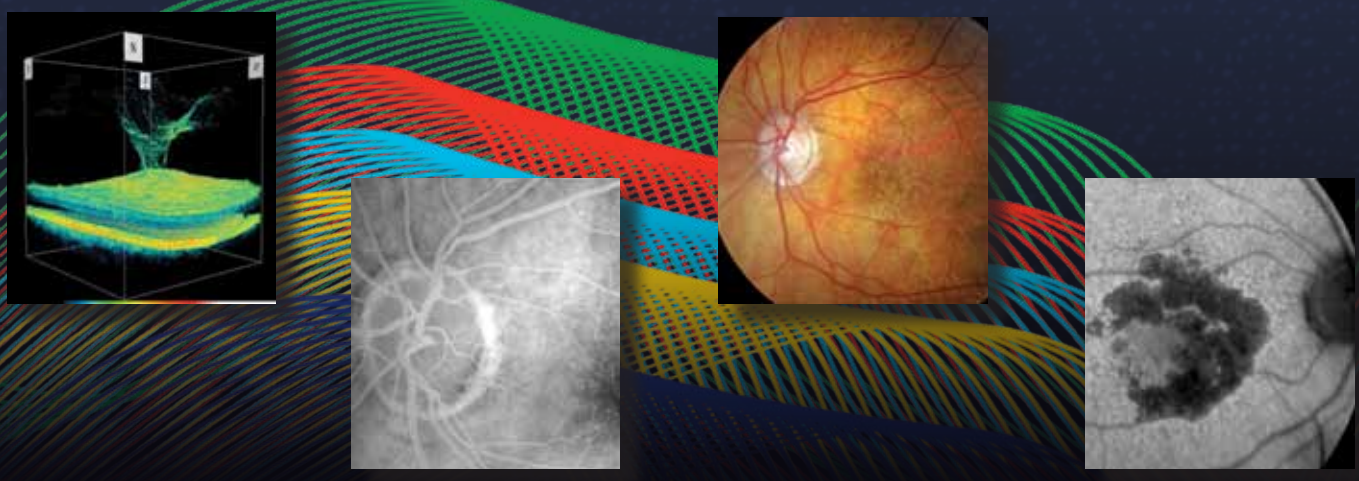
ADVANCES IN 3D OCT AND FUNDUS AUTOFLUORESCENCE

How to incorporate these devices and imaging modalities into clinical practice.



Part 2 of 2
REVIEW of Ophthalmology
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Advances in 3D OCT and Fundus Autofluorescence

How to incorporate these devices and imaging modalities into clinical practice.

At the 2010 American Academy of Ophthalmology Joint Meeting with the Middle East Africa Council of Ophthalmology in Chicago, an expert panel of ophthalmologists gathered to discuss new OCT uses and fundus autofluorescence. The following pages offer a recap of their presentations.

FUNDUS AUTOFLUORESCENCE IN THE MANAGEMENT OF AMD

The days of color stereoscopic imaging are numbered; the future is in autofluorescence and 3D OCT.

by Philip J. Rosenfeld, MD, PhD

I am a newcomer to autofluorescence, and I am slowly convincing my colleagues to incorporate it into their practices. It's a great strategy for making diagnoses and following patients to assess disease progression. I mostly deal with age-related macular degeneration (AMD), so I will explain how I incorporate autofluorescence into my clinical practice to follow patients with AMD.

Geographic Atrophy: Not to Be Ignored

We often focus on choroidal neovascularization (CNV) in AMD, but geographic atrophy (GA) really determines how our patients function on a day-to-day basis. As we treat patients over the years, we are going to face a progression of GA and we

have to come up with a treatment for this disease.

GA has been intensively investigated over the past couple of decades, and Janet Sunness and her colleagues have come up with certain patterns of growth: slow, medium and fast, based on color fundus photography.[1] This ends up being important because we first need to know how this entity grows before we can prove that treatments have been developed to slow or stop its progression.

Historically, color fundus photography has been the gold standard. Then came autofluorescence, and when you compare it to color fundus photography (*see Figure 1*), you can really see a difference. This figure compares color fundus photography with a Topcon autofluorescence image from the same patient showing progression of GA over 2.5 years. Frank Holz took Sunness's work and expanded it to include autofluorescence.[2] He came up with some interesting findings in terms of the way lesions grow based on different patterns of autofluorescence.

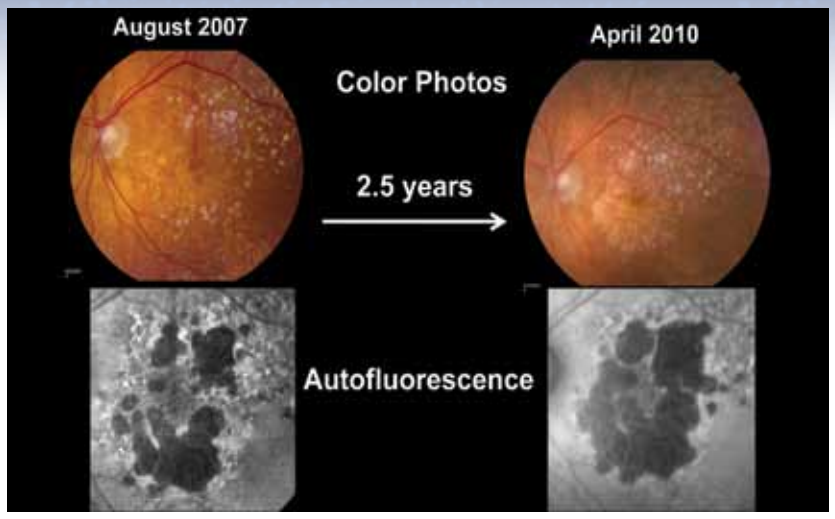

Figure 1. Comparison of color fundus photography to autofluorescence for imaging geographic atrophy.

The key to following the progression of GA is to follow the edge of GA as it progresses toward the foveal center. Early in the disease process, most patients present with areas of patchy GA, but they still have 20/20 vision. Over time, these areas grow

The Dawn of a New Filter

By Richard F. Spaide, MD

Fundus autofluorescence (FAF) comes from a number of different sources. The precursor for all of it comes from the retina, particularly from the outer segments (principally retinoids and also potentially from oxidatively damaged molecules). So the precursors to autofluorescence develop in the retina, and these precursors accumulate as an ordinary part of life. However, in disease states, the precursors can also accumulate prior to phagocytosis of the outer segments by the retinal pigment epithelium (RPE). Once phagocytized by the RPE, many of the components of the other segments are recycled and transported to the photoreceptors for reuse. Indigestible material, particularly that derived from crosslinking between retinoids and themselves or other molecules, are concentrated and stored in liposomes to create lipofuscin. Most of the FAF we ordinarily record is derived from lipofuscin in the RPE. Various diseases can be associated with increased lipofuscin in the RPE, which causes increased autofluorescence. Some disease states, particularly those leading to accumulation of yellowish vitelliform material in the subretinal space, have increased autofluorescence arising from extracellular sources.

(continued on page 4)

and coalesce and eventually, the patient will lose vision. As the GA gets closer to the foveal center, patients become increasingly aware of their decreasing visual field and acuity.

Various imaging strategies have been tested in clinical trials for following GA. These include color fundus photography, autofluorescence, 3D OCT and fluorescein angiography (*see Figure 2*). Fluorescein angiography is avoided in routine clinical care because it's invasive and unnecessary unless CNV is suspected. Most of our clinical experience has been with color fundus photography or autofluorescence. Which of these is better and is autofluorescence imaging strategy superior?

Comparing Technologies

The choice between imaging strategies is currently under debate. Reading centers tend to prefer stereoscopic viewing of color fundus photography, but in today's clinical practice, stereoscopic viewing is rapidly becoming a lost art. Trying to train fellows in stereoscopic viewing nowadays is almost impossible because of autofluorescence and optical coherence tomography (OCT). Autofluorescence and OCT really make stereoscopic viewing unnecessary, especially since the future of imaging and viewing of images will be all digitally based.

A paper by the National Eye Institute at the most recent American Academy of Ophthalmology meeting in Chicago compared color fundus photography with autofluorescence and found that the two were similar in detecting

The Dawn of a New Filter

(continued from page 3)

Detecting Autofluorescence

There are different ways to detect autofluorescence. One is to use confocal imaging (that is the idea behind a scanning laser ophthalmoscope) and the advantage to this method is that only light originating from the retina and the RPE gets imaged by the instrument, but in many cases, it can reject autofluorescence from the lens.

With Heidelberg's Spectralis, the excitation wavelength is 488 nm, which is a blue-green color. According to the company, they have a band pass filter that starts at 500 nm. Essentially, that means they use the fluorescein filters for autofluorescence; they just turn up the gain of the instrument, which means you cannot do fluorescein imaging before autofluorescence imaging because of the residual fluorescein within the eye. Macular pigment is designed to block blue light and absorbs the excitation light produced by the Spectralis. I wanted to be able to image autofluorescence with a fundus camera because at the time, we didn't have a Heidelberg instrument. The problem with using conventional wavelengths used by scanning laser ophthalmology devices is that they also cause the crystalline lens to autofluoresce. So the excitation wavelength was moved to a somewhat longer wavelength as was the peak of the barrier filter. This markedly reduced the autofluorescence from the lens and also removed the problem with macular pigment. There is evidence that blue light can cause apoptosis in RPE cells containing lipofuscin, so there is an additional theoretical advantage to using longer wavelengths. Through improved science and state-of-the-art manufacturing processes, the excitation and barrier filters are approximately 20 times more efficient than older generation fundus autofluorescence filters. The image quality produced is good, but requires user intervention to adjust the image in terms of contrast. This contrast adjustment is done automatically in the Heidelberg Spectralis.

GA, but that area measurements, growth rates and estimates of foveal involvement did differ.[3] These findings are important because patients lose vision with foveal involvement, and foveal involvement is what we are trying to avoid. So knowing when the fovea is threatened or involved is vital information for the clinician and the patient.

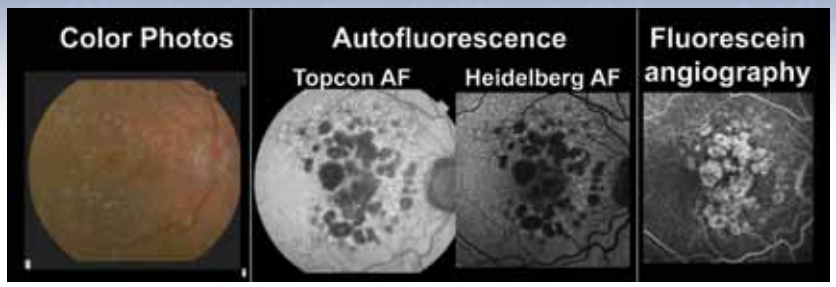

Figure 2. Strategies tested in clinical trials for following geographic atrophy.

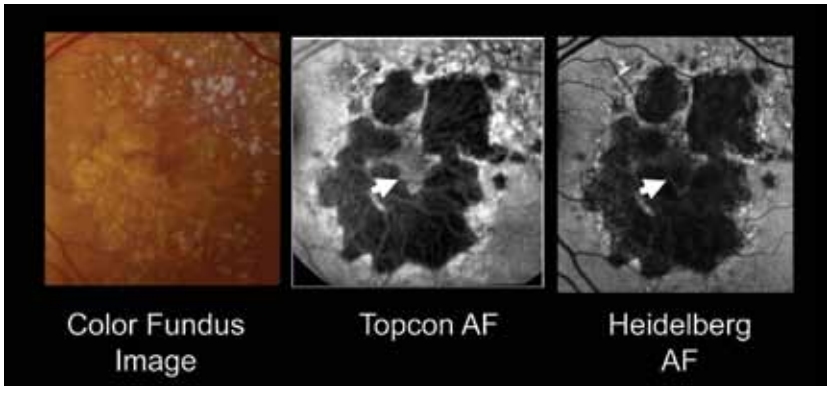

Figure 3. Imaging of GA using different devices.

Tracking Foveal Involvement

So the major questions are, can we measure GA? Can we follow GA, and do we know when it is encroaching on the foveal center?

I am running a clinical trial to determine whether we can stop the growth of GA using a complement inhibitor. All patients enrolled in the clinical trial have vision of 20/63 or better (high-risk drusen cohort, n=30; GA cohort, n=30). They receive either the complement inhibitor known as eculizumab or placebo over 26 weeks and then they are followed for at least one year.

This Phase II study compares different imaging modalities (color fundus photography, Heidelberg Engineering's Spectralis HRA and Topcon Medical Systems' TRC-50DX) to determine the best imaging strategy for GA. The goal is to compare these imaging approaches when establishing boundaries of GA, following boundaries over time, calculating growth rates, determining drug efficacy and identifying foveal center involvement.

Figure 3 compares three different imaging strategies and demonstrates how the Topcon Spaide filters for detecting autofluorescence are superior to color fundus photography and the Heidelberg autofluorescence images. Only the Topcon filters can reproducibly and reliably identify foveal center involvement in cases of GA in which the fovea is not involved; these are just the kind of patients that we follow in clinic and enroll in clinical trials. Due to the excitation wavelength used by the Heidelberg system, the retinal pigment epithelium (RPE) in the central macula does not autofluoresce because the overlying luteal pigment in the retina absorbs the light and prevents the light from ever reaching the RPE. The excitation wavelength delivered by the Topcon Spaide filters is outside the absorption range of the luteal pigments, so a clear, crisp, reliable view of the central macula is achieved.

More than 90 percent of the patients enrolled have a complication when trying to detect foveal involvement with the Heidelberg autofluorescence system. In these cases, I cannot rely on autofluorescence alone; I have to use another modality to detect foveal involvement. With the Topcon filters, I can see what is going on in the foveal center and I can map the boundaries. GA is just easier to identify and follow with the Topcon autofluorescence instrument.

While most of the published studies using autofluorescence to image GA have used the Heidelberg confocal scanning laser ophthalmoscope, in real world clinical practice, the Topcon approach is superior.

Real-Life Applications

The Topcon autofluorescence digital system is ideal for identifying GA and following patients with GA. For clinical trials designed to explore emerging treatments for GA, the Topcon system should be a necessity. Over the next few years, as we continue to learn more about dry AMD and study these emerging therapies, the usefulness of the Topcon filters will become increasingly obvious.

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COMPARISON OF SD-OCT DEVICES AND 3D OCT DRUSEN ANALYSIS SOFTWARE

A look at the history of OCT devices, what they can do and how to use them in clinical practice.

by Peter K. Kaiser, MD

In the 1990s, Zeiss licensed time-domain optical coherence tomography (OCT) technology from James Fujimoto's lab at Massachusetts Institute of Technology (MIT) and made a commercial scanner, but the popularity of the technology for most of us in clinical practice didn't really begin until the software was improved and the Stratus OCT (Carl Zeiss Meditec) came along in 2002. The Stratus was an improvement in both speed and axial resolution over the earlier models, but more importantly, the software algorithms allowed us to follow patients over time. The big explosion in OCT technology came in 2007 with the first spectral domain OCT (SD-OCT) devices coming to market. By evaluating all the images and light and wavelength parameters simultaneously (in contrast to the serial approach used in the older time-domain OCT), there was a huge jump in the speed of image acquisition. Since this technology was in the public domain, many companies could produce spectral domain devices. Let's look at how these devices differ.

Today's SD-OCT Devices

The SD-OCT devices used today all pretty much utilize the same wavelength (*see Figure 1*), although with the advent of enhanced depth imaging (EDI), which I will get into later, we are finding that scanning depth actually matters. In fact, devices with deeper scanning depths are more attractive for EDI because we are now actually able to image the choroid. Axial resolution depends on the wavelength of light you are using and because the wavelengths are all pretty similar, the axial resolutions are also going to be similar. One factor that differs between these devices is scanning speed.

With OCT, faster isn't always better because the faster you go, the more noise is introduced into the images and the more you have to use image averaging to get a good image. The final thing that differs between these devices is the ancillary imaging they include. Aside from OCT, some devices include other imaging capabilities such as color fundus photography, fundus autofluorescence, fluorescein angiography, indocyanine green angiography and

scanning laser ophthalmoscopy.

The shared features of all these devices are that they have improved resolution, more accurate retinal maps, improved registration/orientation (because we have so much information), cube scans and 3D views, which were not possible with previous devices (*see Figure 2*).

Image averaging. As I mentioned, high-speed imaging requires image averaging (a photographic technique) to produce a good image. This technique overlaps multiple images from the same location, and any noise in the image will appear as a difference between the images. So if you overlap multiple images, anything that changes is considered noise and is subtracted out to produce the high-resolution OCT images that we see. Therefore, by using image averaging technology, one can produce higher resolution, higher contrast images with less speckle and noise. Although most companies' devices now perform image averaging, some really don't need to. Also, note that image averaging takes time, which may make it difficult to perform image averaging and image a large cube of the retina.

Device	Wavelength	Scanning Depth	Axial Resolution	Scanning Speed	Ancillary Imaging
Bioptigen 3D SDOCT[1]	840 nm	2.3 mm	3–5 µm	17,000	
Carl Zeiss Meditec Cirrus[1]	840 nm	2 mm	5 µm	27,000	
Heidelberg Spectralis OCT[1]	870 nm	1.9 mm	7 µm	40,000	SLO/FA/ICG/ Autofluorescence
Opko/OTI Spectral OCT/SLO[1]	840 nm	2.3 mm	5–6 µm	27,000	SLO/ICG/ microperimetry
Optovue RTVue-100[1]	840 nm	2.3 mm	5 µm	26,000	
Canon/Optopol SPOCT[1]	840 nm	2 mm	6 µm	25,000	
Canon/Optopol SPOCT • HR[2]	850 nm	2 mm	3 µm	52,000	
Topcon 3D OCT-2000[1]	840 nm	2.3 mm	5–6 µm	27,000	color fundus (12.3 MP)
Topcon 3D OCT-2000 FA (+)[2]	840 nm	2.3 mm	5–6 µm	50,000	color fundus, FA, RF, FAF (+)

[1] 510(k) approved [2] 510(k) pending

Figure 1. SD-OCT hardware comparison.

Views from a Different Dimension

In the past, we could not image the choroid very well with OCT. OCT provided excellent cross-sectional images of the retina and retinal pigment epithelium (RPE), but imaging of the choroid was poor. A new technique was recently developed by Dr. Spaide to provide better imaging of choroid and sub-RPE space: EDI.[1] We are finding that choroidal thickness correlates with age and refractive status, and is thickened in certain diseases such as central serous choroidopathy.

Because spectral domain has such huge datasets, we can not only look at the images in 3D, but we can also look at the data from another dimension, which we were not able to do with time domain OCT: Z-plane or C-scanning. Conventional B-Scanning results from fixed Z-axis, while C-scanning allows for the scans to be performed along the Z-axis creating true en-face images. In other words, we are looking at it from the top down; whereas we are used to looking at it in cross section. So, for instance, if you look at a macular hole from the side, it is pretty obvious, but if you look at it from the top down in the C-scan mode, you can dive into these macular holes. I like to show these to my patients because you can conceptualize for them why their epiretinal membrane, for example, is causing a distortion in their vision.

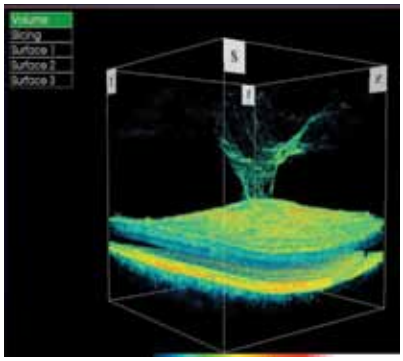

Figure 2. 3D view with Topcon device.

All of the OCT devices are starting to perform C-scan imaging and we are finding new uses for it in terms of macular degeneration in particular (*see Figure 3*).

Hardware-Specific Features

Some of these OCT devices also have an anterior segment imaging mode that allows you to look at anterior segment structures such as whether the lens is in the bag,

Purchase Pointers
By Peter K. Kaiser, MD

If you are looking to update your practice in this area, my best advice is for you to sit down and try the devices; see how easy is it for you to use the software, how quickly can you actually scan a patient and look at the image quality. Do you like it? If you have a practice with glaucoma specialists, for instance, you will want to make sure there's an optic nerve normative database.

A feature that people don't often consider is legacy support, which not all companies offer. You may have Stratus OCT (Carl Zeiss Meditec) information from your old scanner, and if you are upgrading to one of the new spectral domain devices, you still want to be able to look at that Stratus data. The Cirrus HD-OCT (Carl Zeiss Meditec) comes with reader software, but requires two different programs to run at the same time. With other OCT devices, you can also purchase this Stratus reading software. Topcon has actually made a more elegant solution: it built reading software for the Stratus into its new SD-OCT devices. Finally, you will want to consider the company's track record with regard to future support. Will the company be around in four or five years so your device will be continuously upgraded?

identify any problems with the cornea itself, measure the angle, etc. Another thing to consider when you look at these devices is whether there is a way to make a reference image that you can use to pinpoint changes between visits. The 3D OCT-2000 (Topcon) uses the fundus photograph, whereas Cirrus (Carl Zeiss Meditec) uses false fundus representation and Heidelberg's Spectralis OCT uses eye-tracking software. This device has other imaging modes: BluePeak Autofluorescence Imaging, fluorescein angiography, SD-OCT, indocyanine green angiography, infrared imaging, red-free imaging and is able to pinpoint between any of those imaging modalities. The 3D OCT-2000 Spectral Domain OCT also offers fundus autofluorescence, fluorescein angiography, color fundus photography and PinPoint Registration of OCT data as well as the other imaging modalities. So you need to know how the companies are comparing between visits to best decide if you're doing a change analysis.

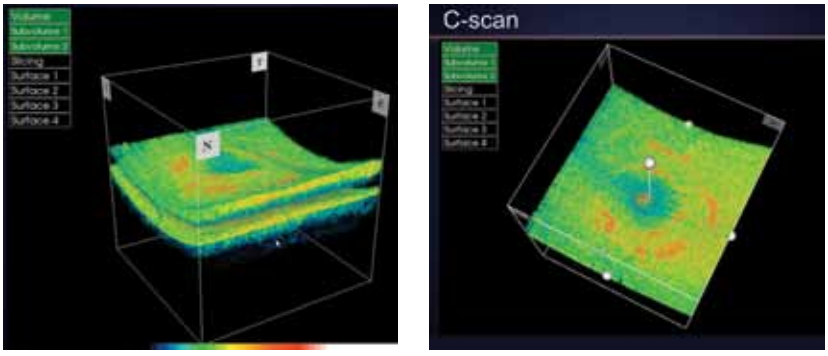

Figure 3. C-scan with the Topcon device (left). Diving down in a C-scan mode from the retina into the choroid (right).

The Spectral OCT/SLO device (Opko Health, Inc.) has a microperimetry unit built in, which allows you to do both microperimetry and change analysis.

Bioptigen has a device that many people may not have heard of (3D SD-OCT), but is starting to gain more favor clinically. The company has been developing this intraoperative scanning head at Duke and we are finding that it may be beneficial in surgery.

Susan Bender is working on a device with Zeiss that offers intraoperative OCT at the time of the surgery

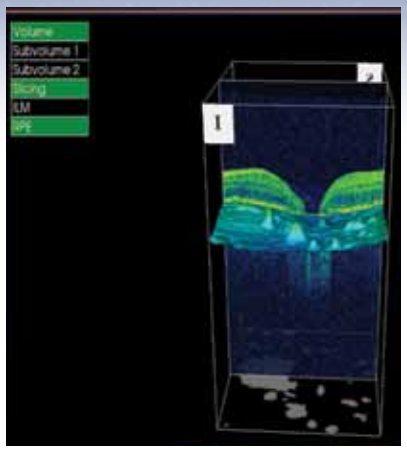

Figure 4. Drusen mapping.

live and in real time.

Finally, the RTVue-100 (Optovue) offers wide-angle scans that can provide massive views of the retina, especially in a case, for instance, differentiating retinoschisis from retinal detachment.

Mapping Drusen and Atrophy in Dry AMD

Evaluating drusen size and volume, as well as geographic atrophy area, is something that is being added very shortly to a few OCT devices. We were fortunate to test both the Cirrus and Topcon versions of this software, and they allow you to actually map changes in these parameters over time. Since the software cannot actually "see" drusen, it assumes that any elevations in the RPE over a certain threshold are drusen and use this to identify anything elevated as drusen (*see Figure 4*).

From a scientific standpoint, you can see how error could be introduced into this type of measurement. So the key aspect of this software is how you can adjust for these elevations (by adjusting this threshold) and basically only evaluate the images that are correct and throw out the images that are incorrect. We are working closely with the companies to work out these issues. As treatments for dry AMD become a reality in the future, this type of analysis will become important.

Comparing the Facts

Now that we have reviewed the available and upcoming OCT devices, you can see that the OCT hardware is all pretty similar, though not all have eye tracking or ancillary imaging capabilities. When choosing an OCT device for your practice, keep in mind that it should be easy to use and patient-friendly to ensure efficient clinical operation. Additionally, the instrument should be competitively priced for all of its features, so you need to ask yourself what imaging capability you want and whether you use that in your clinical practice. The bottom line is that it's all about the software. See the sidebar "Purchase Pointers" for more detailed information.

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IMAGING AND SWEPT SOURCE OCT

Getting a better look at the choroid.

by Richard F. Spaide, MD

Although the choroid is an important part of the eye and many ocular diseases originate from it, we don't always think of it. We can use fluorescein to look at the eye, but it does not image the choroid particularly well. We have used indocyanine green angiography to obtain an image like a spider web of blood vessels and sometimes it is hard to figure out what is going on in the thickness of the choroid. We have also used ultrasound to look at the

choroid, but this method has poor axial resolution, so we developed a way to look at the choroid using spectral domain optical coherence tomography (SD-OCT).

An Expanded Look at SD-OCT

Ordinarily, SD-OCT does not produce particularly good images of the choroid because it has a depth-related roll off in sensitivity and because the melanin in the retinal pigment epithelium (RPE) and choroid is an enemy of coherence signals. What is most important for this discussion is the roll off in sensitivity with depth. *Figure 1* shows you the red curve that illustrates the kind of signal that you get from SD-OCT. There are two parts of this curve and they are mirror images of each other, so one is a conjugate image that is upside-down compared to the other image.

Ordinarily, instrument manufacturers put the peak sensitivity in the vitreous because they are looking at the vitreomacular interface for traction and so forth. But a typical SD-OCT gets dark because of a decrease in sensitivity to light, or, more accurately, to the coherence signal with depth. The idea behind enhanced depth imaging (EDI) is that you just push that peak sensitivity in closer to position around the scleral border. We lose the sensitivity to see the vitreous adequately by doing this. So you get one or the other. On the other hand, you see the scleral border quite easily. So with this method of SD-OCT imaging, we pick the choroid instead of the vitreous because you can't get both at once. This feature is built into Heidelberg and Topcon software (Enhanced Choroidal Mode).

The choroid is basically the thickest at the fovea in normal eyes. It thins a little bit temporally and more so toward the optic nerve. The choroid gets thinner with age, so when you are young, the subfoveal choroidal thickness is about 350 µm and ends up about 250 µm when you are older.

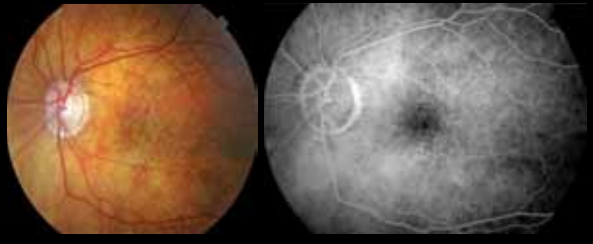
The Choroid Up Close

If there is enough permeability in the choroid to cause the RPE to be pushed up and to make a break in the RPE, then the choroid

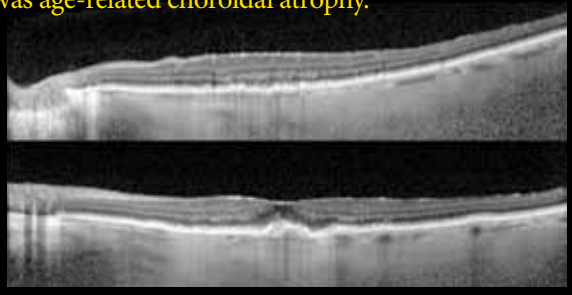
CASE REPORT

By Richard F. Spaide, MD

This patient was referred as an emergency because she had decreased acuity and her referring doctor was concerned that she had exudative macular degeneration. A look at the center of her macula showed that there were almost no visible blood vessels in the choroid. (There is one remaining blood vessel and some optic nerve pallor as well as beta zone atrophy.) Fluorescein showed that she did not have any choroidal neovascularization, but the choroid was so paper thin; it was almost gone. The diagnosis was age-related choroidal atrophy.



Color fundus photo (left) and fluorescein image (right) of the patient in this case.



Optical coherence tomography showing the patient's age-related choroidal atrophy.

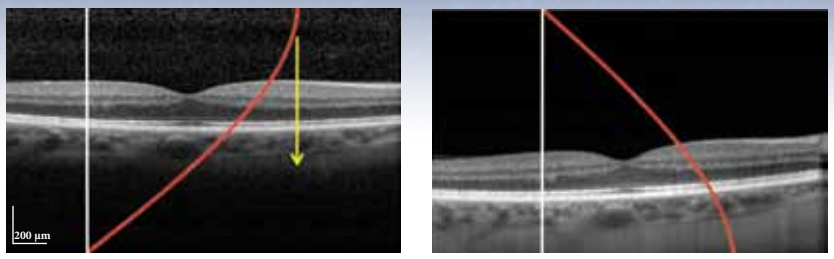


Figure 1. Ordinary (left); Inverted image, flipped (right).

is probably going to be thick too. And a thick choroid helps confirm the diagnosis of central serous chorioretinopathy.

In myopia, we have normal growth of the eye until the age of eight until about 12, then the eye expands. What happens to the choroid? In a -20D myope, for example, it seems that the same amount of choroid gets stretched down into a very thin layer. You also will not find many blood vessels inside the choroid of a myopic patient. The choroid gets so thin around the optic nerve that it can no longer support the life of the RPE. At this point, the choroid dies off and the sclera becomes visible. Older myopes usually have a much larger area of choroidal involvement than just the region of peripapillary atrophy.

Getting a Handle on Swept Source OCT

Light source OCT is a new kind of imaging technique available with time domain and SD-OCT that uses a broadband light source with many wavelengths of light simultaneously coming out at one time. It is actually an easier light source to make, but we have a fairly complicated way to interpret the signal once it comes back out of the eye.

On the other hand, *swept source OCT* is a more complicated light source where, at each point, the wavelength of the light is quickly swept across a band of wavelengths. The resultant signal that gets detected by the machine is done with a system based on photodiodes, which is much more responsive and quicker than the charge-coupled devices (CCDs) used for SD-OCT. Swept source OCT commonly uses a longer wavelength light source because of availability.

The fall-off in sensitivity for SD-OCT with increasing depth is not present to the same extent in swept source OCT. So far, at least in our Topcon prototype swept source OCT, we have not been able to make the peak sensitivity as good as that with SD-OCT, but because the response curve for swept source does not fall off much, you get a good image of both the retina and the choroid at the same time. The sensitivity is not yet there to image the vitreous all that well. One attribute of many swept source OCTs is that the scan rates are extremely fast. Our swept source prototype scans at 101,000 A-scans per second.

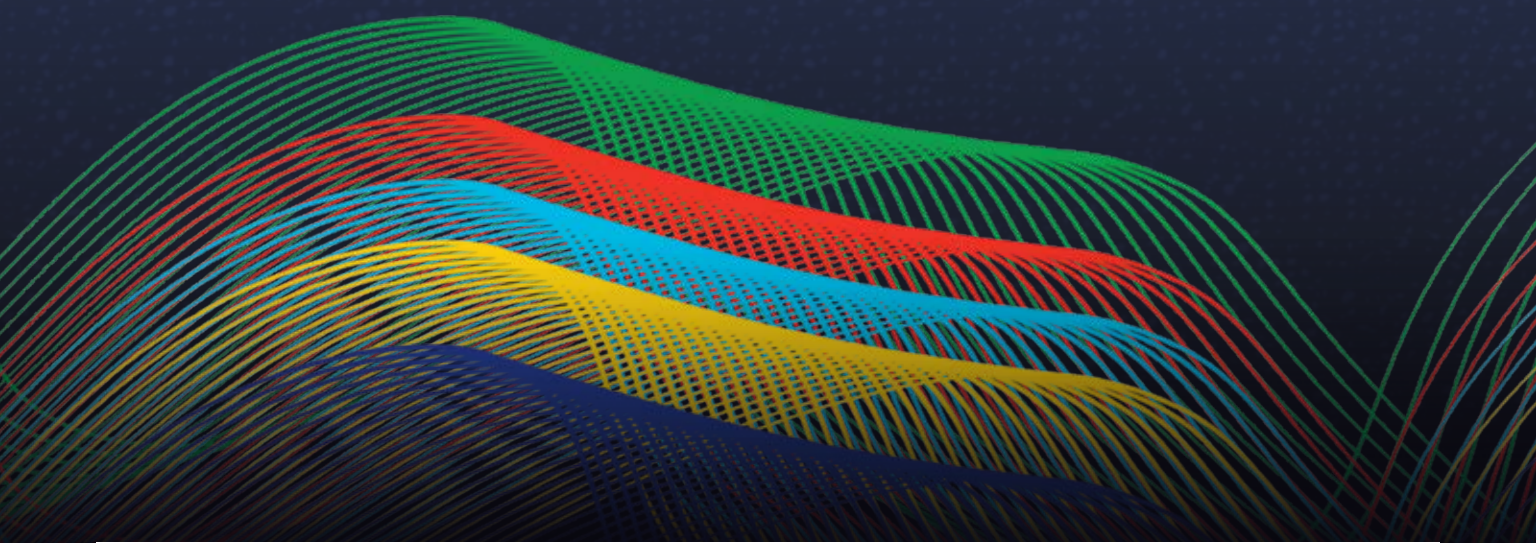
Wavelength, on the other hand, is a bit of a double-edge sword. If you use short wavelengths, you get high resolution, however, shorter wavelengths do not penetrate well. Longer (1µm) wavelengths penetrate better because they are not absorbed as well or reflected as much. But remember, the reflection of light is what gives us the signal, so even though it penetrates better, we are actually getting less signal back.

So with swept source OCT, as it is currently being implemented, there may be somewhat decreased resolution and signal-to-noise ratio, but you get some things back: namely an improved ability to image greater depths as well as speed.

Conclusion

Choroidal imaging method is somewhat of a new frontier in imaging. I believe that we will be able to analyze the thickness and density of blood vessels in the choroid in the fairly near future and get an idea about what is going on in the choroid from a structural standpoint. There are some ways that we can do it now with SD-OCT, but it takes time because you have to average images together, but soon we will have swept source OCT and the image quality is going to improve over time.

Richard F. Spaide, MD, practices at Vitreous, Retina, Macula Consultants of New York, where he specializes in diseases of the retina and vitreous. He has published more than 200 peer-reviewed articles as well as four books about the diagnosis and treatment of retinal diseases. Dr. Spaide is also an Associate Editor of the journal Retina *and is on the editorial board of the* American Journal of Ophthalmology.



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