FLUORESCEIN ANGIOGRAPHY IN THE ERA OF OCTA

This tried-and-true imaging modality remains an asset in the retina clinic for several conditions.

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First developed in 1961, fluorescein angiography (FA) has been the standard for the diagnosis and follow up of myriad retinal vascular diseases.[1,2] It is based on the intravenous injection of fluorescein sodium, a noniodinated contrast agent, followed by the acquisition of serial photographs to visualize the patency and permeability of the retinal vessels.[2]

OCT angiography (OCTA) was introduced into clinical practice in 2015 as a noninvasive imaging technique to visualize blood flow of the retinal and choroidal vasculature at specific depths.[3-5] Although OCTA was initially used to assess macular vascularization, recent reports have documented the possibility of using additional convex lenses to increase the field of view (ie, the extended field imaging technique).[4,6]

Since the introduction of OCTA, the number of fluorescein angiograms per year has been decreasing.[7] In this review, we discuss the pros and cons of using FA and its continued clinical utility.

FA VERSUS OCTA

FA investigates the status of retinal circulation, including the presence of nonperfused areas, microvascular abnormalities, and neovascularization. FA imaging includes dynamic information regarding the transit of blood as well as identification of dye leakage, which is fundamental to assess vascular leakage and the integrity of the blood-retinal barrier (BRB).[4] In addition, FA can investigate retinal pigment epithelium (RPE) disruption, documenting window defect (Figure).[8]

FA has historically been the go-to imaging tool to evaluate the peripheral retina.[9] Although traditional angiograms visualize 30° to 50° of the retinal surface, widefield (> 50° and < 105°) and ultra-widefield (≥ 105°) FA (UWFA) systems have been developed.[10]

However, FA has several limitations, including possible side effects ranging from mild (eg, nausea and vomiting) to moderate (eg, syncope, urticaria, and other skin eruptions) to severe (eg, laryngeal edema, bronchospasm, anaphylaxis, and, rarely, death).[11] Moreover, the visualization of retinal vessels provided by FA is limited to the retinal vasculature because fluorescein rapidly leaks from the vessel fenestrations, masking the underlying tissue fluorescence.[12]

These limitations have been overcome with OCTA, which does not require administration of exogenous contrast.[3] In addition, OCTA can be performed more rapidly than FA, streamlining clinical workflow.[4]

AT A GLANCE

- Despite the growing utility of OCT angiography (OCTA), fluorescein angiography (FA) remains an indispensable examination tool for many pathological conditions, especially with the introduction of ultra-widefield FA (UWFA).
- OCTA is unable to detect neovascular leakage and cannot image the entire retinal field—whereas UWFA can.
- Although FA remains the standard in the evaluation of vascular disorders of the retina, its application in the diagnosis of macular vascular disorders, especially macular neovascularization, has been decreasing with the advent of OCTA.

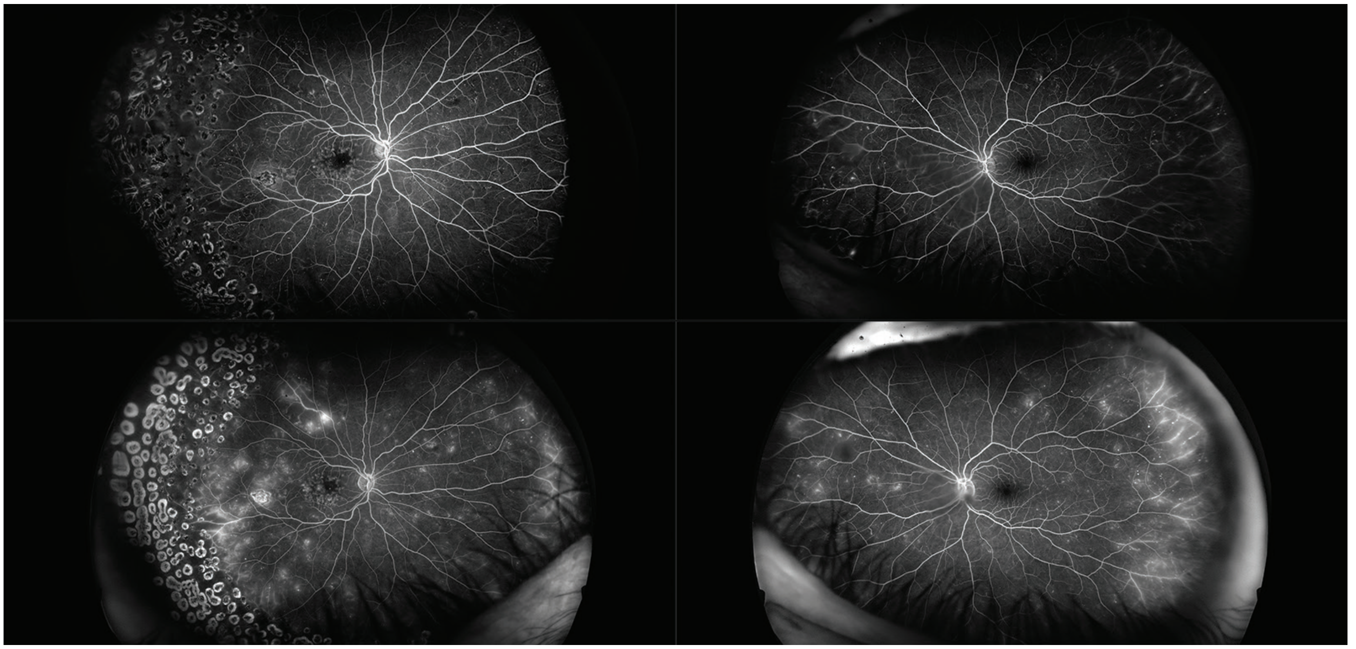

Figure. In this 50-year-old female patient with proliferative DR, the early angiographic phases of UWFA show hyperfluorescent dots in the right (A) and left (B) eyes, suggestive of microaneurysms, and broad peripheral and midperipheral areas of capillary nonperfusion (after retinal photocoagulation in the right eye). In late frames, UWFA reveals peripheral perivascular and mild macular dye leakage in the right (C) and left (D) eyes, suggestive of BRB disruption. Note the window defect in the right eye, indicative of RPE disruption, and intense hyperfluorescence of the retinal surface in right eye due to epiretinal neovascularization.

OCTA has significantly improved our ability to investigate and quantify retinal perfusion; it provides anatomically detailed visualization of the four capillary plexuses of retinal vasculature and the choriocapillaris.[3,13-15] In addition, OCTA allows a quantitative analysis of the retinal vasculature while considering several parameters, including foveal avascular zone size, perfusion density, vessel length density, vessel diameter index, and fractal dimension.[16]

Nevertheless, OCTA cannot provide information about vascular permeability or leakage and blood flow. Furthermore, particularly slow or fast flow may result in a black signal, often misinterpreted as nonperfusion, because OCTA signals have limited dynamic range.[4] OCTA is still limited by several artifacts only partially corrected by modern algorithms. For example, patients with reduced visual acuity may have low fixation stability with motion artifacts.[16,17]

Another issue is related to projection artifacts; in the deeper retinal layers, vessels from the superficial vasculature can appear as a projection caused by scattering.[18] In addition, the presence of retinal layer thinning or macular edema may cause segmentation failure with consequent erroneous visualization of the en face OCTA images.[19]

FA/UWFA IN THE CLINIC

Although OCTA's utility is growing in the clinic, FA—and especially UWFA—remains an indispensable examination tool for many conditions, including diabetic retinopathy (DR), retinal vein occlusion (RVO), uveitis, retinal vasculitis, and pediatric retinal disease.[9]

Diabetic Retinopathy

Ultra-widefield imaging may be particularly useful in the evaluation of DR because much of the condition's abnormalities—ie, microaneurysms, nonperfusion, macular edema, and neovascularization—can occur in the midperiphery and periphery.[20]

Studies comparing UWFA and OCTA for detecting areas of nonperfusion and retinal neovascularization in patients with DR have concluded that widefield OCTA (12 × 12 mm) can be clinically useful for detecting areas of nonperfusion or neovascularization.[21] However, this evaluation was still limited because OCTA is unable to detect neovascular leakage and cannot image the entire retinal field—whereas UWFA can.[15,21]

The ability to precisely quantify the peripheral ischemia (ie, further classify patients with DR based on the risk of developing neovascularization given a certain peripheral ischemia score) using FA is extremely appealing for both research purposes and in the clinical setting.[9]

RVO

UWFA can capture areas of peripheral nonperfusion that may generate VEGF and other factors that promote neovascularization or macular edema, making it a useful imaging modality for evaluating patients who present with signs of RVO.[20,22]

Recently, clinicians have been using UWFA to guide laser photocoagulation only to areas of ischemia, which helps to avoid the destruction of perfused peripheral retina.[10]

Retinal Vasculitis

FA is necessary to diagnose this condition, given its definition: a disruption in the BRB as noted by retinal vascular leakage on FA.[23]

Uveitis

FA allows the identification of active fundus inflammation, modifications, and healing during uveitis therapy.[24] Rarely, FA can be useful in diagnosing specific uveitis entities, but it is mostly valuable in evaluating the activity of inflammatory lesions, detecting macular complications, and assessing optic disc involvement.[24]

Pediatric Evaluations

Thanks to its ability to evaluate the retinal periphery in a single image without the need for patient cooperation, UWFA is the technique of choice for the diagnosis and management of pediatric retinal conditions, such as telangiectasias, microaneurysms, exudates and neovascularization, Coats disease, familial exudative vitreoretinopathy, incontinentia pigmenti, retinopathy of prematurity, Stargardt disease, Best disease, and pediatric uveitis.[20,25]

Macular Neovascularization

Although FA remains the standard in the evaluation of retinal vascular disorders, its application in the diagnosis of macular vascular disorders, especially neovascularization (MNV), has been decreasing with the advent of OCTA.[3] Studies have demonstrated that the sensitivity and specificity of OCTA and FA in the diagnosis of MNV were comparable.[26] In addition, eyes with subretinal, intraretinal, or sub-RPE fluid on OCT and MNV on OCTA were associated with active MNV (requiring treatment).[26] FA is still indicated in difficult cases in which the use of OCTA alone could limit the clinician's ability to make the correct diagnosis.[3] FA can provide dynamic information and investigate the activity of MNV, determining the presence of leakage to verify the necessity of treatment.[27] Moreover, leakage of dye in the later frames of the angiogram is used to diagnose and classify MNV as Type 1, 2, 3, or a combination subtype.[27]

With these tools at our disposal, there could be a paradigm shift for the diagnosis of wet AMD, with noninvasive tools such as OCTA used as the first-line imaging and FA reserved for challenging cases.[28]

HOW TO PICK THE RIGHT TOOL

Although its application has been decreasing with the advent of OCTA, FA provides more detail of the perfusion status of the entire retina. Because FA, which is not influenced by the velocity of the flow, can provide information about vascular leakage and the peripheral retina, it remains the standard in the evaluation of vascular disorders of the retina.

OCTA may play a greater role in the evaluation and quantification of the deep capillary plexus and choriocapillaris, which are masked in FA, and represents an essential tool in the diagnosis of MNV and in monitoring its evolution. ■

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