Classification of Regions of Nonperfusion on Ultra-widefield Fluorescein Angiography in Patients with Diabetic Macular Edema

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• PURPOSE: To classify retinal nonperfusion regions (NPRs) in patients with diabetic macular edema (DME) and assess the relationship with severity of DME.

• DESIGN: Prospective, observational case series.

• METHODS: Forty eyes of 29 patients with treatment-naïve center-involved macular edema secondary to diabetes mellitus were included (The DAVE study, NCT01552408) in this analysis. Ultra-widefield fluorescein angiography (UWF FA) images were transmitted to the Doheny Image Reading Center, where they were corrected using stereographic projection to adjust for peripheral distortion. Two independent, certified graders manually evaluated the NPR and classified the nonperfusion as being associated with leakage or without leakage. The size of these 2 subtypes of NPR were computed in mm^2 and assessed across the entire retina and within 3 concentric retinal zones. The relationship between subtype of NPR and the severity of DME was assessed.

• RESULTS: In 40 eyes with treatment-naïve DME, visual acuity was significantly correlated with central macular thickness (CMT) and macular volume (MV). The NPR with leakage was positively correlated with CMT ($R = 0.408$, $P = .009$) and MV ($R = 0.399$, $P = .011$), whereas the NPR without leakage was negatively correlated with CMT ($R = -0.468$, $P = .002$) and MV ($R = -0.473$, $P = .002$). The NPR with leakage in the posterior region was significantly greater compared to the mid-periphery and the far periphery ($P < .001$), whereas the NPR without leakage was significantly greater in the mid-periphery compared with the far periphery or the posterior region ($P = .001$).

• CONCLUSION: In patients with DME, the severity of DME appears to be positively correlated with NPR with leakage but negatively correlated with NPR without leakage. These findings may have implications for the pathophysiology of DME and the design of protocols for targeted laser in these eyes. (Am J Ophthalmol 2019;206:74–81. © 2019 Elsevier Inc. All rights reserved.)

DIABETIC MACULAR EDEMA (DME) IS A MAJOR contributor to vision loss among patients with diabetes.[1] The incidence of diabetes is increasing in the world, resulting in a corresponding rise in the prevalence of diabetic retinopathy (DR) and DME.

Injury to the retinal microcirculation, a consequence of chronic hyperglycemia, leads to retinal hypoxia, which is thought to be a major contributor to the development of DME.[2–4] Ischemia stimulates the production of vascular endothelial growth factor (VEGF), which can lead to the breakdown of the blood–retinal barriers and may cause DME through an increase in retinal vessel permeability (leakage).[5,6]

Traditionally, the retinal nonperfusion region (NPR) has primarily been characterized by fluorescein angiography (FA). More recently, optical coherence tomography (OCT) angiography has become available and provides superior vascular detail and more consistent visualization of the macular circulation.[7] Although wider OCT angiography scan patterns and "extended field" protocols have become available,[8] assessment of the far peripheral perfusion remains a challenge with current OCT angiography technology. To assess the nonperfusion in more peripheral regions, initial FA-based studies largely relied on montages of multiple smaller 30°- to 45°-field images of the retina. A limitation of montage-based angiography is that the montage invariably includes images that are not all obtained at the same time in the angiography sequence. Subsequent investigations have used ultra-widefield FA (UWF FA) devices, such as the OPTOS systems, which allow capture of a single high-resolution 200° retinal field covering >80% of the retinal surface. Furthermore, the recent ability to project the UWF images stereographically allows for

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correction of the inherent peripheral retinal distortion, thereby allowing accurate measurements of area from posterior pole to the retinal periphery.[9,10] Given these advances in UWF FA imaging technology, this approach has now become the criterion standard for assessment of peripheral nonperfusion in retinal vascular diseases and has been used to study the relationship between retinal NPR and DME severity.[11,12]

This nonperfused hypoxic retina and the surrounding penumbra of "underperfused" retina are believed to upregulate the hypoxia-inducible factor transcriptional cascade, leading to secretion of a multitude of vasoactive cytokines, including VEGF-A and erythropoietin, which lead to both proliferative DR (PDR) and DME.[4] These observations led to renewed interest in targeted retinal photocoagulation (TRP) to areas of peripheral retinal nonperfusion as a potential adjunctive treatment for DME. Initial retrospective studies suggested a potential beneficial effect.[13] This concept was subsequently evaluated in a small prospective randomized trial, the DAVE study, which failed to demonstrate any benefit of TRP for visual acuity, reduction of edema, or in the number of required anti-VEGF injections.

The lack of consistent success of TRP has prompted a re-evaluation of the relevance of peripheral nonperfusion on UWF FA. Although previous studies using UWF FA images have found that retinal nonperfusion is significantly associated with DME in treatment-native patients with DR,[14,15] these initial studies did not correct for the expected nonlinear distortion that can make peripheral lesions appear larger. As a result, the NPR was quantified as the number of pixels instead of using precise areas in mm^2, and an ischemic index was calculated by dividing the NPR by the total retinal area (TRA). Such an approach, however, still does not accurately reflect the actual size of NPR.[10] Studies comparing NPR and ischemic index before and after stereographic projection have shown significant differences, and more recent studies assessing nonperfusion in retinal vascular diseases have used these correction approaches.[11,16]

Recently, after applying stereographic projection to UWF FA images to calculate precise NPR measurements in eyes with DME, Silva and associates[12] did not observe an association between total NPR and the presence of clinically significant macular edema. We also found no relationship between the total NPR and the severity of DME.[17] However, an initial post hoc review of UWF FA images from the DAVE study suggested that not all regions of nonperfusion delineated by masked graders had the same appearance. Whereas some NPR area were entirely "dark," others had a somewhat "grayish" appearance because of associated leakage from larger vessels in the area. We hypothesized that these different subtypes of NPR may have different relevance to the presence and extent of DME and to the response to therapy.

To evaluate this hypothesis, we quantified these separate subtypes of nonperfusion (with and without leakage) in stereographically projected UWF FA images from patients with DME in the DAVE trial and correlated these parameters with OCT-derived measurements of macular edema.

METHODS

• **SUBJECTS:** We analyzed baseline UWF FA images of participants in the DAVE study (ClinicalTrials.gov identifier NCT01552408; Food and Drug Administration Investigational New Drug identifier 113691), a prospective, randomized, interventional clinical trial of patients with DME that compared the efficacy and safety of ranibizumab monotherapy versus combination therapy of ranibizumab with UWF FA–guided retinal photocoagulation targeted to areas of capillary nonperfusion. Institutional review board/ethics committee approval (Sterling IRB, Atlanta, GA) was secured and written informed consent was obtained on all subjects. The study design was consistent with the tenets of the Declaration of Helsinki and complied with the terms of the Health Insurance Portability and Accountability Act. All subjects were >18 years of age and had been diagnosed with ME attributed to diabetes. Eligibility criteria included an Early Treatment Diabetic Retinopathy Study best-corrected visual acuity between 24 and 78 letters (Snellen equivalent, 20/320 and 20/32, respectively), and central retinal subfield thickness ≥300 μm as measured by spectral-domain SD-OCT (Heidelberg Spectralis). Images from 40 eyes of 29 patients with treatment-naïve DME were included in this analysis. All eyes had severe non-PDR or early PDR in addition to DME as defined above.

• **IMAGE ACQUISITION:** The study methodology has been described in detail in previous publications.[9,11] Briefly, UWF FA images were obtained using the Optos 200Tx (Optos plc, Dunfermline, United Kingdom). After intravenous administration of fluorescein dye, UWF FA images were captured at the early (45 seconds), middle (2 minutes and 30 seconds), and late (5 minutes) phases of the angiography, and steered peripherally in 4 directions (superiorly, inferiorly, nasally, and temporally).

• **IMAGE PROJECTION:** Data were collected at the Retina Consultants of Houston (Houston, Katy, and Woodlands, Texas, USA) and images were transmitted to the Doheny Image Reading Center (Doheny Eye Institute, Los Angeles, California, USA) for masked grading. All UWF FA images were projected stereographically using the manufacturer's software (Optos plc).[18] The graders then used the software to register the 4 steered images to the on-axis image to automatically create a montage of all images if the single image failed to display the entire peripheral retina in some patients. The software also allows an accurate measurement of retinal area (in mm^2) by summing the size of all pixels accounting for peripheral image distortion.[11]

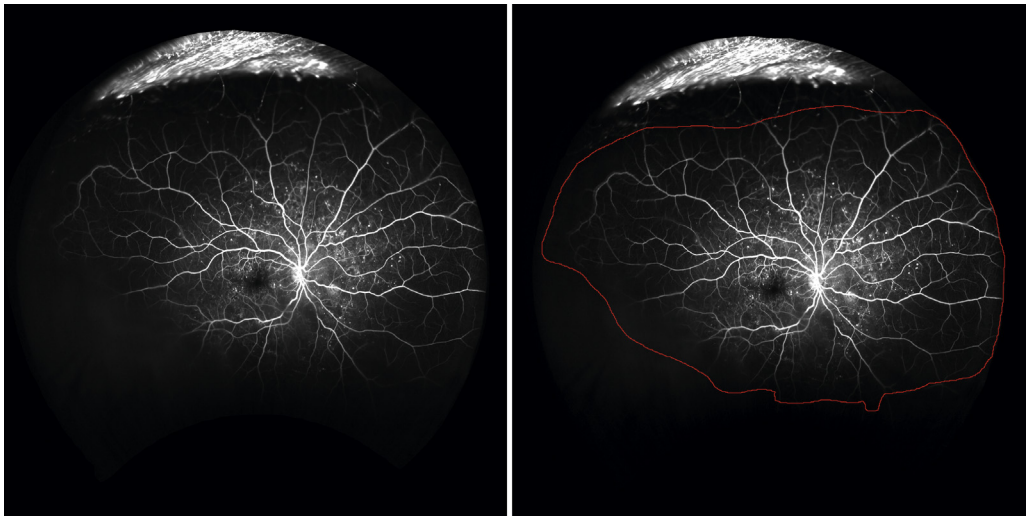

FIGURE 1. Grading of total visible retinal area on a stereographically projected ultra-widefield fluorescein angiographic (UWF FA) image. The UWF FA image is shown on the left and the corresponding image with grading of the total retina area shown as an overlay mask on the UWF FA image. The total retina area was defined as the region over which the retinal vasculature could be clearly visualized and thus gradable for the presence of capillary nonperfusion.

The TRA was defined as the entire region of the fundus where the retinal vasculature was in sharp focus and gradable for the presence of nonperfusion. A region of nonperfusion was identified by the absence of retinal arterioles and/or capillaries with overall hypofluorescence relative to the overall background.

• **IMAGE GRADING:** Projected images were then graded using Image J software (US National Institutes of Health, Bethesda, Maryland, USA). Two masked, trained, reading center–certified UWF FA graders independently performed dual grading of all the images according to previously reported standardized grading protocols.[11] Graders were allowed to adjust the contrast and brightness to optimize visualization of the area of nonperfusion and then manually delineated the peripheral extent of the TRA (Figure 1) and the border of the NPR. The early and middle phase frames were used to determine the presence of a nonperfusion region, and the presence of leakage was evaluated from a midphase FA image using stereoscopic viewing and with reference to early phase images (Figure 2). The NPR with leakage was defined by the presence of a grayish (and not black) appearance at the level of the retina (but still substantially reduced compared with surrounding regions) that appeared to increase from early to late phases with some associated leakage evident from larger vessels passing through the nonperfused region. Some residual dilated capillaries and microaneurysms could still be identified in these regions (Figure 3,A). NPR without leakage was defined as continuous uniform regions of hypofluorescence, which were deemed by the grader to be entirely "dark," just leaving the larger vessel or residual capillaries without any leakage (Figure 3,B).

Grading results were exported as a binary mask and automatically calculated in mm^2 by summing the size of all pixels using software provided by the manufacturer (Optos plc). The data were then averaged between the 2 graders to obtain final values for subsequent correlation analysis with OCT parameters.

• **CLASSIFICATION OF NPR:** To assess the regional distribution of NPR with leakage and NPR without leakage, a prespecified custom grid was applied to the images. Specifically, the regional distribution of NPR with leakage and NPR without leakage were determined within concentric rings centered on the fovea. The UWF images were divided into 3 zones by 2 concentric circles centered on the fovea (10 and 15 mm in diameter), 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-peripheral ring (>15 mm). As reported in our previous publication, the area of NPR in these 3 zones were 63.9 ± 45.5 mm^2, 93.5 ± 68.9 mm^2, and 38.7 ± 35.6 mm^2, respectively.[17]

The NPR "leakage" index was adapted from the ischemic index and similarly calculated, where areas of NPR with leakage were quantified in mm^2 and expressed as a percentage of the TRA in UWF FA images.

• **ASSESSMENT OF DME:** The OCT images were analyzed to confirm the presence and extent of DME. The Heidelberg SD OCT acquisition protocol for the DAVE study consisted of a 6 × 6 mm macular cube (20 × 20, 49 lines, 768 A-scans per line) with 9-times image averaging. CMT was computed as the mean thickness within the foveal central subfield (central 1-mm) and macular volume (MV) was derived from the entire 6- × 6-mm volume. Both CMT and

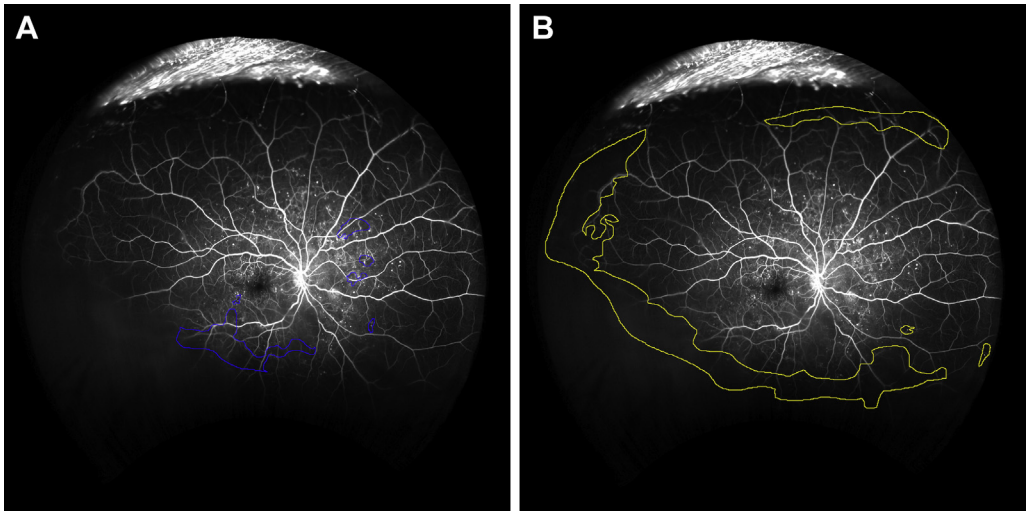

FIGURE 2. Grading of nonperfusion region on a stereographically projected ultra-widefield fluorescein angiographic (UWF FA) image. The UWF FA image with grading of the nonperfusion region (NPR) shown as an overlap. (A) NPR with leakage is shown as a blue overlay and NPR without leakage (B) is shown as a yellow overlay. NPR was identified by the absence of retinal arterioles and/or capillaries with overall hypofluorescence relative to the overall background.

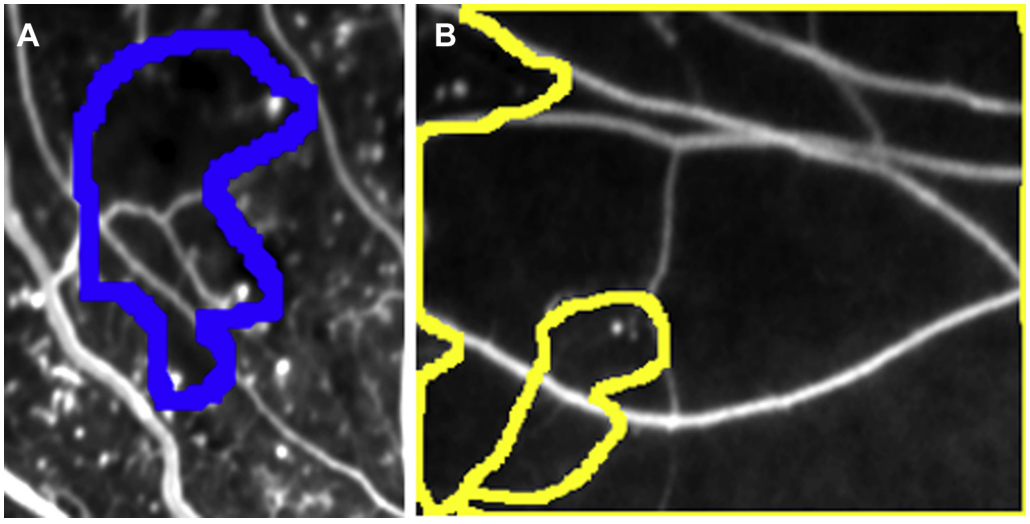

FIGURE 3. Grading of regions of nonperfusion with and without leakage on ultra-widefield fluorescein angiography. High magnification sections of an ultra-widefield fluorescein angiographic image of a patient with diabetic retinopathy are shown to illustrate regions on nonperfusion with leakage. (A) A region of nonperfusion with leakage outlined in blue. (B) A region of nonperfusion without leakage outlined in yellow. The nonperfusion region with leakage was defined by the presence of some grayish background fluorescence (but still substantially reduced compared with surrounding regions), which appeared to increase from early to late phases with some associated leakage evident from larger vessels passing through the nonperfused region. Some residual dilated capillaries and microaneurysms can be identified in these regions. The nonperfusion region without leakage was defined as continuous uniform regions of hypofluorescence, which were deemed by the grader to be entirely "dark."

MV were obtained automatically by Heidelberg Eye Explorer software, although the graders did review the scans to confirm the absence of segmentation errors.

• **STATISTICAL ANALYSIS:** Statistical analysis was performed using SPSS 23 software (IBM Corp, Armonk, New York, USA). The agreement between graders was assessed by intraclass correlation coefficients (ICCs), and an ICC > 0.80 was prespecified as the threshold for good agreement. A Shapiro–Wilk test was used to explore the distribution normality of the continuous variable. Homogeneity of variances was tested using the Levene test.

The comparisons of different types of NPR in different zones were analyzed with 1-way analysis of variance or the Kruskal–Wallis test (when the analysis of variance test was not applicable). The Spearman correlation was used to test for associations between variables (severity of DME with NPR with and without leakage). $P < .05$ was considered statistically significant.

RESULTS

• **DEMOGRAPHIC FEATURES OF THE STUDY EYES:** A total of 40 eyes (6 PDR and 34 nonproliferative DR) from 29 patients with treatment-naïve DME were enrolled. Mean visual acuity was 59.6 ± 13.2 Early Treatment Diabetic Retinopathy Study letters, with a mean CMT of 536.9 ± 192.8 μm and mean MV of 11.9 ± 2.7 mm^3. Visual acuity was significantly correlated with CMT (R = −0.418, $P = .008$) and MV (R = −0.449, $P = .004$). The detailed demographic characteristics of the DAVE trial cohort have been previously published.[4,17]

• **CLASSIFICATION OF NPR IN DIFFERENT RETINAL ZONES:** For the total retina, the mean global NPR was 196.1 ± 123.4 mm^2. The NPR present among the different retinal zones was significantly different ($P < .001$).[17] The NPR with leakage and the NPR without leakage among the different retinal zones were also significantly different (NPR with leakage: $P < .001$; NPR without leakage: $P = .001$). The NPR with leakage at the posterior zone was 39.34 ± 25.84 mm^2, which was significantly larger than the mid-periphery (29.23 ± 24.40 mm^2) or the far periphery (11.47 ± 19.46 mm^2). The NPR without leakage in the mid-periphery was 64.15 ± 70.96 mm^2, which was larger than the far periphery (29.90 ± 31.66 mm^2) and the posterior zone (23.63 ± 39.22 mm^2; Figure 4,A).

• **DISTRIBUTION OF NPR "LEAKAGE" INDEX IN DIFFERENT RETINAL ZONES:** For comparison with parameters reported in other studies, the NPR with leakage area was divided by the TRA to compute a NPR with leakage index. For the entire retina, the mean global NPR with leakage index was 0.13 ± 0.09; and within the specific regions was: posterior zone, 0.13 ± 0.09; mid-periphery, 0.12 ± 0.10; and far periphery, 0.05 ± 0.08. The NPR with leakage index among the different retinal zones was also significantly different ($P < .001$; Figure 4,B).

• **ASSOCIATION OF NPR WITH DME SEVERITY:** The global NPR for the entire retina was not associated with CMT ($P = .146$) or MV ($P = .135$). The NPR in the mid periphery was negatively associated with CMT (R = −0.314, $P = .049$) and MV (R = −0.320, $P = .044$). The NPR in the posterior zone and far periphery were not associated with CMT (posterior zone: $P = .349$; far periphery: $P = .526$) or MV (posterior zone: $P = .324$; far periphery: $P = .512$).

Importantly, the NPR with leakage was positively correlated with CMT (R = 0.408, $P = .009$) and MV (R = 0.399, $P = .011$), indicating that the more extensive the NPR with leakage, the more severe the edema. Contrarily, NPR without leakage was negatively correlated with CMT (R = −0.468, $P = .002$) and MV (R = −0.473, $P = .002$). Similarly, the NPR with leakage index for the entire retina was also positively associated with CMT (R = 0.348, $P = .028$) and MV (R = 0.338, $P = .033$; Table).

• **REPRODUCIBILITY FOR ASSESSING NPR AND SUBTYPES OF NPR:** The ICC between the independent masked graders for total area of NPR was 0.958; and was 0.910, 0.965, and 0.890 for the posterior, mid-peripheral, and peripheral zones, respectively. The ICC between graders for total area of NPR with leakage was 0.945; and was 0.816, 0.880, and 0.275 for the posterior, mid-peripheral, and peripheral zones, respectively. Finally, the ICC between graders for total area of NPR without leakage was 0.993; and was 0.987, 0.992, and 0.993 for the posterior, mid-peripheral, and peripheral zones, respectively.

DISCUSSION

IN THIS STUDY, WE DEVELOPED A STRATEGY FOR SUBCLASSIfying and quantifying the nonperfused regions of the retina into those without evidence of retinal vascular leakage and those with leakage. Importantly, we observed that this subclassification could be performed reliably and demonstrated better correlations with the severity of macular edema in these diabetic eyes.

The distribution of these subtypes of nonperfusion was not even across the fundus. More extensive NPR without leakage was observed in the mid-periphery compared with other regions. The distribution of NPR without leakage is in agreement with previous analyses of overall NPR, which have noted that NPR is usually first recognized in the mid-periphery of the retina, and that the mid-peripheral retina may thus be more prone to develop capillary closure than the central retina in diabetic eyes.[19,20] Silva and associates[12] also observed that the mid-periphery contained the greatest amount of nonperfusion on UWF FA.

NPR with leakage, in contrast, was more extensive posteriorly compared with the more peripheral regions. This is perhaps not surprising because the posterior retina is known to have the highest density of retina vessels and higher overall metabolic activity, which have been suggested to be features which may make this region more prone to leakage.[21] Since retinal edema is clearly present in this region in these eyes with DME, it is expected that

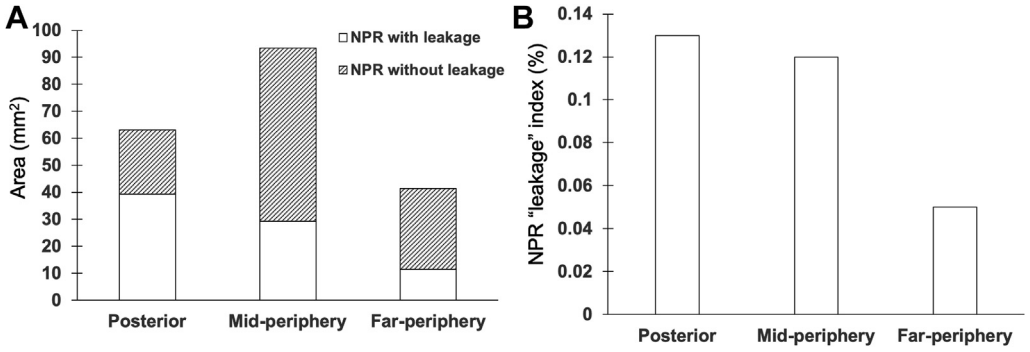

FIGURE 4. Classification of nonperfusion region in different retinal zones. The ultra-widefield images were divided into 3 zones: a posterior zone (within a radius of 10 mm), a mid-peripheral ring (10–15 mm), and a far-peripheral ring (> 15 mm). The distribution of nonperfusion region, including leakage area and without leakage area, is shown on the left, and the distribution of nonperfusion region "leakage" index is shown on the right.

TABLE. Correlation of Nonperfusion Region with Severity of Diabetic Macular Edema

	CMT		MV	
	R	*P* Value[a]	R	*P* Value[a]
NPR	−0.234	.146	−0.240	.135
NPR with leakage	0.408	.009	0.399	.011
NPR without leakage	−0.468	.002	−0.473	.002
NPR "leakage" index	0.348	.028	0.338	.033

CMT = central macular thickness; MV = macular volume; NPR = nonperfusion region; R = Spearman correlation coefficient.

[a]Calculated using linear Spearman correlation. Two-tailed *P* values < .05 were considered statistically significant.

leakage should be present here, and therefore it is not surprising that the nonperfused regions here may have concomitant leakage. This regional variation in NPR with leakage is also demonstrated by the NPR with leakage index, which also varied among the different retinal zones and appeared to decrease with increasing distance from the fovea.

Most importantly, subtyping the regions of NPR revealed new associations with DME severity. Like previous analyses, we could not identify a significant relationship between total NPR and DME severity. The failure to find such an association seemed to be consistent with the overall primary result of the DAVE trial, which failed to demonstrate any benefit of targeted laser to these regions of peripheral nonperfusion. Of note, Sim and associates[22] reported the absence of any relationship between peripheral leakage and macular edema but did observe a trend toward a thicker retina in eyes with a high peripheral leakage index. Their study did not correct for the expected nonlinear distortion, and they quantified the area by expressing the number of pixels. Croft and associates[10] found UWF images inherently include significant distortion and area measurements may have up to a fivefold error if each pixel is assumed to have an equal size on the retina. We observed, however, that the extent of NPR with leakage was positively correlated with DME severity after adjusting the distortion with image projection. In contrast, NPR without leakage was negatively correlated, explaining why total NPR showed no correlation. This observation makes sense, because regions of nonperfusion with leakage may be ischemic but still have viable tissue capable of producing VEGF and other cytokines that can lead to vascular leakage and consequent edema. High VEGF levels are known to contribute to the progression of DME. Numerous clinical studies have confirmed the pathophysiologic role of VEGF in DME,[3,4] and long-term suppression of VEGF has been shown to reduce DME and improve visual acuity.[23,24] In contrast, NPR without leakage may have no viable cells because there is no blood supply and may be incapable of producing vasoactive metabolites; therefore, VEGF production is actually decreased because of severe retinal cell dysfunction. Furthermore, more extensive NPR without leakage may mean less viable retina requiring oxygen supply and overall lower vascular demand to the retina as a whole, which may explain the otherwise counterintuitive negative correlation with DME severity. To sum up, it is possible that only a small amount of retinal ischemia is necessary to trigger the production of VEGF and other cytokines. That DME could be observed at any DR severity level supports this argument. This was further tested in the present study by divided the NPR into 2 major subgroups (nonperfusion with leakage and those without). This observation has potentially important therapeutic implications because lasering areas of NPR without leakage (which do not positively correlate with DME severity) may be fruitless, and possibly even counterproductive given the negative association with DME. In contrast, targeted laser to NPR with leakage may yield better results. This hypothesis

must be validated in future prospective studies. However, as these subtypes of NPR were thus far not distinguished in therapeutic laser studies, they could potentially explain the inconsistent results in these trials, as NPR with leakage may have been variably identified and included in the treatment protocol.

Our observation of the importance of subclassifying NPR in DME eyes is corroborated by studies in other retinal vascular diseases. Sakimoto and associates[25] classified ischemic changes in eyes with branch retinal vein occlusion into 3 grades (full perfusion, partial perfusion, and complete obstruction) and found a significant positive correlation between the CMT and the partial perfusion area. The partially perfused areas in this study may be similar to the NPR with leakage in our study. In Neubauer and associates' study of DME,[26] foveal thickness on OCT correlated significantly with the overall degree of leakage in FA. This is perhaps expected because retinal vascular leakage is thought to be the primary source of fluid accumulation in the retina leading to DME.[27]

The difference between regions of nonperfusion with and without leakage should ideally be studied in careful histologic studies with detailed evaluation of the retinal microvasculature. In the interim, a potentially useful alternative that may provide some insights is OCT angiography. OCT angiography has been shown to better depict the retinal vasculature compared with fluorescein angiography.[28] OCT angiography could be used to verify whether these region of presumed nonperfusion with leakage indeed demonstrate some partial capillary preservation. Of note, it has recently been shown that areas of suspected perfusion recovery in eyes with retinal vascular disease after anti-VEGF therapy were in fact found to be persistently nonperfused when studied by OCT angiography. Wider field OCT angiography (12 × 12 mm) is now available and may be useful for NPR detection,[29] but the wider field comes with the consequence of a reduction in resolution that may impair visualization of the fine retinal vasculature. Zhang and associates[30] reported an "ultra-wide" OCT angiography imaging protocol for DR patients (montaged SD-OCTA images) in the detection of NPR,[30] which can provide up to 100° of high vascular resolution. These wider high-resolution images, however, come at the expense of longer acquisition times, and still do not get as wide as UWF FA. We would recommend that future UWF FA studies also include widefield OCT angiography images to evaluate some of these regions of suspected nonperfusion on UWF FA, even if current OCT angiography technology does not allow the most peripheral regions to be evaluated. These correlative findings should also allow us to further refine our grading approach for UWF FA images.

Our study does have some limitations that should be considered when assessing our results. First, although the data were collected in a prospective, randomized trial, the analyses described in this report are post hoc and the sample size is still relatively small. In addition, although we corrected the peripheral distortion by assuming an ideal axial length of 24 mm, we were not able to apply the corrections using the actual axial lengths for individual subjects. Moreover, as noted above, nonperfusion as assessed by UWF FA was not confirmed by OCT angiography. Nonetheless, the NPR on UWF FA as defined by our grading protocol could be identified and quantified reliably, including for both NPR subtypes. As these NPR subtypes correlated with DME severity, they are still potentially useful as biomarkers for further study.

In summary, by further subclassifying regions of nonperfusion into those with and without leakage we were able to demonstrate correlations between nonperfusion on UWF FA and the severity of DME. Specifically, the amount of nonperfusion with leakage was positively correlated with DME severity whereas nonperfusion without leakage was negatively correlated. If these findings are replicated in future larger, prospective longitudinal studies, they may be useful for prognostication as well as possibly for revising the design of targeted UWF laser studies.

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