UTILITY OF FLUORESCEIN ANGIOGRAPHY IN DME

If you want to assess vessel leakage and peripheral pathology in diabetic eye disease, FA is still your best bet.

By Jason Keil, MD, PhD; Caitlyn Cooper, MA; and Yannis M. Paulus, MD



Diabetic retinopathy (DR) remains a major burden on the health care system and continues to be the leading cause of legal blindness in working-age adults.[1] This will continue to be an immense challenge for the field, given the prediction that 191 million people will have DR and 56 million people will have vision-threatening disease by 2030.[2] Vision loss in DR can be secondary to multiple processes, including vitreous hemorrhage, tractional retinal detachment, macular ischemia, disorganization of the inner retinal layers, and diabetic macular edema (DME). Because DME remains the most prevalent mechanism of decreased visual acuity in patients with diabetes,[3] effective diagnostics and treatment of DME is critical.

IMAGING IN DME

DME is evaluated on clinical examination as well as multimodal imaging, such as OCT, OCT angiography (OCTA), fundus photography, and fluorescein angiography (FA). FA is now used less frequently due to the invasive nature of the test, increased time of acquisition, and potential dye reactions, alongside the proliferation and increasing sophistication of alternative imaging modalities

AT A GLANCE

- Although fluorescein angiography (FA) is now used less frequently, it remains a valuable imaging modality for patients with diabetic macular edema.
- Quantitative leakage on ultra-widefield FA is strongly correlated with diabetic retinopathy severity score as well as risk of disease progression.
- OCT and the increasing use of OCT angiography will further augment the role of FA in retinal vascular diseases such as diabetic retinopathy.

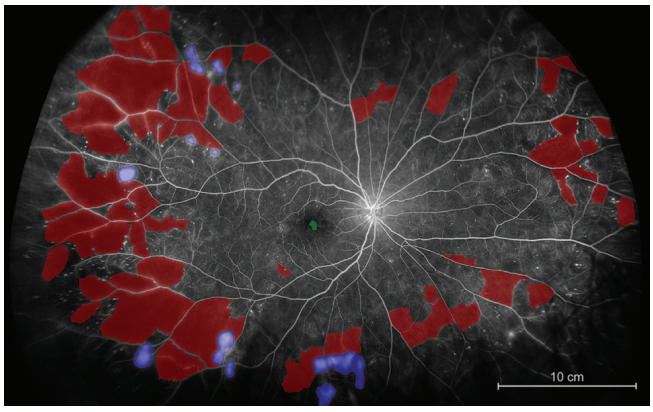

Figure 1. UWF FA of proliferative DR demonstrates areas of nonperfusion (red) and neovascularization (purple) and the foveal avascular zone (green). Following segmentation, biomarker areas can be calculated. Reproduced with permission from Fleifil S et al.[6]

such as OCTA, which can provide high-resolution vascular imaging to illuminate posterior pole vascular pathology. However, FA remains valuable as the only way to directly assess vessel leakage as well as to image retinal perfusion in the periphery. Thus, fluorescein images provide a functional correlate to the anatomic microstructural changes visualized on OCT and OCTA.

Ultra-widefield (UWF) imaging in conjunction with FA has demonstrated that peripheral retinal findings may aid in the identification of patients who will progress to more severe disease (Figure 1). Quantitative leakage on UWF FA is strongly correlated with DR severity score as well as risk of DR progression, including the transition from nonproliferative to proliferative disease.[4-7] Peripheral retinal findings also correlate with the presence of DME,[8-11] including quantitative areas of peripheral retinal nonperfusion, retinal vascular bed area, and the ischemic index. These measurements, all derived from FA images, could be potentially useful biomarkers to predict which patients may develop clinically significant DME. Notably, these studies have only used peripheral retinal data in their analysis, which suggests effects on the blood-retinal barrier in the posterior pole are either correlated with global VEGF levels or that peripheral retinal findings can be used as a proxy for pathologic transformation and breakdown of the blood-retinal barrier in the macula.

THE MECHANICS OF FA

FA functions by imaging the location of the intravenous injected tracer molecule. The intravascular space is imaged, but perhaps more importantly, the efflux of this tracer out of the retinal intravascular space provides a direct measurement of blood-retinal barrier breakdown and leakage from microaneurysms or pathologic neovascular vessels. Direct visualization of leaking vessels that are driving the accumulation of cystic fluid also enables the possibility of precise targeting of focal laser to directly treat pathologic vessels.[12]

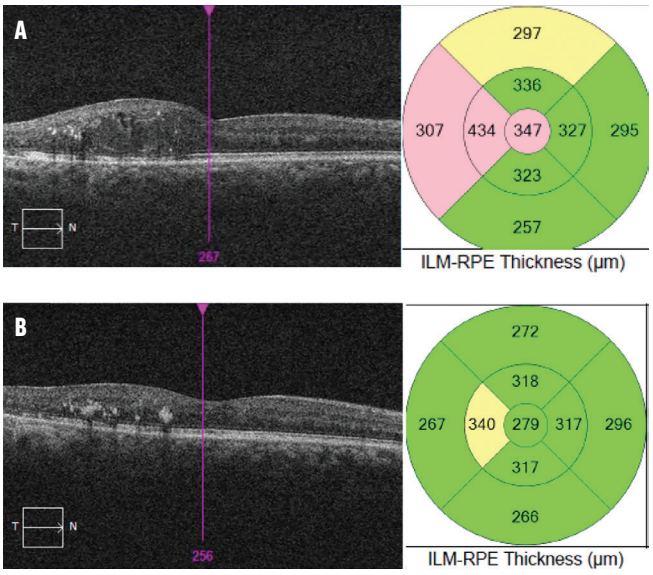

Figure 2. OCT of the macula and thickness measurement mapping before (A) and after (B) endpoint management laser therapy demonstrating a reduction in DME with fewer anti-VEGF injections. Reproduced with permission from Azzouz L et al.[15]

With appropriate protocols, FA can be treated in a quantitative fashion to define areas of nonperfusion, neovascular vessels, and total retinal blood vessels. Furthermore, the efflux of fluorescein dye from the intravascular space into the retina can be measured to quantify leakage. These are time-intensive processes for a clinician to perform, although future measurements are likely to be less dependent on human effort and oversight. Computational advances have recently led to the development of advanced image analysis software and AI algorithms that may lead to automated image interpretation and analysis.[13] This will be an important tool to increase throughput with retina specialist oversight or to potentially automate decision making.

TREATMENT CONSIDERATIONS

Anti-VEGF therapy is often quite successful in resolving cystoid fluid with resultant improvement in visual acuity. However, anti-VEGF therapy is not a panacea for all patients with edema, as some demonstrate persistent disease activity despite therapy. In addition, treatment with an anti-VEGF agent is typically avoided in certain patients, such as those who are pregnant or who have certain medical conditions.

Some patients are resistant to multiple injections and multiple different anti-VEGF agents.[14] In cases where specific areas of leakage are suspected, focal laser remains a viable option for DME monotherapy or as an adjuvant therapy with anti-VEGF injections. Adjuvant focal laser therapy can decrease the number of required injections by 49% and increase the time between injections, effectively decreasing injection burden and endophthalmitis risk (Figure 2).[15] Laser is also an attractive option in situations

FA REMAINS VALUABLE AS THE ONLY WAY TO DIRECTLY ASSESS VESSEL LEAKAGE AND IMAGE RETINAL PERFUSION IN THE PERIPHERY.

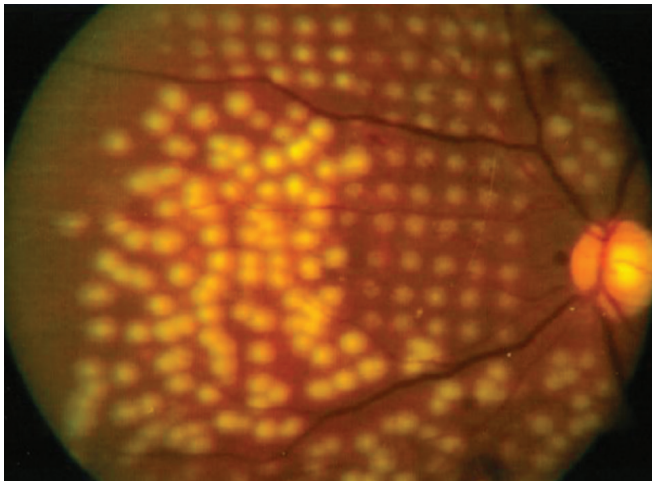

Figure 3. When comparing conventional laser (lower left) with patterned scanning laser (upper right), note the more uniformly spaced, less intense small spots provided by pattern scanning laser therapy. Reproduced with permission from Paulus YM et al.[19]

where intravitreal steroids or anti-VEGF therapy are contraindicated or unavailable. Development of novel laser therapies—such as selective retinal therapy, subthreshold diode micropulse laser, and endpoint management technology—continues to improve the safety of focal laser in ways that are less destructive than traditional photocoagulation (Figure 3).[16-19]

FUTURE UTILITY

OCT and the increasing use of OCTA will further augment the role of FA in retinal vascular diseases and DR specifically. High-resolution vessel imaging can be obtained with OCTA,[20] with the potential to identify microaneurysms that anatomically occur in close proximity to areas of cystoid macular edema. While this is suggestive of pathologic blood-retinal barrier dysfunction, only FA can demonstrate leakage via extravascular extravasation of contrast.

These imaging modalities continue to complement each other, and we continue to value FA as an important imaging modality to help us treat patients with DR and DME. ■

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