmol 55:368. https://doi.org/10.1136/bjo.55.6.368
3. Goto A, Inatani M, Inoue T, et al (2013) Frequency and risk factors for neovascular glaucoma after vitrectomy in eyes with proliferative diabetic retinopathy. J Glaucoma 22:572–576. https://doi.org/10.1097/IJG.0b013e31824d514a

4. Magargal LE, Brown GC, Augsburger JJ, Parrish RK (1981) Neovascular glaucoma following central retinal vein obstruction. Ophthalmology 88:1095–1101. https://doi.org/10.1016/S0161-6420(81)34901-X
5. (1995) A randomized clinical trial of early panretinal photocoagulation for Ischermic Central Vein occlusion: the central vein occlusion study group N report. Ophthalmology 102:1434–1444. https://doi.org/10.1016/S0161-6420(95)30848-2
6. Rabiolo A, Parravano M, Querques L, et al (2017) Ultra-wide-field fluorescein angiography in diabetic retinopathy: A narrative review. Clin Ophthalmol 11:803. https://doi.org/10.2147/OPTH.S133637
7. Tsui I, Kaines A, Havunjian MA, et al (2011) Ischemic index and neovascularization in central retinal vein occlusion. Retina 31:105–110. https://doi.org/10.1097/IAE.0b013e3181e36c6d
8. Spaide RF (2011) Peripheral areas of nonperfusion in treated central retinal vein occlusion as imaged by wide-field fluorescein angiography. Retina 31:829–837. https://doi.org/10.1097/IAE.0b013e31820c841e
9. Thomas AS, Thomas MK, Finn AP, Fekrat S (2019) Use of the ischemic index on widefield fluorescein angiography to characterize a central retinal vein occlusion as ischemic or nonischemic. Retina 39:1033–1038. https://doi.org/10.1097/IAE.0000000000002126
10. Singer M, Tan CS, Bell D, Sadda SR (2014) Area of peripheral retinal nonperfusion and treatment response in branch and central retinal vein occlusion. Retina 34:1736–1742. https://doi.org/10.1097/IAE.0000000000000148
11. Prasad PS, Oliver SCN, Coffee RE, et al (2010) Ultra wide-field angiographic characteristics of branch retinal and hemicentral retinal vein occlusion. Ophthalmology 117:780–784. https://doi.org/10.1016/j.ophtha.2009.09.019
12. Tan CS, Chew MC, Van Hemert J, et al (2016) Measuring the precise area of peripheral retinal non-perfusion using ultra-widefield imaging and its correlation with the ischaemic index. Br J Ophthalmol 100:235–239. https://doi.org/10.1136/bjophthalmol-2015-306652
13. Kwon S, Wykoff CC, Brown DM, et al (2018) Changes in retinal ischaemic index correlate with recalcitrant macular oedema in retinal vein occlusion: WAVE study. Br J Ophthalmol 102:1066–1071. https://doi.org/10.1136/bjophthalmol-2017-311475
14. Wang K, Falavarjani KG, Nittala MG, et al (2018) Ultra-wide-field fluorescein angiography–guided normalization of ischemic index calculation in eyes with retinal vein occlusion. Investig Ophthalmol Vis Sci 59:3278–3285. https://doi.org/10.1167/iovs.18-23796
15. Kim JH, Jung HG, Chung HJ, et al (2015) Simplified correction of ischemic index in diabetic retinopathy evaluated by ultra-widefield fluorescein angiography. Korean J Ophthalmol 29:168–172. https://doi.org/10.3341/kjo.2015.29.3.168
16. Fan W, Nittala MG, Velaga SB, et al (2019) Distribution of nonperfusion and neovascularization on ultrawide-field fluorescein angiography in proliferative diabetic retinopathy (RECOVERY study): report 1. Am J Ophthalmol 206:154–160. https://doi.org/10.1016/j.ajo.2019.04.023

17. Baxter SL, Ashir A, Nguyen BJ, Nudleman E (2019) Quantification of retinal nonperfusion associated with posterior segment neovascularization in diabetic retinopathy using ultra-widefield fluorescein angiography. Ophthalmic Surg Lasers Imaging Retin 50:86–92. https://doi.org/10.3928/23258160-20190129-04
18. Silva PS, Dela Cruz AJ, Ledesma MG, et al (2015) Diabetic retinopathy severity and peripheral lesions are associated with nonperfusion on ultrawide field angiography. Ophthalmology 122:2465–2472. https://doi.org/10.1016/j.ophtha.2015.07.034
19. Nicholson L, Ramu J, Chan EW, et al (2019) Retinal nonperfusion characteristics on ultra-widefield angiography in eyes with severe nonproliferative diabetic retinopathy and proliferative diabetic retinopathy. JAMA Ophthalmol 137:626–631. https://doi.org/10.1001/jamaophthalmol.2019.0440
20. Speilburg AM, Teitelbaum B, Pang Y, Ittiara S (2018) Symmetry of peripheral retinal nonperfusion in diabetic retinopathy by ischemic index. J Optom 11:262–267. https://doi.org/10.1016/j.optom.2017.11.005
21. Patel RD, Messner L V., Teitelbaum B, et al (2013) Characterization of ischemic index using ultra-widefield fluorescein angiography in patients with focal and diffuse recalcitrant diabetic macular edema. Am J Ophthalmol 155:1038–1044. https://doi.org/10.1016/j.ajo.2013.01.007
22. Lange J, Majda H, Zhang J, Li W (2018) Region-specific ischemia, neovascularization and macular oedema in treatment-naïve proliferative diabetic retinopathy. Clin Exp Ophthalmol 46:757–766. https://doi.org/10.1111/ceo.13168
23. Ehlers JP, Jiang AC, Boss JD, et al (2019) Quantitative ultra-widefield angiography and diabetic retinopathy severity: an assessment of panretinal leakage index, ischemic index and microaneurysm count. Ophthalmology 126:1527–1532. https://doi.org/10.1016/j.ophtha.2019.05.034
24. Aghdam KA, Reznicek L, Sanjari MS, et al (2017) Anti-VEGF treatment and peripheral retinal nonperfusion in patients with central retinal vein occlusion. Clin Ophthalmol 11:331. https://doi.org/10.2147/OPTH.S125486

Figures

Image not available with this version

Figure 1

Example UWFA after cropping obscured areas. Posterior pole, mid periphery and far periphery are labeled. In addition, areas of capillary perfusion are demarcated

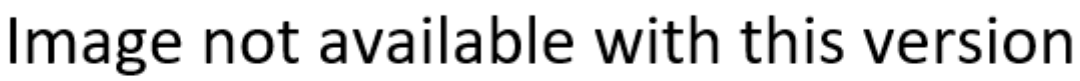

Figure 2

ISI versus location, error bars represent standard error of the mean. In the periphery, there is a higher ISI than the posterior pole. Posterior pole was statistically significant when compared with mid periphery and with far periphery (indicated with *). Mid periphery and far periphery were not statistically significant