Distribution of Nonperfusion and Neovascularization on Ultrawide-Field Fluorescein Angiography in Proliferative Diabetic Retinopathy (RECOVERY Study): Report 1

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• PURPOSE: To explore the distribution of nonperfusion area (NPA) on ultrawide-field fluorescein angiography (UWF FA) in proliferative diabetic retinopathy (PDR) and its relationship with the presence of neovascularization of the optic disc (NVD) and distribution of neovascularization elsewhere (NVE).

• DESIGN: Prospective, observational case series.

• METHODS: Baseline Optos 200Tx UWF FA images of 38 eyes with treatment-naïve early-stage PDR from the RECOVERY (NCT02863354) study were stereographically projected at the Doheny Image Reading Center. Two independent/masked certified graders manually delineated the NPA and the total visible retinal area (TRA). NPA and TRA were then computed in square millimeters using the manufacturer software. Ischemic index (ISI) was calculated by dividing NPA by TRA. NPA and ISI were correlated with the presence and distribution of neovascularization in the corresponding zones.

• RESULTS: Eyes with NVD appeared to have more severe global NPA than those without ($P = .026$). Although the ISI appeared to increase with increasing distance from the foveal center ($P < .001$), NVE was more likely to be located in the posterior pole than the midperiphery or far-periphery ($P < .001$). Presence of NVE in the posterior polar retina appeared to demonstrate more severe ischemia in the posterior pole and midperiphery than those without ($P < .05$), but interestingly, was not correlated with the severity of overall global ischemia or of ischemia in the far-periphery alone ($P > .05$).

• CONCLUSIONS: Whereas the presence of NVD was associated with the severity of global ischemia, the distribution of NVE did not appear to be influenced by the distribution of ischemia. (Am J Ophthalmol 2019;206: 154–160. © 2019 Elsevier Inc. All rights reserved.)

D IABETIC RETINOPATHY (DR) IS A COMMON MICRO-vascular complication of diabetes, with a prevalence of approximately 35% in individuals with diabetes.[1] Retinal ischemia and subsequent release of angiogenetic factor (vascular endothelial growth factor [VEGF]) has been suggested to be an important factor in progression of DR to the proliferative stage (proliferative diabetic retinopathy [PDR]), which is characterized by the presence of neovascularization on the optic disc (NVD) or elsewhere (NVE). Vitreous hemorrhage and traction retinal detachment secondary to NVD or NVE are important causes of severe vision loss in eyes with PDR.[2]

Ultrawide-field (UWF) fluorescein angiography (FA) has become a useful tool in the diagnosis and management of patients with various retinal vascular disorders, including DR. Several UWF imaging studies have demonstrated that extensive and clinically important pathology may be present in the peripheral retina.[3–6] Wessel and associates reported that UWF images showed 3.9 times more nonperfusion and 1.9 times more neovascularization than traditional Early Treatment of Diabetic Retinopathy Study (ETDRS) 7-field images.[3] Talks and associates noted that wide-field imaging detected approximately 30% more NVE than standard 2-field imaging in DR.[6] Extended targeted retinal photocoagulation in the far periphery and anterior equator was found to obtain better PDR regression compared to conventional pan-retinal photocoagulation.[7] Thus, the peripheral retina and its ischemic status appear to be key issues to consider in the treatment of PDR.

Several studies have previously evaluated the relationship between the extent and distribution of ischemia and the location of neovascular lesions in the setting of retinal vascular diseases.[8–10] Regions of nonperfusion in many of these prior studies, however, were only evaluated qualitatively or categorically. Nicholson and colleagues did quantify nonperfusion on UWF FA and observed that posterior pole nonperfusion of more than 10 disc areas remained the key risk factor for new vessel development compared with areas of nonperfusion confined to the periphery in eyes with central retinal vein occlusion.[11] These findings in eyes with central retinal vein occlusion, however, may not extrapolate to eyes with DR, where VEGF profiles may be quite different.[12]

Recent advances in UWF image processing software with stereographic projection techniques are able to compensate for nonlinear distortions and allow the size of lesions or features of interest to be calculated in millimeters or square millimeters with a high level of accuracy.[13] We have previously used these tools to quantify nonperfusion area (NPA) and ischemic index (ISI = NPA/retinal area) in eyes with diabetic macular edema on UWF FA and observed that ischemia in the midperiphery appeared to influence the severity of diabetic macular edema.[14] We did not, however, evaluate the relationship between nonperfusion and neovascularization using this approach. At the same time, we do recognize that the majority of nonperfusion in eyes with DR is located in the periphery (67% in a study by Fan and associates and 86% in a study by Silva and associates).[14,15] As yet, no studies have evaluated the association between precisely quantified retinal ischemia on UWF FA and the distribution of neovascularization in PDR. With the increasing use of anti-VEGF therapy to treat advanced nonproliferative and proliferative DR, which may necessitate the monitoring of individual neovascular lesions, an improved understanding of the relationship between nonperfusion and NV may be of value. The purpose of this study was to define the extent and distribution of areas of nonperfusion in treatment-naïve early-stage PDR on UWF FA and assess its relationship with the presence and location of NV.

METHODS

• SUBJECTS: The RECOVERY study (ClinicalTrials.gov Identifier: NCT02863354) is a prospective, randomized, interventional clinical trial that was conducted to assess the safety and tolerability of 2-mg intravitreal aflibercept injections given monthly or every 12 weeks for the treatment of retinal nonperfusion associated with PDR. The research was institutional review board (Sterling IRB, Atlanta, Georgia, USA) approved and complied with the Declaration of Helsinki. All subjects signed written informed consent and a Health Insurance Portability and Accountability Act (HIPAA) authorization. To be eligible for the study, patients had to be ≥18 years old, with early treatment-naïve PDR caused by diabetes mellitus (type 1 or 2) in the study eye. Early PDR was defined as the presence of retinal neovascularization in an eye in which pan-retinal photocoagulation (PRP) could be safely deferred in the presence of anti-VEGF intravitreal therapy and with no vitreous hemorrhage obscuring retinal imaging. Participants were required to have ETDRS best corrected visual acuity (BCVA) >23 (Snellen equivalent, >20/400) in the study eye, with substantial nonperfusion defined as greater than 20 disc areas as assessed by the investigator. Clear ocular media and adequate pupillary dilation to permit good-quality fundus photography were required. Previous anti-VEGF therapy, steroid therapy, pan-retinal photocoagulation, or vitreoretinal surgery or an optical coherence tomography central subfield thickness >320 μm were major criteria for exclusion.

• RETINAL IMAGE ACQUISITION: At all visits, participants underwent slit-lamp and dilated ophthalmic examination, UWF color fundus photography, and FA using the Optos 200Tx (Optos plc, Dunfermline, United Kingdom), and spectral-domain optical coherence tomography using the Heidelberg Spectralis HRA+OCT (Heidelberg Engineering, Heidelberg, Germany). Study eyes were dilated using tropicamide 1% and phenylephrine 2.5%, and UWF images were obtained using the Optos 200Tx (Optos plc) centered on the fovea. After intravenous administration of fluorescein dye, UWF FA images were captured at the early (45 seconds), mid (2 minutes 30 seconds), and late (5 minutes) phases, and steered peripherally in 4 directions (nasally, temporally, superiorly, and inferiorly).

• IMAGE PROJECTION: Uncorrected native images from the baseline visit were exported and sent to the Doheny Image Reading Center (Doheny Eye Institute, Los Angeles, California) for grading. Images were stereographically projected using manufacturer software as previously described.[16] This projection technique was achieved by ray tracing every pixel through a combined optical model of the Optos 200Tx and a Navarro UWF model eye with an axial length of 24 mm.[16] This optical model represented the projection method applied by the Optos 200Tx scanning laser ophthalmoscopy platform to create the 2-dimensional optomap. The software also allowed the graders to register the 4 steered images to the on-axis image automatically to create a montage of all images. When the whole retina was not visible on one image, a montage image was created. The NPA was measured in square millimeters by summing the size of all pixels of the segmented lesion. The size of a pixel was defined by its location in the macula-centered image and calculated using spherical trigonometry after it was projected back onto a sphere.[17]

• IMAGE GRADING: As in prior studies, a region of nonperfusion was identified by the absence of retinal
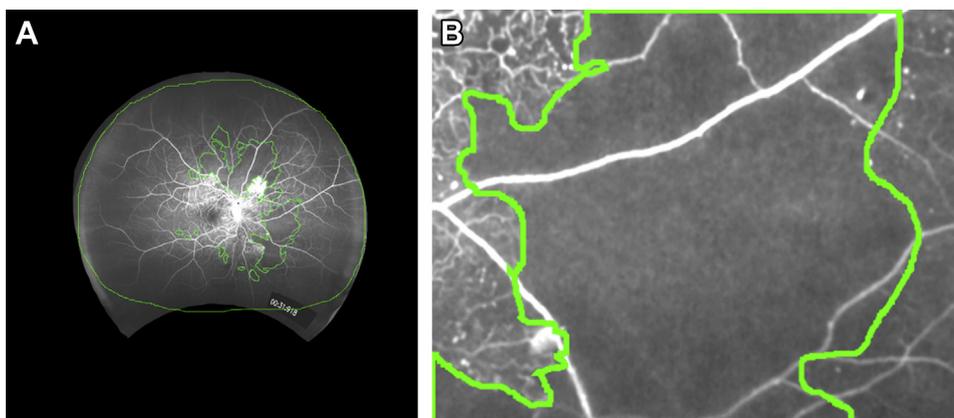
FIGURE 1. Delineation of nonperfusion area and total retinal area (TRA) in proliferative diabetic retinopathy. A. TRA was defined as the total visible retina. B. A region of nonperfusion was identified by the absence of retinal arterioles and/or capillaries with overall hypofluorescence relative to the overall background.
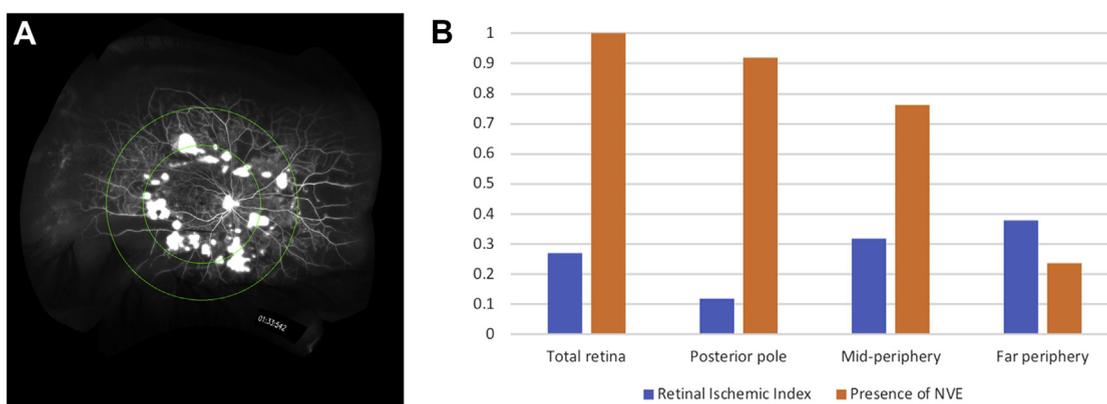
FIGURE 2. Treatment-naïve proliferative diabetic retinopathy on ultrawide-field fluorescein angiography (UWF FA). A. To assess the distribution of neovascularization and nonperfusion, retina on UWF FA was divided into 3 prespecified zones (by radius) by 3 concentric rings centered on the fovea: posterior zone ($<$ 10 mm), midperiphery (10-15 mm), and far periphery ($>$ 15 mm of the fovea). Although neovascularization elsewhere (NVE) was mainly located in the posterior area and midperiphery, nonperfusion was more severe in the periphery than posterior zone. NVE tended to locate in an area with relatively good blood supply adjacent to nonperfused area. This case also had neovascularization on optic disc (NVD). Ischemic index (ISI) for the entire retina was 0.48, which was much higher than the average ISI of 0.27 for the entire cohort and 0.23 for those with NVE but without NVD. B. Histogram plot demonstrated an opposite tendency of distribution between ISI and NVE.

arterioles and/or capillaries with hypofluorescence relative to the overall background (Figure 1).[14] The total retinal area (TRA) was defined as the total visible retina (Figure 1).[18] Two masked, trained, reading center–certified UWF FA graders (W.F. and M.G.N.) independently analyzed the image according to the previously reported standardized grading protocols (Figure 1).[14] Graders were allowed to adjust the contrast and brightness to optimize visualization of the areas of nonperfusion. Using Image J version 1.49b (US National Institutes of Health, Bethesda, Maryland, USA), the graders manually delineated the peripheral extent of the visible retina and the border of the NPA (Figure 1). Grading results were

exported as a binary mask and automatically calculated in square millimeters by summing the size of all pixels using software provided by the manufacturer (Optos plc). The ISI was calculated by dividing the NPA (mm^2) by the TRA (mm^2). If a difference in NPA, TRA, or ISI of >20% was present between graders, the graders met in open adjudication to agree on a single consensus result for each case. When differences smaller than this threshold were present, the results of the 2 graders were averaged to yield a final result for subsequent correlative analyses. Similarly, the center of regions of NVE and NVD were marked in order to define the number and location of these lesions.

• DISTRIBUTION OF ISCHEMIA AND NEOVASCULARIZA-
TION ELSEWHERE: To assess the regional distribution of
NPA (and ISI) and NVE, a prespecified custom grid was
applied to the images. The grid consisted of 2 rings or cir-
cles centered on the fovea with radius of 10 and 15 mm,
dividing the UWF FA image into 3 zones: a posterior
zone (within a radius of 10 mm), a midperipheral ring
(10-15 mm), and a far periphery (>15 mm) (Figure 2A).

• STATISTICAL ANALYSIS: NPA and ISI for the whole
retina as well as within the 3 prespecified zones were
compared between eyes with NVE and/or NVD and those
without. Statistical analysis was performed using the R sta-
tistical analysis package (version 3.3.0). The Shapiro-Wilk
normality test was used to explore the distribution
normality of continuous variables. When the numeric
data were normally distributed, an independent t test was
used to compare means between 2 independent groups,
otherwise the nonparametric analysis (Wilcoxon rank
sum test) was applied. Homogeneity of variances was tested
by the Bartlett test. For more than 2 groups, analysis of vari-
ance or Kruskal-Wallis test (when analysis of variance not
applicable) was performed. Categorical variables were
explored by χ^2 test. When the expected frequency was
less than 5, Fisher exact test was used. Statistical results
were expressed as P values. A P value of less than .05 was
considered statistically significant.

RESULTS

• DEMOGRAPHIC FEATURES OF THE STUDY EYES: A total
of 38 eyes from 38 patients (20 males and 18 females) with
treatment-naïve early-stage PDR were included in the
analysis (Table 1). Mean age was 48.3 ± 11.9 years, with
HbA1c level of 9.8% ± 3.3% and a diabetes mellitus dura-
tion of 14.8 ± 7.8 years (Table 1). Mean BCVA of the
study eye was 78.3 ± 7.3 EDTRS letters (Table 1).

• DISTRIBUTION OF NONPERFUSION AREA AND
ISCHEMIC INDEX IN DIFFERENT RETINAL ZONES: When
considering the entire retina, the mean global NPA was
236.9 ± 142.9 mm^2. The NPA among the different retinal
zones was significantly different ($P < .001$; Table 2), and
more extensive in the far periphery (103.6 ± 97.6 mm^2,
43.7% of total NPA) than in the midperiphery (99.2 ±
54.2 mm^2, 42.9%) and, in particular, the posterior zone
(34.2 ± 24.2 mm^2, 14.4%; Table 2).

For the entire retina, the mean global ISI was 0.27 ±
0.14, corresponding to a regional distribution of posterior
zone, 0.12 ± 0.08; midperiphery, 0.32 ± 0.17; and far
periphery, 0.38 ± 0.27. Thus, the ISI showed a positive
correlation with distance from the center, with more severe
ischemia with increasing distance from the fovea ($P < .001$;
Table 2 and Figure 2B).

TABLE 1. Demographic Features of Study Eyes

Demographic Features	Values
No. of eyes (no. of patients)	38 (38)
Age of first visit, yr	48.3 ± 11.9
Sex, male/female	20/18
Visual acuity (ETDRS)	78.3 ± 7.3 (Snellen equivalent, 20/40 to 20/20)
HbA1c, %	9.8 ± 3.3
DM duration, yr	14.8 ± 7.8

Numeric data are presented as means ± standard deviation.
ETDRS = Early Treatment of Diabetic Retinopathy Study;
HbA1c = glycated hemoglobin; DM = diabetes mellitus.

TABLE 2. Regional Distribution of Nonperfusion Area and
Ischemic Index in Proliferative Diabetic Retinopathy on
Ultrawide-Field Fluorescein Angiography

	NPA, mm^2	P	ISI	P
Posterior	34.2 ± 24.2	<.001	0.12 ± 0.08	<.001
Midperiphery	99.2 ± 54.2		0.32 ± 0.17	
Far periphery	103.6 ± 97.6		0.38 ± 0.27	
Total	236.9 ± 142.9		0.27 ± 0.14	

Numeric data are presented as means ± standard deviation.
Values of P (2-tailed) <.05 were considered statistically signif-
icant.
NPA = nonperfusion area; ISI = ischemic index.
Posterior = <10 mm, Midperiphery = 10-15 mm, Far-
periphery = >15 mm.

• RETINAL ISCHEMIA AND NEOVASCULARIZATION ELSE-
WHERE: Among the 38 eyes, 35 (92.1%) had NVE in the
posterior polar retina, 29 (76.3%) had NVE in the midper-
iphery, and 9 (23.7%) had NVE in the far periphery
(Figure 2). Distribution of NVE among the different zones
was significantly different ($P < .001$; Figure 2B).

Presence of NVE in the posterior polar retina appeared to
demonstrate more severe ischemia (NPA: $P = .013$, ISI: $P =$
.013; Table 3) in the posterior pole and midperiphery (NPA:
$P = .003$, ISI: $P = .002$) than those without, but interest-
ingly, was not correlated with the severity of overall global
ischemia or of ischemia in the far-periphery alone ($P >$
.05; Table 3). The presence of NVE in the mid- or far periph-
ery did not correlate with the severity of retinal ischemia (P
> .05; Table 3).

• RETINAL ISCHEMIA AND NEOVASCULARIZATION OF
THE DISC: Twenty-two of the 38 (57.9%) eyes had NVD.
Eyes with NVD were noted to have a significantly larger
global NPA compared to those without (298.2 ±
158.8 mm^2 vs 192.3 ± 114.8 mm^2, $P = .026$; Table 4).
Regional analysis showed that eyes with NVD tended to

TABLE 3. Correlation of Retinal Ischemia With the Presence of Neovascularization Elsewhere in Proliferative Diabetic Retinopathy on Ultrawide-Field Fluorescein Angiography

	NVE in Posterior Retina			NVE in Midperiphery			NVE in Far Periphery		
	Presence (n = 35)	Absence (n = 3)	P	Presence (n = 29)	Absence (n = 9)	P	Presence (n = 9)	Absence (n = 29)	P
NPA, mm^2									
Posterior	36.4 ± 23.9	8.3 ± 8.2	.013	31.1 ± 21.6	44.2 ± 30.5	.262	23.3 ± 13.1	37.5 ± 26	.184
Midperiphery	104.5 ± 53	37.3 ± 18.2	.003	92.3 ± 47.2	121.4 ± 71.1	.275	111.5 ± 42	95.4 ± 57.6	.373
Far periphery	105 ± 100.5	86.9 ± 62.1	.96	105.1 ± 107.2	98.5 ± 61.4	.736	160.5 ± 150.7	85.9 ± 68.7	.173
Total	245.9 ± 144.5	132.6 ± 68.9	.122	228.5 ± 146.1	264.1 ± 136.5	.478	295.3 ± 188.5	218.8 ± 124	.417
ISI									
Posterior	0.123 ± 0.08	0.028 ± 0.028	.013	0.105 ± 0.073	0.149 ± 0.103	.262	0.079 ± 0.044	0.127 ± 0.088	.184
Midperiphery	0.338 ± 0.17	0.116 ± 0.056	.002	0.294 ± 0.151	0.404 ± 0.225	.196	0.351 ± 0.129	0.31 ± 0.187	.475
Far periphery	0.391 ± 0.276	0.277 ± 0.127	.644	0.342 ± 0.242	0.513 ± 0.321	.162	0.421 ± 0.289	0.37 ± 0.266	.711
Total	0.278 ± 0.145	0.14 ± 0.058	.085	0.247 ± 0.132	0.334 ± 0.169	.184	0.292 ± 0.151	0.26 ± 0.144	.589

Numeric data are presented as means ± standard deviation.

Values of P (2-tailed) <.05 were considered statistically significant.

NVE = neovascularization elsewhere; NPA = nonperfusion area; ISI = ischemic index.

have more severe NPA in the midperiphery (P = .031; Table 4) and far periphery (P = .029; Table 4) but interestingly not in the posterior polar region (P > .05; Table 4).

DISCUSSION

IN THIS ANALYSIS OF UWF FA IMAGES IN TREATMENT-NAÏVE early-stage PDR, we precisely quantified retinal nonperfusion in square millimeters and evaluated its relationship with the distribution of neovascularization. Eyes with NVD were observed to have more severe global ischemia than those without. The relationship between NVE and nonperfusion, however, was less consistent. Only posterior polar NVE demonstrated a correlation, but only with nonperfusion in the posterior pole and midperiphery.

Overall, in our study we observed that these eyes with early PDR had a mean global NPA of 236.9 mm^2. This level is considerably higher than the value of 196.1 mm^2 from our previous report from a cohort of eyes with diabetic macular edema (DAVE study).[14] Of note, those eyes had less advanced background retinopathy. Our values for NPA in the present study may also be compared to those measured by Silva and associates.[15] Silva reported an NPA of 196.8 mm^2 in eyes without predominately peripheral lesions (PPL), compared to eyes with PPL that had an NPA of 306.1 mm^2.[15] The very large amounts of NPA in the PPL group in Silva's study is somewhat surprising, as only 33% of subjects had evidence of PDR (compared with 100% in our study). On the other hand, the PPL group in Silva's study had a much longer duration of diabetes mellitus (26 years vs 15 years), and unlike our cohort where all PDR subjects were limited to only early PDR, the PDR

subjects in Silva's study may have had considerably more advanced disease.

In concordance with the NPA, the average ISI for the entire retina in the present study was 0.27, which is also higher than that of the no-PPL group (0.25) but smaller than the PPL group (0.43) in Silva's study.[15] In addition to the above reasons, the observed differences may also be due to a relatively bigger TRA in our study (877 vs 726.5 mm^2), as a larger TRA (the "denominator") can lead to a smaller ISI. The larger TRA in our study may be a reflection of our steering and montaging approach, which may have allowed a larger area to be visualized. At the same time, even the TRA in our study is still considerably smaller than the reported TRA in normal subjects (977 mm^2).[18] This may reflect the difficulties in capturing images of the entire retina in real-world subjects where media opacities and patient cooperation may present acquisition challenges. This reality further argues for the use of ISI as a preferred metric over the absolute area of nonperfusion.

The ISI in our study also varied among the different retinal zones and appeared to increase with increasing distance from the fovea. This finding corroborated our observation from eyes with diabetic macular edema in the DAVE study.[14] Also, in both studies, the vast majority of nonperfusion was located in the mid- and far peripheries (86% in the present study and 67% in DAVE).[14]

Despite the increasingly severe ischemia with greater eccentricity, the distribution of NVE appeared to show a paradoxically inverse correlation, with NVE more commonly appearing in the posterior pole compared to the mid- and far periphery (Figure 2). Jansson and associates also reported that the majority of NVE lesions may be identified in the posterior polar region, and in particular inferonasal to the optic nerve and along the superior vascular arcades.[19]

TABLE 4. Correlation of Retinal Ischemia With the Presence of Neovascularization on Optic Disc in Proliferative Diabetic Retinopathy on Ultrawide-Field Fluorescein Angiography

| | NVD | | |
	Presence (n=16)	Absence (n=22)	P
NPA, mm^2			
Posterior	35.8 ± 21.8	33 ± 26.2	.53
Midperiphery	121.7 ± 55.2	82.8 ± 48.2	.031
Far periphery	140.7 ± 114.6	76.5 ± 74.6	.029
Total	298.2 ± 158.8	192.3 ± 114.8	.026
ISI			
Posterior	0.121 ± 0.074	0.112 ± 0.089	.53
Midperiphery	0.389 ± 0.179	0.27 ± 0.156	.04
Far periphery	0.457 ± 0.299	0.328 ± 0.236	.162
Total	0.321 ± 0.155	0.228 ± 0.125	.056

Numeric data are presented as means ± standard deviation.

Values of P (2-tailed) <.05 were considered statistically significant.

NVD = neovascularization on optic disc; NPA = nonperfusion area; ISI = ischemic index.

Fema and associates noted incident neovascularization in 282 eyes out of 3121 patients with background DR followed over a 1-year period and reported that the superotemporal quadrant (6 mm from the optic disc) was the most frequent initial site.[20] In Wessel and associates' study, although UWF images showed 3.9 times more NPA than traditional ETDRS 7-field images, only 1.9 times more neovascularization was detected.[3] This apparent paradoxical relationship between NVE and ISI distribution may offer additional clues into the pathophysiology of these neovascular lesions (Figure 2B). It may be that the areas of greatest nonperfusion are severely injured and thus incapable of mounting a proliferative response with VEGF stimulation. Thus, NVE may arise in these more healthy areas posteriorly that are capable of responding to the rising levels of VEGF. This hypothesis is supported by the fact that eyes with posterior polar NVE had more severe nonperfusion in the adjacent midperiphery.

There may be other factors (aside from ischemia), however, that may significantly impact the distribution of NV. The vitreous-retina relationship is thought to be important in preretinal vascular proliferation. In regions where there is complete vitreous separation, there may not be a favorable scaffold for NV to develop and organize, and thus these areas may be relatively resistant to NV development. On the other, in areas where there may be firm vitreous attachment (eg, at the disc or along the vascular arcades) with surrounding areas of vitreous detachment, there may be a predisposition to develop proliferation.[21]

In contrast to NVE, there was a more clear-cut relationship between the severity of NPA and the development of NVD. The vessels on the optic disc are perhaps the furthest from the ischemic retina (which as noted above, is primarily located in the mid- and far-peripheral retina), and thus large amounts of nonperfusion and ischemia may potentially be required in order for a sufficiently high VEGF gradient to reach the optic nerve. Thus, the presence of NVD (as opposed to only NVE) may provide a surrogate for a more severely ischemic eye. As such, it is not surprising that a large area of NVD (greater than approximately one-fourth or one-third of a disc area), presents a high risk for vision loss in eyes with PDR.[22]

Our study is not without limitations, including its relatively small sample size and the presumed inability to capture the entire normal vascularized retinal area (based on the expected TRA from previous normative studies) in some subjects. In addition, as the study was only limited to eyes with early PDR, the findings may not generalize to eyes with more advanced PDR. Moreover, because eyes were required to have at least 20 disc areas of nonperfusion to be included in the study, our findings may not apply to early PDR patients with less severe ischemia. Given the relationship between ischemia and proliferation, however, we would expect such eyes to be uncommon.

Our study, however, also has many strengths including its prospective design, the use of a standardized UWF FA acquisition protocol with eye steering, and the use of 2, independent, certified reading center graders with expertise in UWF FA grading. In addition, we corrected for peripheral distortion using stereographic projection methods. We have previously reported that measurements may be altered by nearly 15% if stereographic projection correction is not applied.[13]

In summary, in eyes with early PDR, retinal nonperfusion appears to increase with increasing distance from the fovea. Eyes that develop NVD appear to have more severe overall ischemia compared with eyes that do not. NVE appears to develop more commonly in the posterior polar retina compared to more peripheral regions, and the topographical distribution of NVE appears to be influenced by factors other than ischemia alone.

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