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Original Research

Ischemic index and distribution of retinal capillary non-perfusion in neovascular glaucoma

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Abstract

Introduction: Neovascular Glaucoma (NVG) is a condition normally caused by hypoxic posterior ocular disease, which produces angiogenic factors such as vascular endothelial growth factor (VEGF) that stimulate new vessel proliferation of the anterior segment and angle, eventually leading to angle closure, reduced outflow of aqueous humor and increased intraocular pressure. Without treatment elevated intraocular pressure can rapidly progress to loss of vision. Treatment includes addressing the intraocular pressure and reducing the ischemic drive with panretinal photocoagulation (PRP) of the ischemic retina. Recent imaging advancements allow for ultra-widefield fluorescein angiography (UWFA) which expand the amount of peripheral retina that can be evaluated for non-perfusion. Here we aim to study patterns of non-perfusion in NVG using a group of PRP naïve patients with recent onset NVG. **Methods**: This study is a retrospective single-center cross-sectional study of patients seen at LAC + USC Medical Center from January 2015 to April 2020 with new onset NVG, without PRP and with UWFA completed. The percentage of ischemic index of the retina was calculated from the UWFA and evaluated in three distinct zones centered on the fovea: the posterior pole, the mid periphery, and far periphery. To increase sample size, a confirmatory group was included, with PRP allowed prior to UWFA but not before diagnosis. In addition, the time between diagnosis and UWFA was increased to 6 months. **Results**: A total of 11 eyes met inclusion criteria for the primary group. 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. A total of 24 eyes met criteria for the confirmatory group. Ischemic index for the confirmatory group was found to be 93% in the far periphery, 75% in the mid periphery, and 35% at the posterior pole. There was a statistically significant difference between the far periphery, posterior pole and mid-periphery. **Conclusion**: This knowledge can be used to further guide treatment and understand risk for NVG.

Keywords: Central retinal vein occlusion; Diabetic retinopathy; Ischemic index; Neovascular glaucoma; Ultra-widefield fluorescein angiography

1. Introduction

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 [15–21], and recalcitrant diabetic macular edema [22]. 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.

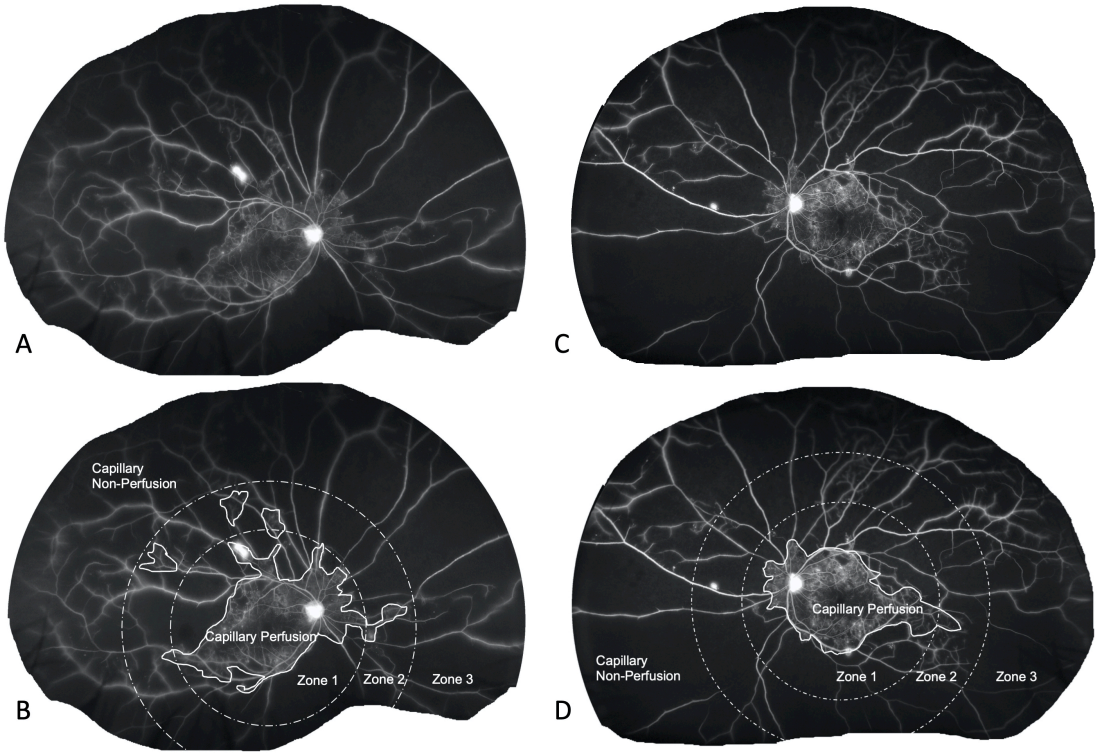

Fig. 1. Representative ultra-wide field fluorescein angiogram of 2 patients demonstrating areas of capillary non perfusion. Two example UWFAs after cropping obscured areas (A and C) and after analysis regions are depicted (B and D). Zone 1 (posterior pole), zone 2 (mid periphery) and zone 3 (far periphery) are labeled using a dashed line in B and D. The border between capillary non-perfusion, which is seen as darker due to lack of capillary plexus perfusion, and capillary perfusion is demarcated with a solid line in B and D. For image B, zone 1 has an ISI of 59%, zone 2 has an ISI of 94%, and zone 3 has an ISI of 100% (complete capillary non-perfusion). For image D zone 1 has an ISI of 65%, zone 2 has an ISI of 99%, and zone 3 has an ISI of 100%.

2. Materials and 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 intraocular pressure (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 primary study endpoint because it would make it difficult to properly assess the laser treated areas for non-perfusion and could alter the dynamics of NVG formation. UWFA from remaining patients were evaluated to ensure that areas of capillary non-perfusion were able to be identified. If the image was poor quality, such as images with media opacity, or corneal edema, so that the grader could not discern areas of capillary perfusion and non-perfusion, these were excluded. If the patient was found to have laser scars consistent with PRP, the image was excluded. From a total of 77 NVG patients with UWFA, 11 eyes from 10 patients met inclusion and exclusion criteria.

A second group was included and pooled with the first data set to increase sample size and confirm results. This group had modified exclusion criteria, which allowed for UWFA within 6 months of diagnosis and patients with PRP after the diagnosis of NVG, but not before. Eyes with dense PRP that were not able to be interpreted were excluded. The total confirmatory analysis added another 13 eyes, leading to a total of 24 eyes.

In the study center, UWFA is performed using Optos 200 Tx after intravenous injection of 5 mL sodium fluorescein 10%. A single grader who was a trained ophthalmologist graded the images. A mid to late phase fluorescein angiogram was used for analysis, and the particular image chosen was based on the field of view of the image, with larger fields of view preferred, and lack of media obscuration. 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-

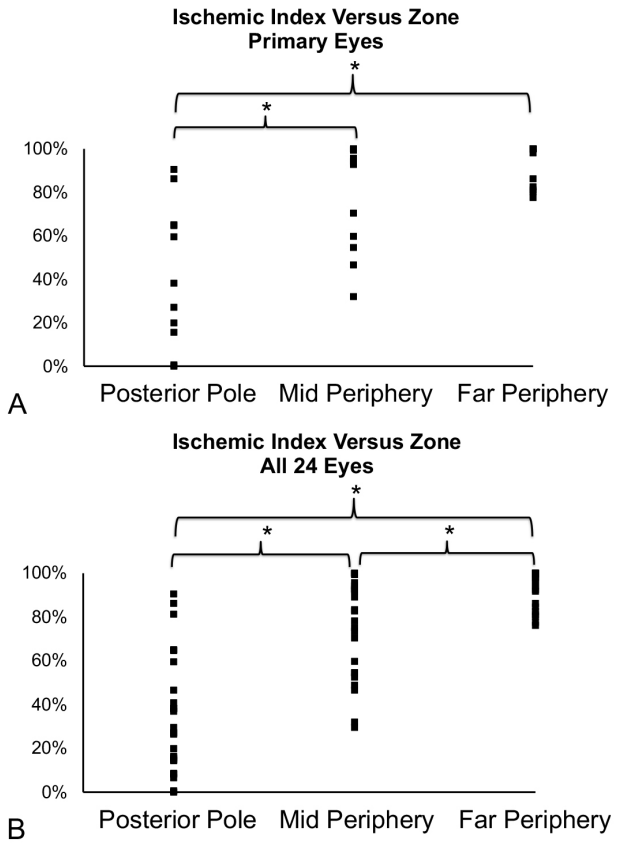

Fig. 2. Scatter plot showing ischemic index based on zone. Each point corresponds to a specific measurement. (A) Depicts the primary dataset with n = 11 eyes. In the periphery, there is a higher ISI than the posterior pole. Posterior pole was statistically significant when compared with mid periphery and with far periphery (indicated with *). Mid-periphery and far periphery were not statistically significant. (B) Depicts the expanded dataset with n = 24 eyes. There was a statistically significant difference in the mean for all three zones. Similar to the primary dataset, there is a large range of ISI for the posterior pole with a range from 0%–90%. However, ISI increases in the periphery and the range of values decreases, with no value less than 76%.

fovea lengths from the fovea. Zone 3, defined as the far periphery, was >3 disc-fovea lengths from the fovea. These three regions were demarcated and used for analysis with ImageJ software. The UWFA were evaluated and areas that had no capillaries were identified and outlined on the image. Ischemic index (ISI) was calculated as a proportion of non-perfusion to total area of a particular zone divided by the total area of that particular zone. Total ISI was calculated as the total pixel count of capillary non-perfusion divided by the total pixel count of the full image. Portions of the image that were obscured were not included in analysis. Fig. 1 shows an example of UWFA after obscured peripheral areas were cropped. The areas of capillary non-perfusion can be seen as darker, without the capillary plexus.

Statistical analysis

The ISI in zones 1, 2, and 3 were calculated along with 95% confidence intervals and compared using a repeated measures ANOVA, using a significance value of $p < 0.05$ with SPSS software (version 28.0 IBM Corp., Armonk NY, USA).

3. Results

Patient demographics for the primary study group 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 (HTN). 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 neovascularization elsewhere (NVE), and 10 of 11 eyes had neovascularization of the disc (NVD).

ISI for the total retina was 76%. The ISI increased when moving from the posterior pole (42%) to mid periphery (77%) and far periphery (91%). A scatter plot of the data is shown in Fig. 2A. There was statistical significance between zone 1 and zone 2, and zone 1 and zone 3 ($p < 0.001$ and $p < 0.001$ respectively). Zone 2 and zone 3 did not meet criteria for statistical significance ($p = 0.081$).

For eyes with NVG due to PDR, average ISI was 72% for the entire measured retina, 32% in the posterior pole, 72% in the mid-periphery, and 92% in the far periphery. There was statistical significance between zone 1 and zone 2, zone 1 and zone 3, and zone 2 and zone 3 ($p < 0.001$, $p < 0.001$, $p = 0.032$ respectively).

Confirmation analysis with the expanded group, which had UWFA within 6 months of diagnosis and allowed for PRP after development of NVG had a total of 24 eyes. Demographic information of this patient group is listed in Table 2. Average ISI was 73% for the entire measured retina, 35% in the posterior pole, 75% in the mid-periphery, and 93% in the far periphery. There was statistical significance between zone 1 and zone 2 ($p < 0.001$), zone 1 and zone 3 ($p < 0.001$), and zone 2 and zone 3 ($p < 0.001$). A scatter plot of the data is shown in Fig. 2B.

4. 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 patients with PDR [16,23] and CRVO [13,14] 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.

Table 1. Patient demographics and ischemic index.

Age	Gender	Etiology	IOP	HTN	NVE	NVD	Ischemic index			
							Zone 1	Zone 2	Zone 3	Total
50	M	PDR	40	+	+	+	16%	46%	78%	56%
74	M	CRVO	42	+	–	–	86%	100%	100%	95%
51 (OU)	M	PDR	46	+	+	+	59%	94%	100%	90%
			34		–	+	65%	99%	100%	93%
63	F	PDR	51	–	–	+	1%	60%	86%	50%
59	M	PDR	34	+	–	+	65%	100%	100%	92%
48	F	PDR	52	+	+	+	0%	32%	80%	49%
61	F	PDR	60	+	–	+	20%	70%	100%	79%
62	M	CRVO	45	+	–	+	90%	93%	81%	86%
66	F	PDR	45	–	–	+	38%	96%	98%	85%
53	M	PDR	44	+	+	+	27%	55%	82%	59%
Mean			45				42%	77%	91%	76%

Legend: IOP, Intraocular pressure at presentation; HTN, hypertension; NVE, neovascularization elsewhere; NVD, neovascularization of the disc.

Table 2. Patient demographics table for the additional 13 eyes.

Average age	56 years old
Gender	7 Male, 6 Female
Percentage of patients with PDR	85% (11 of 13)
Percentage of patients with CRVO	15% (2 of 13)
Average ischemic index in Zone 1 (all 24 eyes)	34.8%
Average ischemic index in Zone 2 (all 24 eyes)	74.9%
Average ischemic index in Zone 3 (all 24 eyes)	93.1%

Legend: PDR, Proliferative diabetic retinopathy; CRVO, central retinal vein occlusion.

In diabetes, NVG signifies an advanced stage of diabetic retinopathy. Our findings are consistent with prior studies demonstrating higher levels of ischemia 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 [24]. Nicholson *et al.* [19] used levels of ischemia to set a threshold of 118.3 disc diameters of ischemia for identification of proliferative diabetic retinopathy. Speilburg [20] 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%. 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% [22].

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.* [7] 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. We comparably found an average ISI of 76% in our cohort of patients. However, unlike in Tsui's study, our patients all had NVG, which is a more advanced stage, and in 9 out of 11 eyes, the etiology of NVG was PDR and only two eyes had CRVO.

Even though the avenue of study regarding worsening ISI with neovascular glaucoma compared to NPDR or PDR without NVI or NVG may appear intuitive, it is important to directly study and measure ISI to gain insight and knowledge for future management. It is imperative to not only look at overall ISI, but to also evaluate its distribution throughout retina.

In this study, we demonstrate that while there is significant variability in ischemic index of the posterior pole (which varies from ISI 0% to 90%) and the mid-periphery (which varies from ISI 32% to 100%), as well as overall ISI (which varies from 49% to 95%), the far periphery uniformly demonstrated high levels of ISI, with no subject having less than 78% ISI and many patients having complete ischemia. This means that on an individual basis the total average ISI, posterior pole and mid-periphery are less likely to be useful clinically for evaluating risk for development of neovascular glaucoma, as progression can occur through a large range of ISI values. However, based on this data, it is unlikely that patients with low values of ISI in the far periphery will progress to neovascular glaucoma without significant increases in non-perfusion. Likewise, this data points to the fact that it may be incomplete to ignore peripheral ISI with non-widefield analysis when evaluating patients who are at risk for NVG. The periphery needs special attention with respect to risk evaluation and likely management of NVG. These all represent new findings, that

were not previously possible to evaluate prior to UWFA and a select group of patients with treatment naïve new onset neovascular glaucoma.

Interestingly, none of the patients meeting inclusion and exclusion criteria in this study had NVG from ocular ischemic syndrome. This low prevalence of ocular ischemic syndrome is consistent with prior work at LAC + USC site, where out of 245 NVG patients, only 10 were found to have ocular ischemic syndrome [25]. In addition, without direct study of ocular ischemic syndrome, it is not possible to directly transfer the knowledge gained here without inference.

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.

To address the small sample size and further confirm findings, a separate analysis of patients with UWFA provided up to 6 months after diagnosis, and with allowed PRP after diagnosis of NVG but prior to UWFA was also completed. Overall a total of 24 eyes were included. In some instances it is difficult to accurately depict areas of perfusion and non-perfusion through PRP, so this was used as a separate confirmatory analysis, and images were removed that were unable to be analyzed thoroughly. However, results from the increased sample size demonstrated similar findings. In addition, there was statistical significance between all three zones in this enlarged study population.

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. However, given the nature of the disease, large sample studies may not be possible. Often patients present to emergency rooms at various times of the day when fluorescein angiogram may not be available; in addition, patients often have severe corneal edema which obscures fundus view. In our center, from all patients who had NVG, only a small portion (77 eyes) had received fundus imaging and from those, only 11 eyes met inclusion criteria.

Another limitation of this study, is that we were unable to analyze 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.

5. Conclusions

In conclusion, this is the first study in our knowledge to use UWFA in patients with newly diagnosed NVG. While there was significant ISI variability in the average, posterior pole, and mid-periphery, the far periphery uniformly had high levels of ischemia. The data here demonstrates the clinical importance of widefield imaging and an independent analysis directed at the far periphery for patients at risk of NVG. Future directions and implications of this data may include analysis of patients with prior or subsequent PRP, and directing PRP 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 reliably predict patients who are at high risk for developing NVG, not only in the setting of CRVO and PDR but also in the setting of ocular ischemic syndrome.

Abbreviations

CRVO, Central retinal vein occlusion; CVOS, Central Vein Occlusion Study; HTN, Hypertension; ISI, Ischemic Index; NVD, Neovascularization of the disc; NVE, Neovascularization elsewhere; NVG, Neovascular glaucoma; PDR, Proliferative diabetic retinopathy; PRP, Panretinal photocoagulation; UWFA, Ultra-widefield fluorescein angiograph.

Author contributions

HA contributed to the study conception, data analysis, and manuscript revision. CD contributed to material preparation, data collection, the first draft of the manuscript, and manuscript revision. BW participated in manuscript revision. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This research study was conducted retrospectively from data obtained for clinical purposes. Ethics approval was obtained from the Los Angeles County + University of Southern California Medical Center Institutional Review Board approval and in accordance with the ethical standards of the 1964 Declaration of Helsinki. This study was retrospective and does not include identifiable information. Individual informed consent was not required.

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Conflict of interest

The authors declare no conflict of interest.

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