OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY FEATURES OF DIABETIC RETINOPATHY

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Purpose: To describe the optical coherence tomography angiography features of diabetic retinopathy.

Methods: Using a 70 kHz optical coherence tomography and the split-spectrum amplitude decorrelation angiography algorithm, 6 mm × 6 mm 3-dimensional angiograms of the macula of 4 patients with diabetic retinopathy were obtained and compared with fluorescein angiography for features cataloged by the Early Treatment of Diabetic Retinopathy Study.

Results: Optical coherence tomography angiography detected enlargement and distortion of the foveal avascular zone, retinal capillary dropout, and pruning of arteriolar branches. Areas of capillary loss obscured by fluorescein leakage on fluorescein angiography were more clearly defined on optical coherence tomography angiography. Some areas of focal leakage on fluorescein angiography that were thought to be microaneurysms were found to be small tufts of neovascularization that extended above the inner limiting membrane.

Conclusion: Optical coherence tomography angiography does not show leakage but can better delineate areas of capillary dropout and detect early retinal neovascularization. This new noninvasive angiography technology may be useful for routine surveillance of proliferative and ischemic changes in diabetic retinopathy.

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Diabetic retinopathy is a microangiopathy that causes capillary occlusion, vascular hyperpermeability, and neovascularization (NV) in the retinal vasculature.[1] Detailed clinical examination for grading disease severity for risk of progression and vision loss is the standard of care,[2] but ophthalmic angiography has played a critical role in the understanding and care of the disease. Early Treatment of Diabetic Retinopathy Study (ETDRS) examined the fluorescein angiographic features of the posterior pole of patients with nonproliferative diabetic retinopathy and correlated the specific features with their risk of disease progression.[3,4] Fluorescein angiography (FA) is also used to identify retinal neovascularization (RNV) in situations where clinical examination cannot detect RNV or distinguish from other anomalous appearing vessels on the retinal surface.

Although angiography provides valuable additional information compared with clinical examination or fundus photography, it is not part of the routine diabetic eye examination. Fluorescein angiography requires venipuncture and intravenous injection of a dye that has a moderate risk of nausea and a rare but well-documented risk of anaphylaxis and death.[5] Also, a standard protocol FA acquires images over 10 minutes with repeated exposure to a very bright light source,[6] which can cause significant discomfort for patients.

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Optical coherence tomography (OCT) angiography, a novel imaging technique that uses decorrelation between resampled images to detect flow to construct two- and three-dimensional images of blood flow within the eye, offers an alternative angiographic technique without some of the drawbacks of FA. Our group has developed the split-spectrum amplitude decorrelation angiography algorithm for efficiently detecting flow signals for angiography.[7] Applying this algorithm, an OCT angiogram in areas up to 6 mm × 6 mm can be acquired in 3.5 seconds without intravenous injection. This study describes features of diabetic retinopathy as seen on OCT angiography.

Methods

Patients were selected from the Retina Division of the Casey Eye Institute for the diagnosis of proliferative diabetic retinopathy, clear media, and the ability to fixate. They underwent comprehensive ophthalmic examination and FA. Three-dimensional OCT angiography scans were acquired over 6 mm × 6 mm regions using a commercially available 70 kHz OCT (RT-VUE XR; Optovue, Fremont, CA) with a scan pattern of 5 repeated B-scans at 216 raster positions and each B-scan consisting of 216 A-scans. Flow was detected with the highly efficient split-spectrum amplitude decorrelation angiography algorithm,[7,8] and motion artifact was removed by three-dimensional orthogonal registration and merging of two scans. Retinal angiogram was created by projecting the flow signal internal to the Bruch membrane in en face orientation. The signal above the internal limiting membrane was further segmented to isolate RNV. Specific features seen on OCT angiogram were then compared with FA features of the same area. Images were examined for classic features of diabetic retinopathy, such as microaneurysms (MAs) and RNV, as well as angiographic characteristics described by the ETDRS Report No. 11,[4] including foveal avascular zone (FAZ) enlargement and irregularity, capillary dropout, and arteriolar abnormalities.

Patients were enrolled after obtaining an informed consent in accordance with a protocol approved by the Institutional Review Board at Oregon Health & Science University and in compliance with the Declaration of Helsinki.

Results

Four patients with proliferative diabetic retinopathy were imaged for the study. Their characteristics are summarized in Table 1.

Table 1. Patient Characteristics

Subject	Age	Gender	DM Type	Imaged Eye	Visual Acuity
1	41	F	Type 2	OD	20/20
2	47	M	Type 2	OS	20/40
3	28	M	Type 1	OS	20/30+2
4	53	F	Type 1	OS	20/50

OD, right eye; OS, left eye.

Foveal Avascular Zone Size and Shape

For all eyes imaged, the FAZ size and shape were gradable according to the ETDRS grading criteria using OCT angiography. Optical coherence tomography angiogram disclosed the area of perifoveal capillary loss that corresponded well to FA. Figure 1 shows an OCT angiogram with superposed ETDRS grid that shows that the size of the FAZ is between 300 μm radius (dotted circle) and 500 μm (solid inner circle). At the same magnification, it was easier to grade OCT angiogram for FAZ characteristics than FA, as the capillaries were seen at a higher contrast on OCT angiogram.

In one case, the FAZ was difficult to grade on FA as the capillary details were obscured by leakage even in early transit (Figure 2). With OCT angiography, the details were not affected by leakage and the FAZ size and shape could be easily graded (Table 2).

Capillary Dropout and Arteriolar Characteristics

Areas of capillary dropout beyond the FAZ were readily identified with OCT angiogram in all eyes. Figure 3 demonstrates good correlation in the areas of capillary dropout between OCT angiogram and FA. In this case, OCT angiography identified additional areas of capillary dropout not seen on FA as early diffuse fluorescein leakage made some areas of capillary dropout indistinguishable from areas with intact capillaries in FA. In other cases, areas of capillary dropout that were obvious on OCT angiogram were difficult to resolve with FA (e.g., upper right hand corner of Figure 2). In this series, OCT angiography was more consistent in demonstrating the presence or absence of retinal capillaries than FA.

An area of intraretinal microvascular abnormality, characterized by dilated terminal vessels surrounded by an area of capillary loss, was identified with OCT angiography and FA. The exact shape of the intraretinal microvascular abnormality differed slightly between 2 images (Figure 2). Arteriolar narrowing and wall staining seen on FA was seen as extreme attenuation of vessel caliber on OCT angiography (Figure 3).

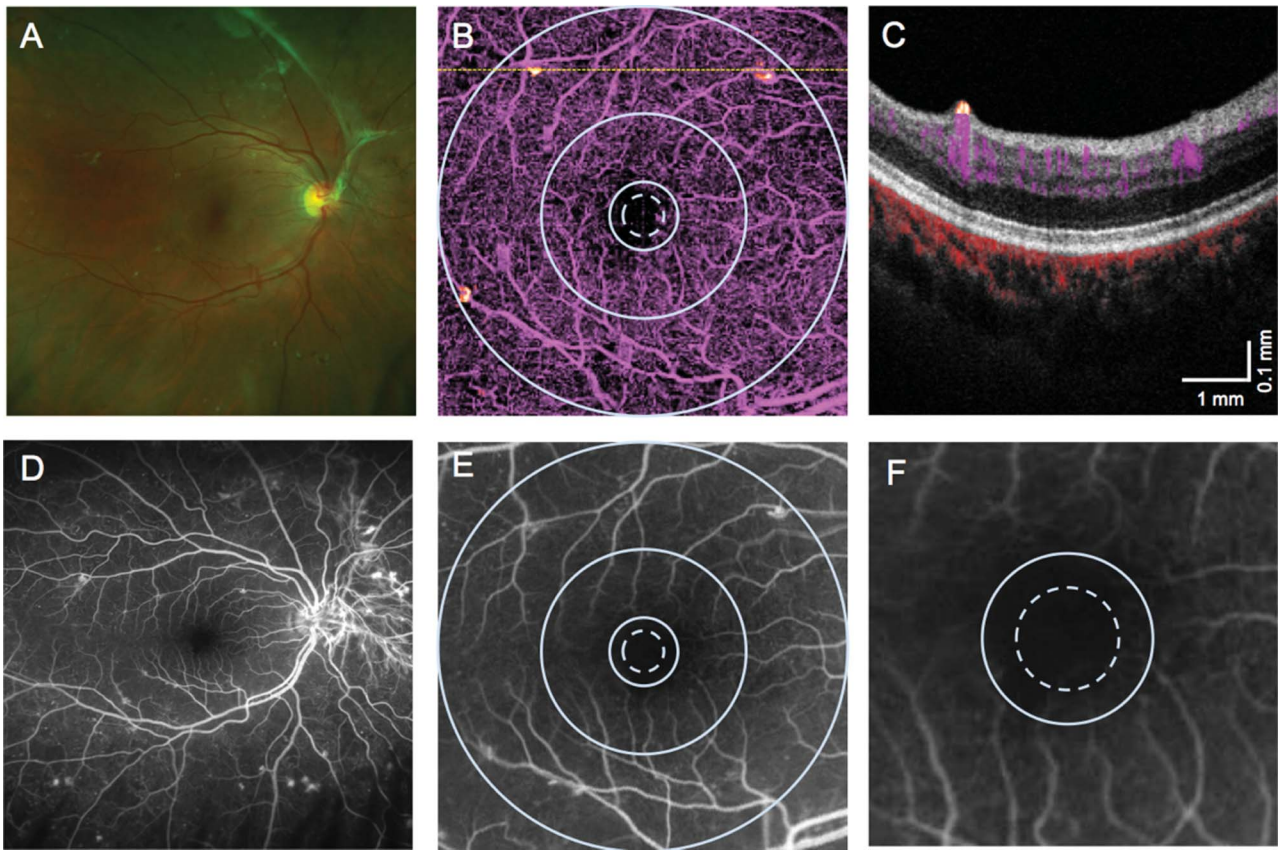

Fig. 1. Right eye of a patient with diabetic retinopathy with wide-field scanning laser ophthalmoscopy color image (**A**) and FA (**D**). **B.** A 6 mm × 6 mm en face OCT retinal angiogram with the ETDRS grid superposed showing FAZ enlargement temporally between the 300 μm (dotted) and 500 μm diameter circles. **C.** A cross-sectional OCT angiogram corresponding to the dotted line on (**B**) showing a small area of flow signal above the internal limiting membrane in yellow, consistent with neovascular tissue that was not clinically evident. **E** and **F.** Fluorescein angiography cropped to 6 mm × 6 mm with the ETDRS superposed and a magnified FA showing FAZ enlargement temporally, respectively.

Microaneurysms and Neovascularization

Optical coherence tomography angiography with 6 mm × 6 mm field of view could not identify MAs seen on FA. (Figure 2). On FA of one patient, areas of focal hyperfluorescence with leakage in the perifoveal area that were thought to be large MAs were determined to be small tufts of NV on OCT angiography (Figure 3). With the segmentation of the flow signal at the level of the internal limiting membrane and projecting the signal in the cross-sectional orientation, it was evident that these lesions were vertical RNV protruding into the vitreous (Figures 1–3). Clinically, these lesions appeared like MAs.

Although RNV close to the internal limiting membrane were readily identified, flow signal from the vessels that were highly elevated from the retinal surface displayed as shadows rather than flow signals because the most elevated portion of RNV was outside the depth range of OCT imaging (Figure 4).

Features described in the ETDRS that are inherently specific to FA and unlikely to have correlates in OCT angiography such as retinal pigment epithelial defects, severity of late fluorescein leakage, and determining their source were not evaluated for this study.

Discussion

Optical coherence tomography angiography can identify FAZ enlargement and irregularity, as well areas of capillary dropout. Kim et al[9] has demonstrated the FAZ using 1.5 mm × 1.5 mm central foveal scan, and Schwartz et al[10] demonstrated capillary dropout in a diabetic patient also using a 3 mm × 3 mm scan. This is the first demonstration of macular microvasculature in diabetic retinopathy using a larger 6 mm × 6 mm OCT angiogram. Unlike FA, where capillary details are best seen in the transit phase and thus cannot always provide reliable details of the FAZ of both eyes,[11] OCT angiography, not dependent on a dye injection, can potentially provide equally clear capillary details of both eyes. Diffuse fluorescein leakage from the choroidal and retinal circulation, MAs, and

Table 2. Optical Coherence Tomography Angiographic Findings

Subject	FAZ Size, μm	Outline of FAZ	Capillary Dropout	NV and Other Vascular Abnormalities	Figure
1	300–500	More than half	Central	Extensive NVD, small tufts of NVE along temporal arcades	1, 4
2	<300	Questionable	Superotemporal and inferotemporal	Isolated NVE temporally, IRMA inferotemporally	2
3	300–500	Less than half	Central and extensive loss throughout temporal macula	Perifoveal NVE and NVD (not shown), arteriolar pruning temporally, arteriolar narrowing and staining superiorly	3
4	300–500	More than half	Central, superotemporal, and inferotemporal	Extensive NVD, NVE inferiorly	

IRMA, intraretinal microvascular abnormality; NVD, neovascularization at the disk; NVE, neovascularization elsewhere.

NV that can obscure capillary details in FA do not obscure those details in OCT angiography. Furthermore, the relative difficulty in resolving capillary details in lightly pigmented fundi does not pose a challenge in OCT angiography, as the separation of the choroidal flush from the retinal circulation is not dependent on the degree of blocking of posterior fluorescence by the retinal pigmented epithelium. In this small series, OCT angiography was more consistent than FA in demonstrating capillary details.

Detection of RNV on FA depends on identifying characteristic vessels with profuse leakage in the late frames. With OCT angiography, RNV is detected by observing flow signal above the internal limiting membrane. We were able to identify lesions on FA that appeared indistinguishable from an MA to be RNV using OCT angiography, as the new vessels appeared as a punctate area hyperfluorescence with leakage. Understanding that FA does not always identify all NV may explain why some diabetics with vitreous hemorrhage do not have a definitely identified NV on their FA.

A limitation of OCT angiography is its small field of view. The largest view available currently (6 × 6 mm) is still significantly smaller than the standard photographic field (~20 vs. 30° in standard photographic field). The difference is more dramatic when compared with ultra-widefield angiography. Studies have suggested that ultra-widefield angiography may be more helpful in classifying diabetic retinopathy as more pathology is revealed compared with classic 7 ETDRS fields.[12] Certainly, a wider field of view would increase the sensitivity of detecting NV and reveal additional areas of capillary nonperfusion.[13] But, a carefully graded FA involving only the standard fields 1 and 2 has been shown to valuable in assessing

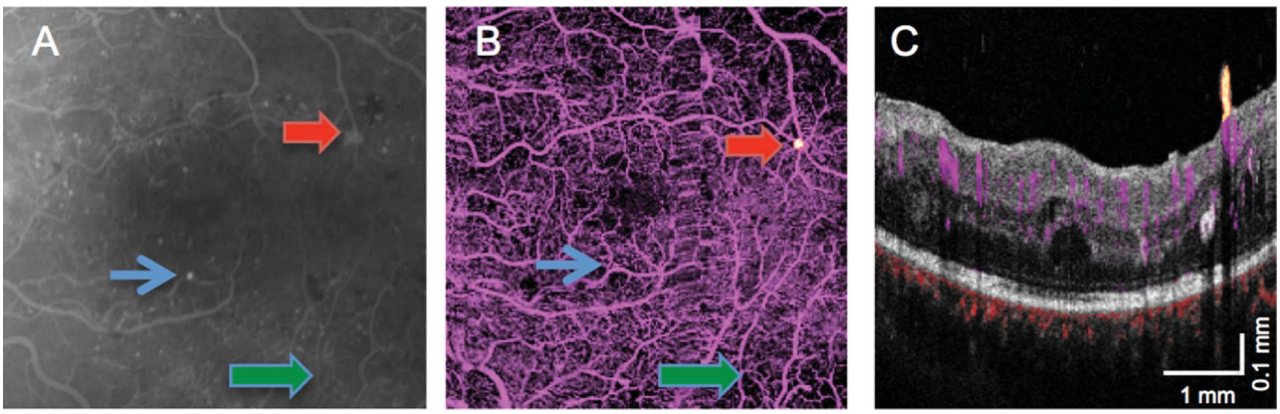

Fig. 2. Macular images (6 × 6 mm) from the left eye of a patient with proliferative diabetic retinopathy. **A.** Early frame fluorescein angiogram. Numerous MAs are seen throughout the macula as punctate areas of hyperfluorescence. The green arrow points to an area of intraretinal microvascular abnormality (IRMA). The red arrow points to a small area of hyperfluorescence that leaked mildly in the late frames. **B.** En face OCT angiogram showing flow signal above the internal limiting membrane (ILM, yellow dot pointed out by the red arrow), consistent with a tuft of NV. The area of IRMA was also identified by OCT angiogram (green arrow). The largest MA on FA (blue arrow) was not identifiable on OCT angiogram. A vertical strip of blur temporal to the center represents motion artifact that persisted after orthogonal image registration. **C.** Cross-sectional OCT angiogram at the level of the NV (yellow) shows it to be anterior to the ILM. Retinal circulation is colored in magenta and choroidal circulation (below Bruch membrane) is colored red. Clinically, this appeared as a MA.

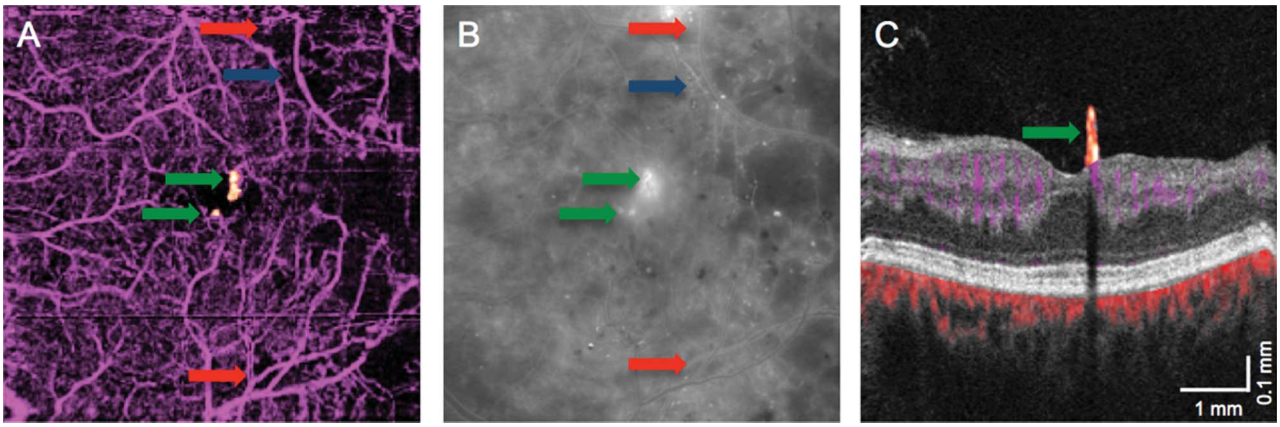

Fig. 3. En face OCT angiogram (**A**) and midphase FA (**B**) of a diabetic patient disclose areas of capillary dropout in the temporal macula with pruning of the arterioles. In FA, diffuse leakage obscures an area of capillary dropout seen on OCT angiography (red arrows). An arteriole with wall staining (blue arrow) in FA is shown to be a barely visible ghost vessel on OCT angiography. Focal areas of leakage near the fovea thought to be large MAs on FA were shown to be NV (green arrow) on cross-sectional OCT angiogram (**C**).

the risk of progression of disease, and the assessment of microvasculopathy in the posterior pole may still be useful.[3] The depth range of OCT imaging is a limitation as well because highly elevated RNV could be cropped and present as shadow rather than flow. These limitations could be eased in the future by the use of faster OCT technology and deeper range of imaging.

With the 6 mm × 6 mm OCT angiogram, it was difficult to identify MAs. A higher resolution but smaller field (3 × 3 mm) OCT angiograms can identify some MAs but not reliably.[10] This difficulty is likely due to relatively low flow in MAs and relatively low scan density used in OCT angiography. Identification of MAs on angiogram may not have value in predicting the risk of progression, but their identification is a part of standard-of-care focal laser treatment for diabetic macular edema.[14,15] Identifying all leaking MAs within 3,000 μm from the center of the macula and treating those is a part of the standard protocol in the treatment of diabetic macular edema, which requires at the minimal 6 mm × 6 mm field of view. With the arrival of anti-vascular endothelial growth factor therapy and demonstration of their superiority to focal laser therapy for center involving edema,[16] the indication for focal laser therapy as primary treatment for diabetic macular edema has narrowed. However, at the present, OCT angiography cannot replace FA for the purpose of focal laser photocoagulation planning.

Other vascular features, such as arteriolar wall staining and intraretinal vascular abnormalities, had divergent appearances on OCT angiography and FA. These differences, as well as the difficulty of

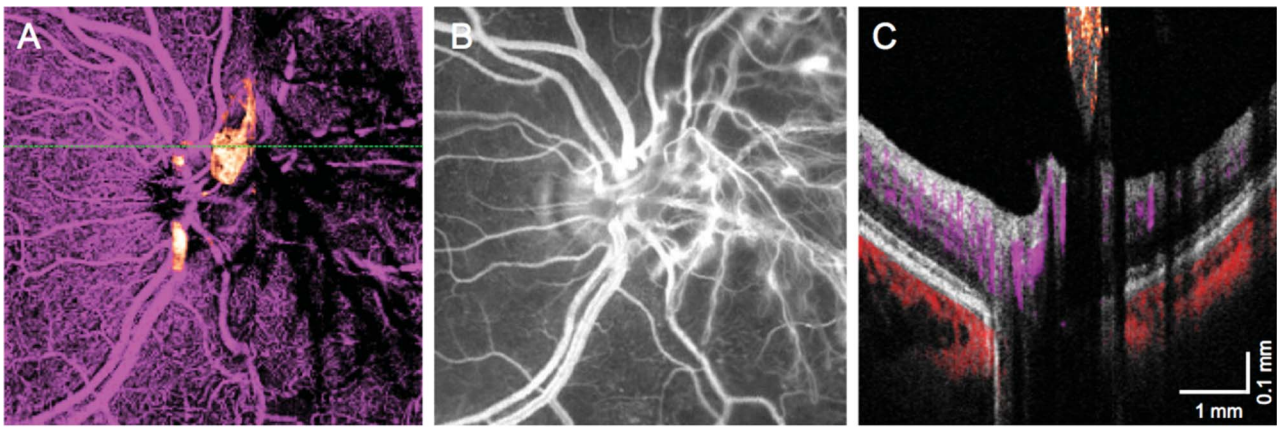

Fig. 4. A right eye with neovascularization of the disk (NVD). **A.** En face OCT angiogram discloses flow in the abnormal vessels above the disk. The NVD was cropped outside the OCT scan volume nasal to the disk and is seen as shadows rather than flow. **B.** Neovascularization of the disk is clearly seen on FA. Clinically, the NVD appeared elevated above the retinal surface. **C.** A cross-sectional OCT angiogram through the area of the NVD shows flow signal (orange) in the neovascular tissue that is close to the retinal surface. Further nasally, similar shadowing seen in (**A**) is displayed in cross-section.

identifying MAs, are demonstrative of the fundamental difference in how the two technologies derive their signal for detection. The contrast in FA depends on the presence of dye, not on their movement. Therefore, the pathology that causes accumulation of dye, such as a MA, is displayed with greater clarity. In OCT angiography, the contrast depends on movement or flow. Thus, certain fluorescein angiographic features such as staining and leakage have no direct equivalence in OCT angiography. However, even in this small study, it is evident that the lack of leakage and staining is both a disadvantage and an advantage as it allows OCT angiography to detect features that could be obscured by leakage in FA. More study is needed to understand the value of these differences in everyday clinical settings.

Although this study demonstrated that OCT angiography can detect many of the features of diabetic retinopathy seen on FA, the small number of patients and limited range of severity of disease make it difficult to make conclusions about sensitivity or specificity of OCT angiography. This study is only a step in the application of OCT angiography to diabetic retinopathy. Several further steps are needed to improve and validate OCT angiography before it can be widely applied in clinical practice and clinical trials. Standardized fields and sampling densities need to be adopted and validated in larger studies. Standardized manual grading procedures or automated algorithms are needed to detect and measure clinically relevant features such as retinal nonperfusion, NV, MA, and intraretinal microvascular abnormality. These measurements need to be assessed for repeatability, reproducibility, agreement with clinical and FA, and ultimately correlation with patient function and clinical outcome.

In summary, this study demonstrates the OCT angiographic features of diabetic retinopathy. Its rapid acquisition time, the absence of need for an intravenous dye, identification of small neovascular tufts, and areas of capillary dropout not obscured by leakage are some of the advantages over FA. These advantages may make this technology useful for routine surveillance of diabetic retinopathy. Its current limitations are the small field of view, relatively low resolution, and difficulty in identification of MAs over a large area.

Key words: diabetic retinopathy, OCT angiography, en face OCT.

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