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Automated Quantification of Capillary Nonperfusion Using Optical Coherence Tomography Angiography in Diabetic Retinopathy

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Abstract

Importance—Macular ischemia is a key feature of diabetic retinopathy (DR). Quantification of macular ischemia has potential as a biomarker for DR.

Objective—To assess the feasibility of automated quantification of capillary nonperfusion as a potential sign of macular ischemia using optical coherence tomography (OCT) angiography.

Design, Setting, and Participants—An observational study conducted in a tertiary, subspecialty, academic practice evaluated macular nonperfusion with 6 × 6-mm OCT angiography obtained with commercially available 70-kHz OCT and fluorescein angiography (FA). The study was conducted from January 22 to September 18, 2014. Data analysis was performed from October 1, 2014, to April 7, 2015. Participants included 12 individuals with normal vision serving as controls and 12 patients with various levels of DR.

Main Outcomes and Measures—Preplanned primary measures were parafoveal and perifoveal vessel density, total avascular area, and foveal avascular zone as detected with 6 × 6-mm OCT angiography and analyzed using an automated algorithm. Secondary measures included the agreement of the avascular area between the OCT angiogram and FA.

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Author Contributions: Dr Jia had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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*Acquisition, analysis, or interpretation of data:*Hwang, Gao, Liu, Lauer, Bailey, Wilson, Jia.
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Results—Compared with the 12 healthy controls (11 women; mean [SD] age, 54.2 [14.2] years), the 12 participants with DR (4 women; mean [SD] age, 55.1 [12.1] years) had reduced parafoveal and perifoveal vessel density by 12.6% (95% CI, 7.7%-17.5%; $P < .001$) and 10.4% (95% CI, 6.8%-14.1%; $P < .001$), respectively. Total avascular area and foveal avascular zone area were greater in eyes with DR by 0.82 mm^2 (95% CI. 0.65-0.99 mm^2; $P = .02$) and 0.16 mm^2 (95% CI, 0.05-0.28 mm^2; $P < .001$). The agreement between the vascular areas in the OCT angiogram and FA had a κ value of 0.45 (95% CI, 0.21-0.70; $P < .001$). Total avascular area in the central 5.5-mm-diameter area distinguished eyes with DR from control eyes with 100% sensitivity and specificity.

Conclusions and Relevance—Avascular area analysis with an automated algorithm using OCT angiography, although not equivalent to FA, detected DR reliably in this small pilot study. Further study is necessary to determine the usefulness of the automated quantification in clinical practice.

Macular ischemia is a key feature of diabetic retinopathy (DR). Because DR is an important determinant of visual function and prognosis,[1-5] quantification of macular ischemia has potential as a biomarker for DR. An ideal biomarker reliably detects the disease with high specificity from an accessible modality that requires little intervention or training. Objective and reproducible measurement of capillary loss, however, is not a trivial problem. Earlier attempts[6-9] to assess the degree of macular ischemia were highly labor intensive and required detailed manual segmentation or systematic qualitative grading based on standard photographs. Although these studies confirmed the value of measurement of macular ischemia, the methods are seldom applied for everyday clinical use.

Automated quantification of macular ischemia could translate its theoretical usefulness into clinical practice. We report on our experience quantifying capillary nonperfusion as a potential sign of macular ischemia in DR with optical coherence tomography (OCT) angiography and fully automated vessel density, macular avascular area, and foveal avascular zone (FAZ) area analysis, taking advantage of this procedure's ability to obtain a high-contrast macular angiogram that is independent of pigmentation, leakage, or dye injection.[10-13] This study explored the feasibility of using measurements derived from OCT angiography and automated image analysis as potential biomarkers for DR.

Methods

Patients with various levels of DR were selected from the Retina Division of the Casey Eye Institute for clear media and the ability to fixate. Participants provided written informed consent; they did not receive financial compensation. The study's protocol was approved by the institutional review board of Oregon Health & Science University and conducted in compliance with the Declaration of Helsinki.[14] The study was performed from January 22 to September 18, 2014; there was no follow-up. Data analysis was performed from October 1, 2014, to April 7, 2015. The participants underwent standard ophthalmic examination and fluorescein angiography (FA). The level of retinopathy was determined by the treating physician using the International Diabetic Retinopathy Severity scale.[15] Optical coherence tomography angiography scans were acquired over 6 × 6-mm regions using a 70-kHz OCT (RTVue-XR Avanti; Optovue, Inc) with a scan pattern of 2 repeated B scans at 304 raster

positions, with each B scan consisting of 304 A scans. Flow signal is detected by examining consecutive scans of the same area and comparing the differences or decorrelation between the scans. The efficiency of detecting flow signal was improved with the split-spectrum, amplitude-decorrelation angiography algorithm,[16-18] which divides the OCT spectrum into narrower spectral bands and averages the decorrelation of these bands. This process significantly improves the signal to noise ratio, allowing a high-quality 6 × 6 mm angiogram using a commercially available 70-kHz system to be obtained without extending the acquisition time.[12,19] We then removed motion artifacts by aligning the images in x and y directions, then merging those images.[20] En face projection of the flow signal internal to the retinal pigment epithelium created the retinal angiograms. Two scans were performed for each eye, and the scan with better signal strength was chosen for analysis. Images with a signal strength index below 50 or significant residual motion artifacts were excluded from the study. We selected the eye with clearer media for the study eye. When the media were similar, the eye that was selected by the physician for transit in FA was chosen for inclusion in the study.

We selected 12 age-matched individuals as controls from a pool of healthy volunteers with clear media and without retinal disease, including age-related macular degeneration, epiretinal membrane, retinal vascular occlusions, or systemic diagnoses of diabetes mellitus, hypertension, or cardiovascular disease. After providing written informed consent, the control participants also underwent standard ophthalmic examination and imaging with OCT angiography using the protocol described above. The control retinal images were analyzed for the mean decorrelation signal in FAZ (central area with 0.6-mm-diameter) to establish the reference for detection of flow in the macula. The individuals serving as controls did not undergo FA.

Vessel density was calculated as the percentage of pixels with flow signal greater than the threshold (2.3 SDs above the mean decorrelation signal for the FAZ for the controls). Parafoveal vessel density was calculated for the ring-shaped area between a 0.3- and 1.25-mm radius from the center of the macula. Perifoveal vessel density was calculated for the area between 1.25 and 2.75 mm from the foveal center (Figure 1B). A circular area with a diameter of 5.5 mm was used instead of the entire 6 × 6-mm^2 area to reduce the effects of the artifacts at the edge of the scan.

Flow signal lower than 1.2 SDs above the mean decorrelation signal in the FAZ of the controls identified the avascular areas. An algorithm removed avascular areas of less than 50 contiguous pixels (0.02 mm^2). These restrictions localized the avascular area to the FAZ in the controls and prevented areas within the normal capillary network from being counted. Total avascular area was calculated by summing these areas including the FAZ (Figure 1C). The area values were corrected for magnification variation associated with axial length variation as previously described[21].

The Mann-Whitney test was used to compare these parameters between the patients with DR and the healthy controls. The diagnostic accuracy of each parameter was assessed by sensitivity and area under the receiver operating characteristic curve (AROC).[22] Repeatability of each bio-marker was assessed by evaluating the intraclass correlation for

eyes that had 2 high-quality images. Two images were acquired without using image registration or eye tracking and were completely refocused each time. Parafoveal and perifoveal vessel density, as well as the FAZ area of the eyes with DR, were analyzed for correlation to logMAR visual acuity. All statistical tests were done using SPSS, version 20 (IBM).

Each FA was qualitatively graded by a masked grader for capillary dropout using modified Early Treatment of Diabetic Retinopathy Study (ETDRS) criteria and the classic grid of concentric circles with diameters of 1, 3, and 6 mm.[7] The severity grading scale was limited to no capillary nonperfusion, questionable capillary dropout, and definite capillary dropout. The areas of capillary dropout identified by the OCT angiography automated algorithm were compared with the FA grading for agreement in localization of capillary dropout detection, not for correlation with quantitative analysis done with grids of different radii as described above. A reliability analysis using the κ statistic was performed to determine the consistency between FA and OCT angiography.

Results

Twelve control eyes and 12 eyes with DR had adequate OCT angiography image quality for image analysis. Two eyes with DR were excluded from the study because of residual motion artifacts following registration that resulted in poor-quality images. Because OCT angiography is extremely sensitive to motion, some images had significant artifacts even with the motion correction algorithm. Operator learning curve, media opacity, and patient cooperation were factors in poor-quality images. Of 12 participants with DR (4 women; mean [SD] age, 55.1 [12.1] years), 9 (75%) had proliferative DR, 2 (17%) had mild nonproliferative DR, and 1 (8%) had moderate nonproliferative DR. Seven individuals had diabetic macular edema. Best-corrected Snellen visual acuity ranged from 20/15 to 20/150. The details of each participant are presented in eTable 1 in the Supplement. Of the 12 control participants, 11 were women, and the mean age was 54.2 (14.2) years.

Compared with the controls, the parafoveal and perifoveal vessel densities were significantly reduced in eyes with DR, and the FAZ area and total avascular area were greater in eyes with DR (Table 1, Figure 1). Two of the controls had nonperfusion areas outside the FAZ detected by the automated algorithm in one ETDRS sector each. Those areas were small (eFigure in the Supplement). Holding the specificity at 95%, the FAZ area was the least sensitive biomarker for DR and the total avascular area in the central 5.5-mm site was the most sensitive (Table 1 and eTable 2 in the Supplement). The AROC of 1 for total avascular area indicated that it could detect DR with 100% sensitivity and specificity. The overall diagnostic accuracy for the FAZ was the lowest, at AROC 0.77. The limit of false-positive error was set at 0.0125, using Bonferroni correction for multiple analyses.

Within-visit measurement repeatability of these markers was assessed by analyzing eyes with 2 high-quality scans in the same visit (Table 2). The pooled SD of retinal vessel density measurements ranged from 2.5% to 6.6%. The overall pooled SD was 4.0%, which corresponded to a coefficient of variation of 4.8%. The repeatability was good compared with the difference between the DR and control groups (Table 1 and eTable 2 in the

Supplement), which were 12.6% (95% CI, 7.7%-17.5%; $P < .001$) for the parafoveal vessel density and 10.4% (95% CI, 6.8%-14.1%; $P < .001$) for the perifoveal vessel density. The repeatability of the FAZ area was greater in the DR group (0.05 mm^2), which was less than the difference between the DR and control groups (0.16 mm^2 [95% CI, 0.05-0.28 mm^2]; $P < .001$). The repeatability of the total avascular area was also worse in the DR group (0.11 mm^2), but this was much smaller than the difference between the DR and control groups (0.82 mm^2 [95%CI, 0.65-0.99 mm^2]; $P = .02$). The Pearson correlation coefficient values between logMAR visual acuity and parafoveal vessel density, perifoveal vessel density, and FAZ size were not significant: 0.19 ($P = .55$), −0.08 ($P = .81$), and −0.17 ($P = .60$), respectively.

Regarding the localization of nonperfusion between OCT angiography and FA (Table 3), OCT angiography identified areas of nonperfusion in 44 of 53 quadrants (sensitivity, 83.0%), with the FA grader identifying at least definite capillary dropout. Optical coherence tomography angiography was in agreement with FA that there was no capillary dropout in 10 of 15 quadrants (specificity, 66.7%). Of 40 quadrants that were graded as questionable capillary dropout on the FA, 13 (32.5%) did not have identified areas of nonperfusion on OCT angiogram and 27 (67.5%) did. Excluding the quadrants that were graded as questionable on FA, the FA and OCT angiography agreed on the presence or absence of nonperfusion in 68 (79.4%) of the quadrants. The Cohen κ coefficient assessing the agreement was 0.45 (95% CI, 0.21-0.70; $P < .001$).

Optical coherence tomography angiography detected nonperfusion in some areas where leakage of fluorescein obscured the area of perfusion. However, there were some areas of nonperfusion clearly seen on FA but not detected by the automated algorithm on OCT. In these areas, small specks of flow signal, possibly noise, broke up the area of nonperfusion, making them smaller than the algorithm detection threshold of 50 contiguous pixels (Figure 2).

Discussion

Macular ischemia is associated with visual function and useful for predicting DR progression.[1-5] In the age of antivascular endothelial growth factor therapy for DR, the assessment of macular ischemia may become more important because the effects of antivascular endothelial growth factor therapy can obscure clinical findings that predict the risk of progression.[23] Fluorescein angiography has been the primary method for evaluating macular ischemia, but it has limitations. The contrast varies with the timing of dye injection, the degree of pigmentation, and media opacity.[24] Low contrast can obscure the details of capillaries, making automated computerized evaluation of macular ischemia difficult.[25-27] Although rigorous, standards-based qualitative grading has been shown[1] to be meaningful and reproducible, it is labor intensive and seldom used. In practice, FA evaluation of retinal ischemia remains subjective and semiquantitative. Optical coherence tomography angiography has the potential of providing objective automated evaluation of macular capillary nonperfusion as a potential sign of ischemia since it can detect flow signal at high contrast independent from factors that affect contrast in FA. This study evaluated the

feasibility of using OCT angiography to automatically quantify capillary nonperfusion as a potential sign of macular ischemia.

Vessel density measurements estimate the degree of capillary loss over an area. Because the transverse resolution and sampling intervals of the 6 × 6-mm volume scan (19.4 μm) are greater than capillary width (approximately 5.0 μm),[28,29] the apparent capillary width on en face OCT angiogram is larger than the actual value, which results in an overestimation of the vessel density.[30] These values calculated from OCT angiography are nevertheless useful for distinguishing eyes with DR from healthy eyes since the degree of overestimation is consistent because the association between the capillary width and sampling density remains relatively constant.

The threshold for vessel detection for this study was determined empirically by comparing vascular areas with the FAZ of healthy eyes. In the future, in vitro modeling using capillary phantom[31] may set a more accurate threshold for vessel detection. In this study, vessel density measurements showed statistically significant differences between the DR and healthy eyes but had limited sensitivity to detect DR.

The repeatabilities for vessel density and avascular area measurements were good compared with the difference between the DR and control groups and were sufficient for single measurements to detect individual differences between the 2 groups. Although the FAZ area had better repeatability compared with the total avascular area in absolute terms (millimeters squared), it was not a good diagnostic variable because of the small difference between the DR and control groups and the high population variability within the control group. Although the FAZ area has been most frequently analyzed in the literature,[7,26,27,32] its relatively high variability in healthy individuals makes it less useful as a biomarker for detecting DR.[28,33] However, the total avascular area appears to be an excellent biomarker for DR because healthy eyes have essentially no retinal avascular area outside of the FAZ, but eyes with DR had greatly increased macular avascular area outside of the FAZ.

Fluorescein angiography has been the criterion standard for detecting capillary dropout. In practice, however, inconsistent contrast and fluorescein leakage limits its ability to detect capillary dropout reliably. These factors and other differences in technology may explain the modest agreement between OCT angiography and FA in detection of nonperfusion. When there were disagreements, OCT angiography identified areas of nonperfusion that leakage had obscured on FA. Optical coherence tomography angiography infrequently missed areas of nonperfusion identified in FA. Motion artifacts and the relatively low threshold for detecting flow may have reduced its sensitivity.

The relatively small 6 × 6-mm field used in this study excludes disease outside the macula and may underreport disease, particularly compared with wide-field angiography. Although the degree of macular ischemia in DR has been correlated with the risk of progression of retinopathy[8,27] and the severity of peripheral ischemia,[3] this relatively small field remains a limitation of technology. The efficiency of the split-spectrum amplitude-decorrelation angiography algorithm allows angiography over a wider field of view[16]; a higher-speed OCT

and montaging techniques can improve the field of view detected by OCT angiography in the future.

This study had a small sample of patients. Most of these patients had proliferative disease and only 3 eyes had nonproliferative disease. Whether these biomarkers would perform as well in patients with less advanced retinopathy or detect disease in individuals with diabetes mellitus who do not have clinically evident retinopathy is not known. Further study with a larger number of patients, including those with a distribution of the full spectrum of DR, is necessary to adequately evaluate the technology as a biomarker. A prospective design would be required to assess the prognostic value of OCT angiography for disease progression.

Conclusions

In this pilot study, we used OCT angiography to demonstrate automated and objective quantification of capillary nonper-fusion as a potential sign of macular ischemia in DR. This fully automated analysis of the macular capillaries may make objective details of microvasculopathy more accessible to health care professionals. In addition, the rapid, noninvasive, dye-free acquisition of images may make more routine use of angiography possible. This technique was able to measure non-perfusion with good repeatability. There was reasonable agreement between OCT angiography and the FA, especially given the fundamental differences in the technology. Further clinical study is needed to fully demonstrate the usefulness of OCT angiography–derived biomarkers in DR.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Key Points

Question

What is the feasibility of automated quantification of capillary nonperfusion as a potential sign of macular ischemia?

Findings

An automated algorithm using optical coherence tomography angiography can detect and quantify macular nonperfusion in diabetic retinopathy.

Meaning

Macular avascular area detected with this algorithm could be a useful biomarker in diabetic retinopathy, but further study is needed.

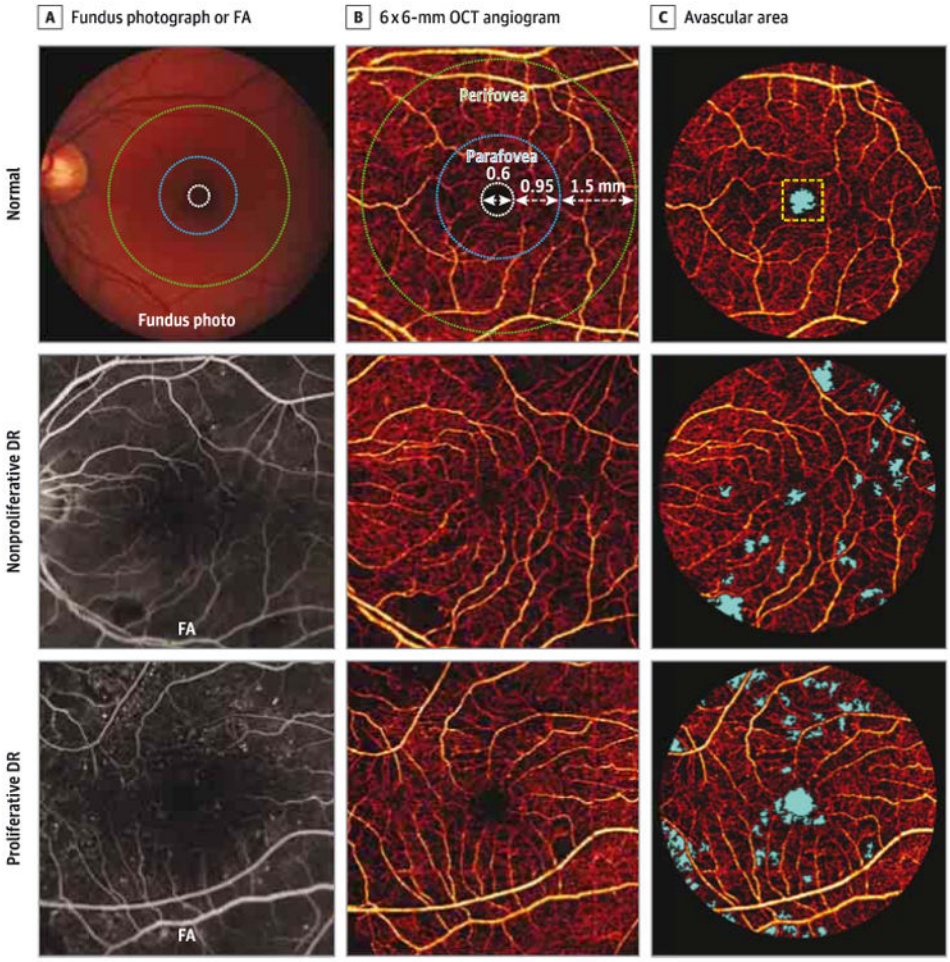

Figure 1. Automated Avascular Area Detection in Optical Coherence Tomography (OCT) Angiography

Example images of normal (control). nonproliferative diabetic retinopathy (DR), and proliferative DR. FA indicates fluorescein angiography. Dotted circles in the first row indicate sectors for perifovea (green circles) and parafovea (blue circles). In the third column, light blue corresponds to automatically detected areas of nonperfusion (highlighted by dashed box in the first row).

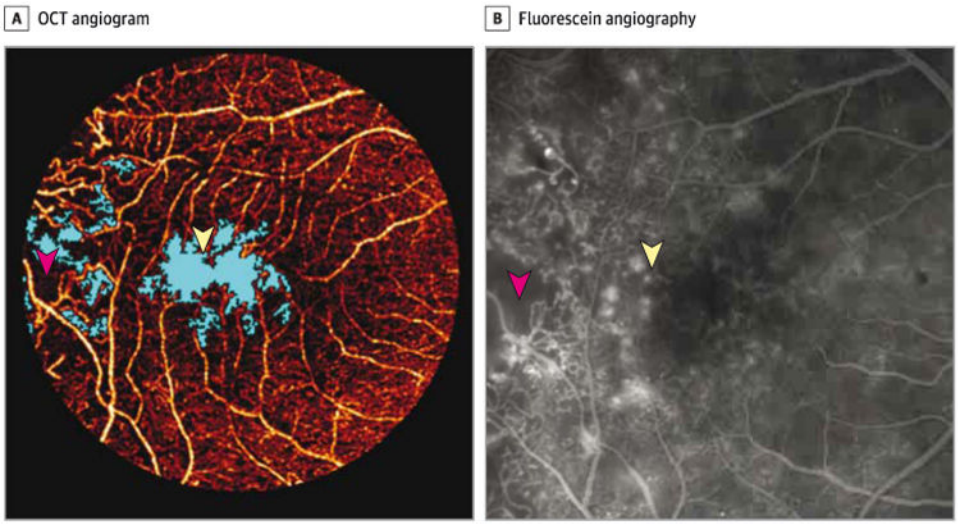

Figure 2. Nonperfusion as Seen on Optical Coherence Tomography (OCT) Angiography vs Fluorescein Angiography (FA)

A, An OCT angiogram showing nonperfuson area detected in an eye with diabetic retinopathy in light blue. B, The corresponding FA. Yellow arrowheads disclose an area of capillary dropout seen on OCT but not FA. Red arrowheads point to an area of nonperfusion seen on FA that was not detected by the aIgorithm.

Table 1

Vessel Densities and Avascular Areas in DR and Control Eyes

Characteristic	Pooled SD				
	Control (n = 12)	DR (n = 12)	*P* Value[a]	Sensitivity, % (95% CI)[b]	AROC
Vessel density, %					
Parafoveal	89.6 (4.2)	77.0 (7.0)	<.001	58.3 (27.8-84.7)	0.96
Perifoveal	91.2 (3.3)	80.7 (5.1)	<.001	75.0 (42.8-94.2)	0.96
Area, mm^2					
FAZ	0.17 (0.05)	0.33 (0.19)	.024	50.0 (21.2-78.8)	0.77
Total avascular	0.18 (0.07)	1.00 (0.27)	<.001	100 (73.4-100)	1

Abbreviations: AROC, area under receiver operating characteristic curve; DR, diabetic retinopathy: FAZ, foveal avascular zone.

[a]Calculated using the Mann-Whitney test. Using Bonferroni correction for multiple analyses, tine limit of false-positive error is 0.0125.

[b]Sensitivity to detect DR with specificity held at 95% on the AROC.

Table 2

Within-Visit Repeatability of OCT Angiography Measurements[a]

Characteristic	Control (n = 9)	DR (n = 6)
Vessel density, % area		
Parafoveal	3.0	6.6
Perifoveal	2.5	3.8
Area, mm^2		
FAZ	0.030	0.046
Total avascular	0.044	0.111

Abbreviations: DR, diabetic retinopathy; FAZ, foveal avascular zone.

[a]Repeatability was measured by pooled SD.

Table 3

Agreement Between OCT Angiography and FA Capillary Nonperfusion Grading by ETDRS Macular Quadrants

OCT Angiography	Capillary Nonperfusion FA	No Nonperfusion FA	Questionable FA
Capillary nonperfusion	44	5	27
No nonperfusion	9	10	13

Abbreviations: ETDRS, Early Treatment of Diabetic Retinopathy Study; FA, Fluorescein angiography; OCT, optical coherence tomography.