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MULTI-MODALITY IMAGING: LATEST EVOLUTIONS IN OCTA AND UWF

As the array of safe and efficacious medical and surgical options for retinal diseases expands, so does the need for state-of-the-art imaging to aid diagnosis, treatment, and follow-up. Retina specialists with expertise in these new tools — including optical coherence tomography angiography (OCTA) and ultra-widefield (UWF) imaging — shared their insights during a dinner program sponsored by Carl Zeiss Meditec at the last meeting of the American Society of Retina Specialists (ASRS) in Boston, Massachusetts.

ANSWERING THE "WHY?"

Clinicians discuss the latest imaging technologies for retina practice

BY PETER K. KAISER, MD

As we introduce you to an exciting new technology, our goal is to give you the "why." The reason I say the "why" is this: we all have optical coherence tomography (OCT), and many of us do not yet have OCT angiography (OCTA). The question I often hear is: why should I get OCTA?

I will present a brief overview of OCTA and the advances we can look forward to.

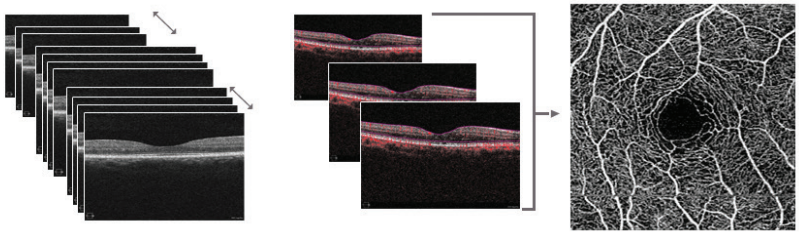

Figure 1. ZEISS AngioPlex technology detects motion of scattering particles within sequential OCT B-scans. An AngioPlex Map consisting of reconstruction of the perfused microvasculature within the retina and choroid.

OCTA BASICS AND BEYOND

OCTA uses motion contrast to visualize vasculature, assuming the only motion in the retina should be blood flow. The ZEISS AngioPlex technology (Figure 1) uses an algorithm that compares contrast on repeated B-scans in the same location, revealing areas with constant contrast and areas with contrast change over time, indicating the location of a vessel. The software takes the B-scan, detects change, and then displays it En Face.

We have depth resolution with OCT, and the same principle can be applied to OCTA. We can choose the area we want to analyze and use the software to choose a superficial view, a deep retinal view, a choriocapillaris view, or a slab (Figure 2). The AngioPlex color code software option helps identify pathology such as choroidal neovascularization (CNV) beneath the superficial retinal vessels.

OCTA offers several key advantages over fluorescein angiography (FA). With no need to inject dye, there's no risk of dye leakage. We can visualize flow in different layers of the retina separately, and the images are depth-encoded. OCTA enables us to take high-resolution, high-contrast images of the microvasculature, and it provides a superior view of vessel morphology.

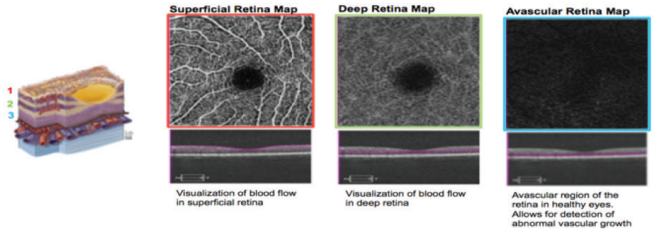

Figure 2. AngioPlex Map is a 2D representation of the retinal vasculature of particular regions of interest.

If you look at a type 1 or occult CNV, for example, often it's oozing on FA, and you can't determine what is going on. Whereas, with OCTA the image is depth-encoded, and you can easily visualize the CNV if present. Similarly, when you suspect macular telangiectasia, the view on FA is obscured by oozing from the telangiectatic vessels, but the vessels look incredible on OCTA. In fact, OCTA is much more reliable for diagnosing macular telangiectasia, obviating the need for FA.

Among the disadvantages of OCTA are the lack of leakage information and the initial cost. Many people think OCTA requires all new hardware. That is only partially true. If you have a relatively recent Cirrus HD-OCT device, and you don't have the OCTA software, the device is certainly fast enough to handle it. It also isn't true that you need a Swept Source device for OCTA; however, the faster the imaging, the better you can image motion.

The company is continually upgrading, refining, and adding functionality to the software. At every symposium, we have something new to discuss. The beauty of OCTA is that it's a hardware, and with every software upgrade, we can go back and review our older images with the newer software.

OCTA is also subject to imaging artifacts, most of which are related to motion. Software is being developed that can automatically remove projection artifacts.

COMING SOON

Two new features are currently being reviewed by the US Food and Drug Administration and should be available soon. With the AngioPlex Metrix, we will be able to evaluate central microvascular perfusion changes and visualize changes in foveal avascular zone size and geometry. The AngioPlex Change Analysis will enable us to compare Early Treatment Diabetic Retinopathy Study and foveal avascular zone density across two visits. The AngioPlex Widefield Montage feature is currently in development and not yet available in the United States.

READ ON

In the next few articles, our faculty will be delving a bit more deeply into the features, functions, and utility of OCTA, and they also will be discussing HD ultra-widefield imaging. All of which we hope will help you answer the "Why?"

PETER K. KAISER, MD

- Professor of Ophthalmology, Cleveland Clinic Lerner College of Medicine; Vitreoretinal Surgeon, Cole Eye Institute; Founding Director, Digital Optical Coherence Tomography Reading Center, Cole Eye Institute
- pkkaiser@gmail.com
- Financial disclosure: Consultant (ZEISS)

PRACTICAL APPLICATIONS FOR OCTA IN DIABETES AND VASCULAR DISEASE

Seeing beyond FA

BY AMIR H. KASHANI, MD, PHD

Optical coherence tomography (OCT) and OCT angiography (OCTA) depends on underlying OCT technology. By using layer-specific definitions in OCTA, we can acquire En Face images of retinal blood flow that weren't available before. These images allow capillary-level resolution of retinal vessels as well as depth-encoded information.

A 2015 study suggested that OCTA in combination with standard OCT is as good as fluorescein angiography (FA) for evaluating macular complications of diabetic retinopathy.[1]

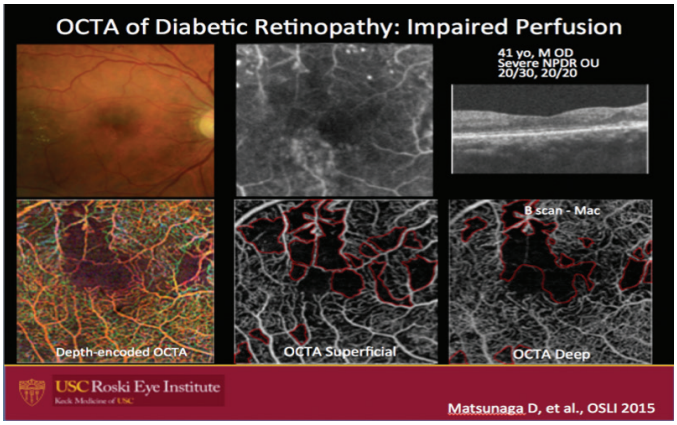

Figure 1. OCTA shows nonperfusion that is clearly affecting the fovea.

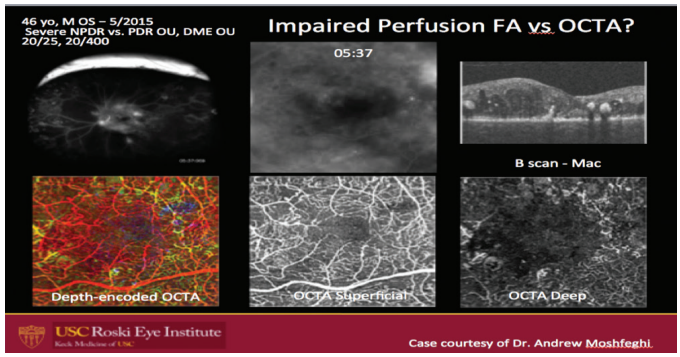

Figure 2. OCTA reveals superficial retinal vessels not visible on FA.

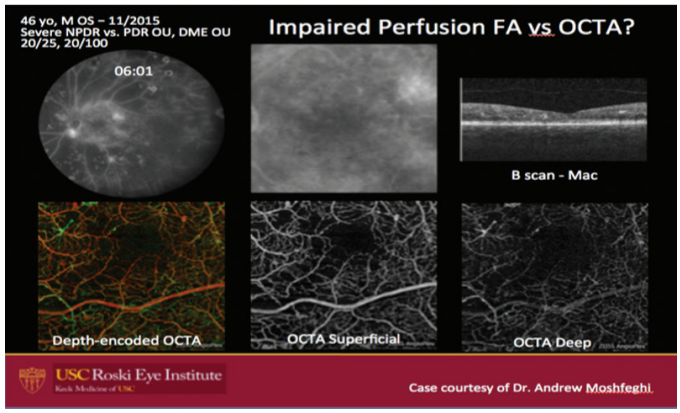

Figure 3. The intraretinal vasculature remains, the edema is gone, and the patient's visual acuity improved to 20/100 6 months after starting anti-VEGF therapy.

While I still use FA, all of the clinically relevant findings within the macula are likely visible with OCTA.

I use OCTA for all of my patients who have diabetes or vascular disease. As you perform OCTA more frequently, evaluating the images and identifying differences in the patterns becomes intuitive. Often, you can see details that are not visible on FA. The cases that follow are two examples of how OCTA can inform our diagnoses and prognostic assessments.

WHEN OCTA IS ENOUGH

This 41-year-old man has severe nonproliferative disease (Figure 1). The color fundus photograph is not impressive, showing primarily hard exudates. The FA shows microaneurysms, and no neovascularization is evident in the periphery on examination. The patient's visual acuity is 20/30. The FA suggests macular ischemia is present, but it does not show its exact location. There is no macular edema, so this patient does not require anti-VEGF treatment.

The OCTA (Figure 1, bottom left) really helps us understand the severity of this patient's disease. We can clearly see the nonperfusion that is affecting the fovea. One capillary is standing between the fovea and the rest of the region of impaired perfusion. That tells us this patient's visual acuity might worsen faster than we would have otherwise suspected. In this case, after the initial FA, serial OCT and OCTA are sufficient to monitor the ischemia and to detect any macular edema.

OCTA PROMPTS CHANGE IN MANAGEMENT

This 46-year-old man has borderline proliferative diabetic retinopathy and macular edema in both eyes (Figure 2). His visual acuity is 20/400. The wide-field image shows neovascularization and significant areas of nonperfusion involving the macula. This patient may benefit from panretinal photocoagulation (PRP). Late-phase FA shows leakage, indicating macular edema and possible early neovascularization. What is the best course of treatment? PRP and aggressive anti-VEGF therapy or PRP and a short course of anti-VEGF? We must consider how much we can improve 20/400 visual acuity and macular ischemia.

As it turns out, superficial retinal vessels are clearly visible on OCTA, even though the FA suggests the macula is ischemic. If not for the OCTA, I might have discouraged the patient from pursuing aggressive treatment, thinking his vision was not likely to improve. The patient was not interested in PRP and wanted to maximize his chances of preserving visual potential and acuity. He opted for monthly anti-VEGF injections. The intraretinal vasculature is still there 6 months later, and the edema is gone (Figure 3). The patient's visual acuity improved to 20/100, and he continues to receive anti-VEGF injections.

By demonstrating the remaining perfusion in the macula, OCTA did a much better job of showing that this patient could possibly regain some vision than either clinical examination or FA. I felt confident encouraging him to continue with monthly anti-VEGF therapy since there was perfusion of the macula.

RESEARCH CONTINUES

Ongoing studies continue to explore potential applications for OCTA, not only in diabetic retinopathy but also vein occlusion and uveitis,[2-4] particularly as new advances in technology are introduced. ■

1. Matsunaga DR, Yi JJ, De Koo LO, Ameri H, Puliafito CA, Kashani AH. Optical coherence tomography angiography of diabetic retinopathy in human subjects. *Ophthalmic Surg Lasers Imaging Retina*. 2015;46:796-805.
2. Kim AY, Chu Z, Shahidzadeh A, Wang RK, Puliafito CA, Kashani AH. Quantifying microvascular density and morphology in diabetic retinopathy using spectral-domain optical coherence tomography angiography. *Invest Ophthalmol Vis Sci*. 2016;57:OCT362-370.
3. Kashani AH, Lee SY, Moshfeghi A, Durbin MK, Puliafito CA. Optical coherence tomography angiography of retinal venous occlusion. *Retina*. 2015;35:2323-2331.
4. Kim AY, Rodger DC, Shahidzadeh A, et al. Quantifying retinal microvascular changes in uveitis using spectral-domain optical coherence tomography angiography. *Am J Ophthalmol*. 2016;171:101-112.

AMIR H. KASHANI, MD, PHD
■ Assistant Professor, USC Roski Eye Institute, Los Angeles, California
■ ahkashan@usc.edu
■ Financial disclosure: Research Grants and Honoraria (ZEISS)

WHAT OCTA CAN TEACH US

Revelations in the diabetic eye

BY CAROLINE R. BAUMAL, MD

Several factors give optical coherence tomography (OCT) and OCT angiography (OCTA) an edge over fluorescein angiography (FA). OCTA is noninvasive, and it displays high-resolution images quickly. It gives us a detailed view of the retina with structural and blood flow information, and the 3-D images it displays can be segmented, which is not possible with FA. In fact, we now know that FA shows us only the superficial retinal plexus, and we see so much more with OCTA.

Does OCTA give us enough information to make an accurate clinical decision? Consider the following case.

IS THIS ENOUGH INFORMATION?

A woman I recently saw in clinic was referred for a diabetic tractional retinal detachment of the right eye. For this discussion, however, I will focus on her left eye. A widefield image showed evidence of minimal panretinal photocoagulation, and an FA revealed neovascularization with some late leakage and peripheral ischemia.

Figure 1 shows the FA beside the OCTA. The OCTA demonstrates the neovascularization of the retina with adjacent areas of nonperfusion. A color-coded picture of the optic nerve shows some neovascularization of the disc. Is this enough information to decide how to treat this eye? Well, there's more.

The 3 mm by 3 mm OCTA (Figure 2A) shows an irregular foveal avascular zone, capillary dropout in the perifoveal region, and microaneurysms. The 6 mm by 6 mm OCTA (Figure 2B) gives us a more global idea of the capillary nonperfusion, and we can see more of the structural OCT of the fovea. A 12 mm by 12 mm OCTA (Figure 2C) shows neovascular fronds at the edge of the image and extrafoveal vitreomacular traction on the structural OCT.

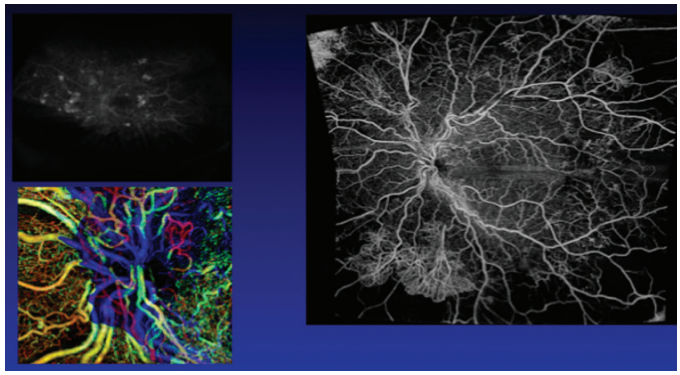

Figure 1. The OCT angiogram shows peripheral neovascularization with adjacent areas of nonperfusion.

Is this enough information to treat this patient? Can we decide that this patient needs treatment for proliferative diabetic retinopathy but does not have diabetic macular edema at this time? Yes. I can safely say that if I only have the information of the patient's OCTA and OCT, I would be able to treat her effectively.

WHAT WE HAVE LEARNED FROM OCTA THUS FAR

By superimposing a patient's FA over his OCTA in diabetic eyes, we learned that not all microaneurysms seen on FA are visible on OCTA, suggesting that flow might not be present in all microaneurysms, or the flow is below the threshold of OCTA detection. In addition, OCTA has taught us that some of the microaneurysms imaged by FA are actually capillary loops.

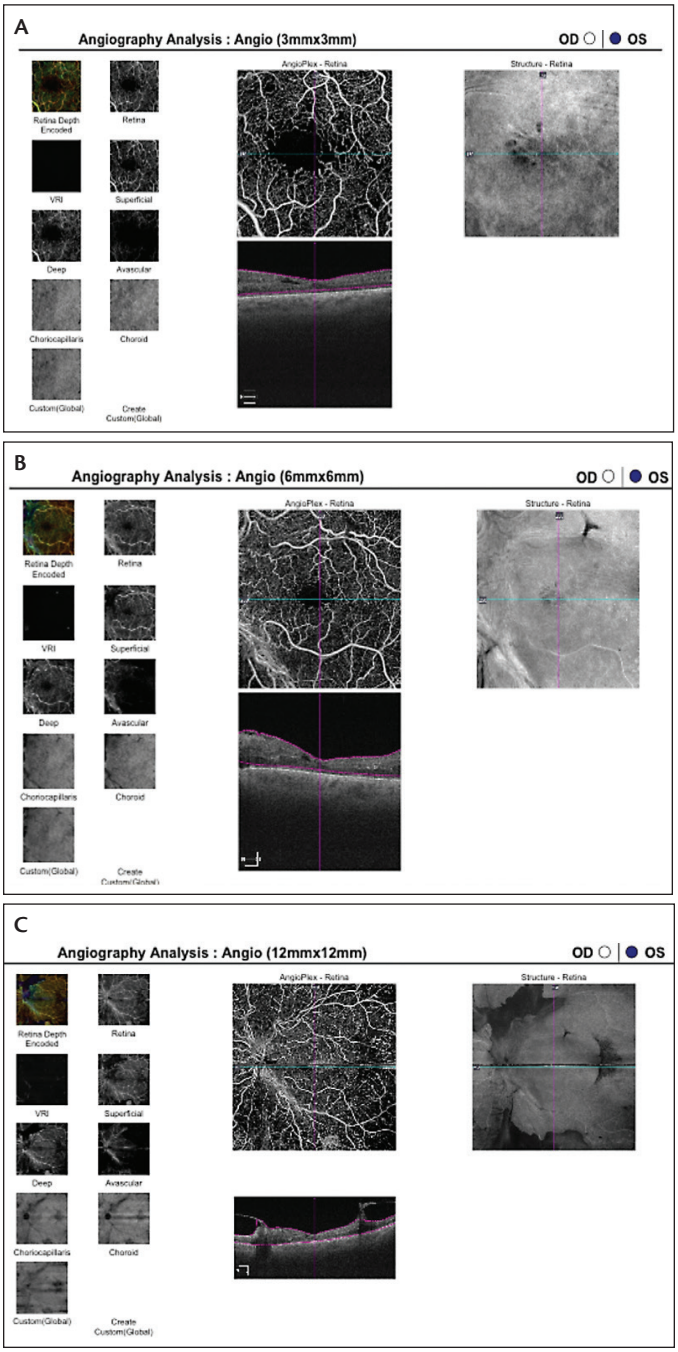

Figure 2. Do these OCTA studies provide enough information to decide on a treatment plan for this eye (A, B, C)?

The next thing we learned is that OCTA can predict subclinical diabetic retinopathy.[1] In a study performed at New England Eye Center, OCTA revealed foveal microvascular changes that were not detected on clinical examination in diabetic eyes. The authors concluded that OCTA may be able to detect diabetics at risk of developing retinopathy and may have utility as a screening tool to noninvasively detect diabetes before the systemic diagnosis is made.

We have learned something else from OCTA. As we know from histopathology, the retina has multiple capillary networks — superficial, intermediate, and deep — and OCTA has shown us that by using depth-resolved segmented images, we see more detailed information looking at the superficial and deep retinal plexuses separately than if we look at the total information. While FA demonstrates only the superficial capillary plexus of the retina, OCTA gives more detail of flow in the individual plexuses as well as the choroidal circulation.

CONCLUSION

OCTA has multiple applications in diabetes with more to come in the future. It has great potential as a noninvasive screening tool to identify patients who are at risk for diabetic retinopathy and to noninvasively monitor for progression. It has potential to evaluate novel pharmacologic therapies for diabetic retinopathy to see if retinal perfusion and flow can be improved in ischemic eyes. ■

1. de Carlo TE, Chin AT, Bonini Filho MA, et al. Detection of microvascular changes in eyes of patients with diabetes but not clinical diabetic retinopathy using optical coherence tomography angiography. *Retina*. 2015;35:2364-2370.

CAROLINE R. BAUMAL, MD
- Associate Professor of Ophthalmology, New England Eye Center, Tufts Medical Center, Tufts University School of Medicine, Boston, Massachusetts
- CBaumal@tuftsmedicalcenter.org
- Financial disclosure: Speaker (Genentech, Optovue, ZEISS)

Images shown in this case are taken with the ZEISS PLEX Elite 9000 Swept Source instrument.

OCTA APPLICATIONS IN AMD AND OTHER CNV

Addressing diagnostic dilemmas

BY ERIC W. SCHNEIDER, MD

As we explore the utility of optical coherence tomography (OCT) and OCT angiography (OCTA) to help manage choroidal neovascularization (CNV), we are learning how it compares with conventional angiography and how we can use it to guide our treatment decisions.

I have found OCTA particularly useful for addressing what I call diagnostic dilemmas: asymptomatic CNV or disease that appears to be refractory. The following cases illustrate the value of this technology for these types of cases.

SECOND OPINION: IS THIS REFRACTORY DISEASE?

A 52-year-old man with a history of pseudoxanthoma elasticum was referred to me for a second opinion of refractory CNV in both eyes. He had received multiple anti-VEGF injections in both eyes. On examination, degenerating vitelliform lesions were present bilaterally with some retinal pigment epithelium (RPE) modeling in both eyes (Figure 1).

OCT showed a subretinal hyporeflective space with clumped hyperreflective material at the location of the vitelliform debris (Figure 1). The fluorescein angiogram (FA) showed angioid streaks but no clear evidence of CNV.

As is my practice, I obtained an OCTA (Figure 2). In the right eye, highlighted in yellow, there is a small CNV present. This is somewhat difficult to appreciate, but if you look at many of these, you will see the characteristic hyporeflective halo that typically accompanies CNV on OCTA.

The patient felt his vision in both eyes had improved after initial anti-VEGF therapy, so he elected to continue bilateral injections despite my opinion that he had CNV in the right eye only. After three additional injections in each eye, macular thickness and subretinal fluid had decreased in the right eye while there was no change in the left eye.

The patient was lost to follow-up for 4 months. When he returned, I noted significantly increased macular thickness in the right eye and no change in the left eye. After two additional bilateral anti-VEGF injections, fluid in the right eye had again decreased; there was no change in the left eye (Figure 3).

Largely by chance, this case provides a dechallenge-rechallenge event that proves the accuracy of the initial OCTA findings. Without the aid of OCTA, the left eye could be considered "refractory" owing to the presence of chronic "subretinal fluid" in spite of active therapy. In such cases,

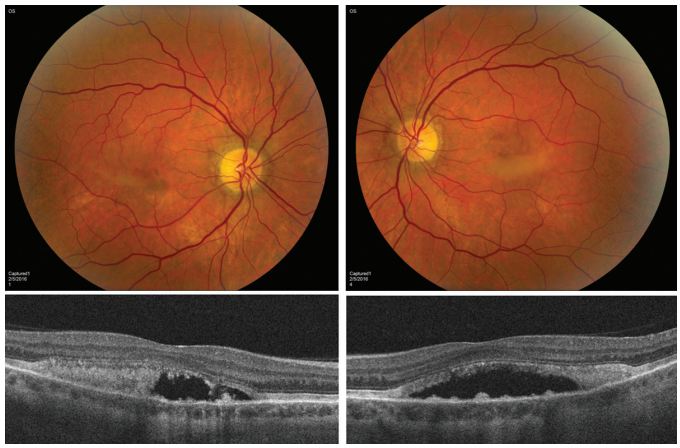

Figure 1. The patient with a diagnosis of pseudoxanthoma elasticum was referred for a second opinion of refractory CNV in both eyes.

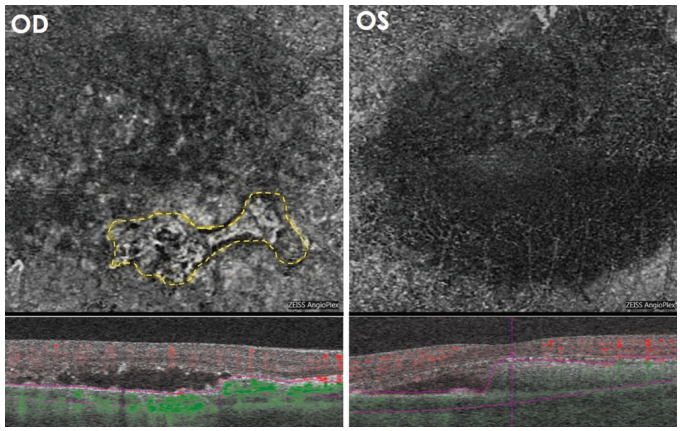

Figure 2. Note the small CNV membrane, highlighted in yellow, in the right eye.

OCTA can be used to confirm the absence of CNV and avoid unnecessary treatment.

NEW FINDINGS FOR AN ASYMPTOMATIC EYE

This 40-year-old woman underwent submacular surgery in 2002 for an idiopathic CNV. The original FA from 2002 shows a classic membrane in the inferior parafoveal region (Figure 4A). When I saw her in 2016, there was some pigment modeling and scarring inferior to the fovea (Figure 4B). Her visual acuity was 20/40, and the macula was dry on structural OCT. Looking at the OCTA, however, we see an obvious CNV (Figure 4C), likely

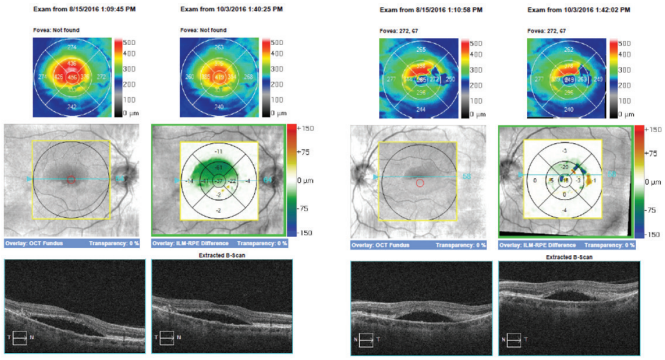

Figure 3. Additional anti-VEGF therapy reduced macular thickness and subretinal fluid in the right eye only.

an inactive remnant of the original membrane dating to 2002.

With the introduction of OCTA, we are finding that eyes such as this, with inactive or non-exudative CNV, are relatively common but were previously overlooked as conventional invasive angiograms were not routinely performed on eyes without evidence of exudation.

CONCLUSION

OCTA is an excellent tool for confirming the presence or absence of CNV. There are two commonly encountered diagnostic dilemmas in which OCTA is particularly useful:

1. refractory CNV in which OCTA can confirm the absence of CNV in the setting of treatment-resistant hyporeflective subretinal spaces on structural OCT with equivocal conventional angiography findings, and

2. asymptomatic CNV in which OCTA can identify CNV in the absence of signs of exudation on examination or structural OCT. ■

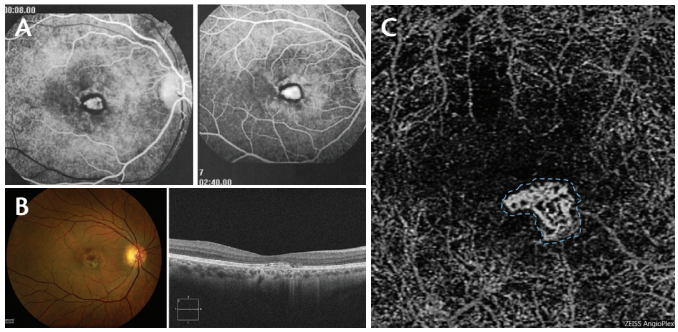

Figure 4. The patient underwent submacular surgery in 2002 (A). At a follow-up visit in 2016, the patient's visual acuity was 20/40, and the macula appeared dry on OCT (B). OCTA revealed a previously undetected CNV membrane (C).

ERIC W. SCHNEIDER, MD
■ Tennessee Retina, Nashville
■ eschneider@tnretina.com
■ Financial disclosure: Speaker (ZEISS)

CLARUS 500 HD UWF IMAGING

Competition enters the ultra-widefield imaging space

ROGER A. GOLDBERG, MD, MBA

Since its mainstream introduction in 2012, ultra-widefield (UWF) imaging has had a significant impact on eye care. For optometrists, general ophthalmologists, and retina specialists alike, UWF imaging has enabled the visualization and documentation of the peripheral retina in pathologies ranging from retinal tears and detachments to diabetic retinopathy, vein occlusions, uveitis, vasculitis, and choroidal and retinal masses. With UWF technology, we can detect early or more extensive disease not readily visible in a clinical examination or via standard seven-field imaging.

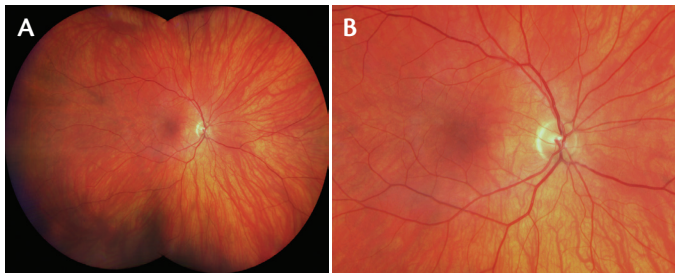

Figure. The Clarus 500 maintains exceptional resolution for UWF images and a 200° view (A). The same image as A, showing the resolution of the optic nerve and macula (B).

With the ZEISS CLARUS 500, ZEISS has now entered the UWF imaging market, bringing competition and innovation to this space. The ZEISS CLARUS 500 offers true color images, a view at 200° that still captures high-resolution details of the optic nerve and macula, and easy image acquisition for patient and photographer.

TRUE COLOR IMAGES

The ZEISS CLARUS 500 has state-of-the-art optics and produces excellent true color images by using ZEISS broadline fundus imaging technology. A broad rectangle of light is scanned across the retina using a monochromatic camera. True color images are generated through sequential illumination by broad-spectrum red, green, and blue light-emitting diodes (LEDs). When combined, these three light sources produce a natural-looking image of the fundus as it appears through direct observation. A single 133° image is acquired in 0.2 seconds.

UWF CAPABILITIES

In UWF mode, the ZEISS CLARUS 500 captures two images sequentially, and the software automatically merges the photos to produce a 200° image. The software can auto-merge up to five images to capture a specific lesion.

The camera has partial confocality, which reduces eyelid and eyelash artifacts. It can image through non-mydriatic pupils with a minimum size of 2.5 mm.

HIGH RESOLUTION AT HIGH MAGNIFICATION

While the ZEISS CLARUS 500 has outstanding UWF capabilities, the resolution of the camera is still 7 µm. Zooming in on the UWF image produces the same high-quality image seen with traditional high-end fundus imaging systems (Figure). This gives the ZEISS CLARUS the benefits of a traditional fundus camera, including optic disc photos, which can be acquired in stereo, ocular adnexal, and ocular surface images, along with high-resolution macula photos, with the UWF visualization of the peripheral retina. The ZEISS CLARUS 500 offers both blue- and green-channel fundus autofluorescence, as well as infrared, in addition to true color images.

COMFORT AND CONVENIENCE

The ZEISS CLARUS 500 is designed for the patient's comfort, with a familiar design that stabilizes the patient's head and moves the optics like a traditional fundus camera. A simple user interface, as well as the live infrared preview, allows the photographer to optimize alignment and remove image artifacts before capturing an image, thus reducing the need for recaptures.

CONCLUSION

ZEISS, a long-time innovator in ophthalmic diagnostics, has now entered the UWF imaging market with the ZEISS CLARUS 500. This new retinal camera captures the true color images of the entire retina (200°) without sacrificing resolution of the optic nerve or macula. Indeed, competition spurs innovation, which benefits patients and providers alike. ■

ROGER A. GOLDBERG, MD, MBA
- Retina specialist at Bay Area Retina Associates, Walnut Creek, California
- rgoldberg.eyemd@gmail.com
- Financial disclosure: Investigator and Consultant (ZEISS)

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