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Imaging chorioretinal vascular disease

PA Keane and SR Sadda

Abstract

Since its first description more than 40 years ago, fluorescein angiography had a crucial role in the diagnosis and management of chorioretinal vascular disorders such as neovascular age-related macular degeneration. Although fluorescein angiography permits visualization of the retinal microcirculation in exquisite detail, visualization of the choroidal circulation is more limited. Moreover, fluorescein angiography provides only minimal information regarding the functional consequences of vascular disease and allows, at best, only semi-quantitative assessment of retinal thickness. In recent years, the development of other chorioretinal imaging modalities, such as indocyanine green angiography, fundus autofluorescence, and optical coherence tomography (OCT), has addressed many of these issues. In particular, OCT has become an integral tool for vitreoretinal specialists as it allows high-resolution cross-sectional images of the neurosensory retina to be obtained in a non-invasive manner. The latest generation of commercial OCT technology—spectral domain OCT—offers high-speed scanning that allows complete coverage of the macular area, generation of three-dimensional retinal reconstructions, and precise image registration for inter-visit comparisons. The high speed of spectral domain OCT also facilitates B-scan averaging, which reduces speckle noise artefact and allows unparalleled visualization of the outer retina and choroid. In the near future, further advances in OCT technology (eg Doppler OCT) are likely to dramatically enhance the diagnosis and management of patients with chorioretinal vascular disease.

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Doheny Image Reading Center, Doheny Eye Institute, Keck School of Medicine of the University of Southern California, Los Angeles, CA, USA

Correspondence: SR Sadda, Doheny Image Reading Center, Doheny Eye Institute, DEI 3623, 1450 San Pablo Street, Los Angeles, CA 90033, USA
Tel: +1 323 442 6503; Fax: +1 323 442 6460; E-mail: ssadda@doheny.org

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Introduction

In 1961, Novotny and Alvis[1] produced the first fluorescein angiograms providing images of the chorioretinal vascular system. Since that time, chorioretinal imaging—principally stereoscopic photography and fluorescein angiography—had a crucial role in the management of patients with chorioretinal vascular diseases such as neovascular age-related macular degeneration (AMD). More recently, the development of a new imaging modality, optical coherence tomography (OCT), has addressed many of the limitations of these traditional imaging techniques, and reinforced the central role of imaging in the management of these patients. In this article, we describe the principal chorioretinal imaging techniques in use today, as well as a number of new technologies currently in development that may transform the management of chorioretinal vascular disease.

Fluorescein angiography

Fluorescein angiography possesses a number of features that have made it central to the management of chorioretinal vascular disease.[2] In particular, it permits visualization of the retinal microcirculation in exquisite detail, allowing identification of vascular abnormalities and areas of retinal non-perfusion. It also enables visualization of many pathologic changes affecting the choroidal vasculature (Figure 1). Through the assessment of vascular leakage, fluorescein angiography also provides important functional information (ie the integrity of the blood–retinal barrier). These features have allowed fluorescein angiography to show its worth in a wide variety of clinical settings, as well as in the context of important randomized clinical trials (eg the Early Treatment of Diabetic Retinopathy Study (ETDRS) for diabetic retinopathy).[3]

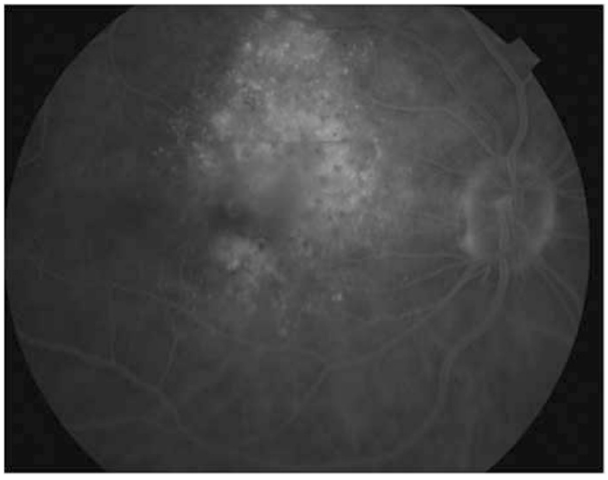

Figure 1 Fluorescein angiogram showing evidence of late stippled hyperfluorescence consistent with fibrovascular pigment epithelium detachment.

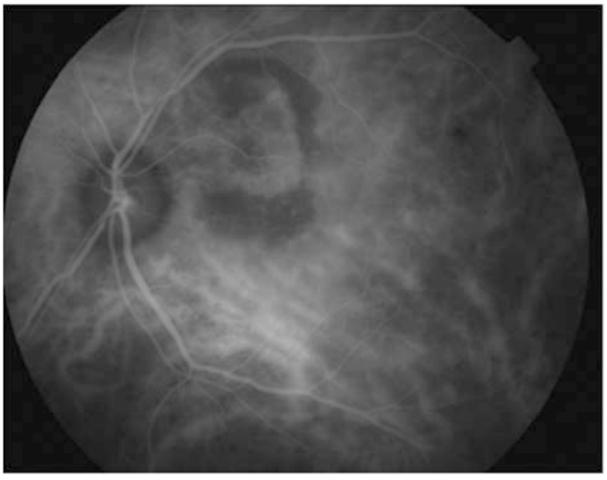

Figure 2 Indocyanine green angiography showing evidence of peripapillary choroidal neovascularization.

Limitations of fluorescein angiography

Despite these advantages, fluorescein angiography has a number of limitations. First, it is an invasive procedure with complications that range from minor (nausea and vomiting) to serious (anaphylaxis). Second, its ability to visualize the choroidal circulation is limited, with considerable loss of vascular detail over time because of progressive dye leakage. Third, even with the use of stereoscopic images, it has a limited axial resolution that allows—at best—semi-quantitative measurement of retinal thickness that is subject to considerable variability.[4] Finally, fluorescein angiography provides only limited information regarding the structural and functional consequences of vascular disease. Fortunately, in recent years, advances in other chorioretinal imaging modalities have addressed many of these deficiencies.

Indocyanine green angiography

Indocyanine green angiography, first described in 1972, allows enhanced visualization of the choroidal circulation—unlike fluorescein, indocyanine green is almost completely bound to protein and tends not to leak through the fenestrated capillaries of the choriocapillaris obscuring the larger choroidal vessels (Figure 2).[5] Despite this, initial usage was limited by the poor fluorescence efficiency of indocyanine green, and the limited ability to produce high-resolution images on infrared film. Since the 1990s, however, the development of high-speed, high-resolution digital imaging systems has resolved many of these issues.[6] Although still not commonly performed in clinical practice, indocyanine green angiography has improved our understanding of disorders such as neovascular AMD (especially retinal angiomatous proliferation and polypoidal choroidal vasculopathy), central serous chorioretinopathy, and chorioretinal inflammatory disorders.[7]

Fundus autofluorescence

Autofluorescence is an intrinsic property of many structures within the eye (eg retinal pigment epithelium (RPE)), such that transient emission of light occurs when these structures are illuminated by an exogenous source.[8] Autofluorescence of the RPE is related to the intracellular accumulation of lipofuscin, a byproduct of incomplete photoreceptor outer segment degradation. Lipofuscin accumulation is a hallmark of normal aging in many cells, but may also be a common downstream pathogenic mechanism in a number of retinal degenerative diseases. As a result, fundus autofluorescence (FAF) imaging has generated considerable interest in recent years for patients with both inherited and acquired retinal degenerations (Figure 3). In fact, FAF imaging has recently been approved by the US Food and Drug Administration as a primary end point in clinical trials of non-neovascular AMD (geographic atrophy).[9]

The role of FAF imaging in chorioretinal vascular disease is less well established. In neovascular AMD, for example, the continuity of the FAF signal over the lesion may provide prognostic information.[10] In patients with this disorder, FAF may be relatively normal ('continuous') early on, a finding that correlates with better visual acuity, and presumably represents continued RPE viability. However, with longer-standing disease, decreased FAF is often seen, a finding that correlates with decreased visual acuity, and presumably represents photoreceptor loss and RPE atrophy. FAF imaging may also be of diagnostic use in less commonly

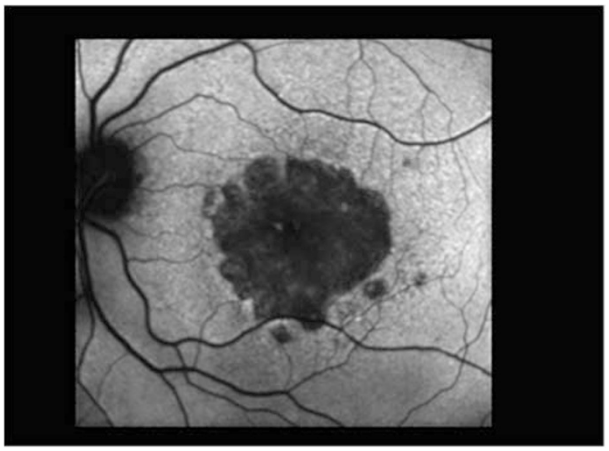

Figure 3 Fundus autofluorescence image obtained with a confocal scanning laser ophthalmoscope—geographic atrophy may be clearly seen as a central area of hypoautofluorescence.

seen retinal vascular disorders such as type 2 idiopathic juxtafoveal telangiectasia, in which central depletion of macular pigment results in a characteristic loss of normal foveal hypofluorescence.[11]

Optical coherence tomography

OCT, first described in 1991, allows high-resolution cross-sectional images of the neurosensory retina to be obtained in a non-invasive manner.[12] As a result, retinal imaging with OCT has quickly become an integral tool for the management of chorioretinal vascular disorders.

Time domain OCT

OCT works by measuring the properties of light waves reflected from tissue (analogous to ultrasonography).[13] In the original OCT systems, movement of a reference mirror allowed acquisition of depth information over time—'time domain' OCT. The release of the first commercial time domain OCT systems, in 1996 (OCT1) and 2000 (OCT2), quickly established the clinical benefits of OCT—in particular for the depiction of the vitreomacular interface. However, it was the release of the third generation of time domain OCT devices in 2002 that heralded the widespread adoption of OCT by retinal specialists. OCT3 (Stratus OCT, Carl Zeiss Meditec, Dublin, CA, USA) offered faster scanning speed (400 A-scans per second) and higher resolution (8–10 microns axially)—features that provided significant advantages for the management of chorioretinal vascular diseases.

Clinical applications of time domain OCT

Macular oedema is a common cause of vision loss in patients with retinal vascular disease.[14] The greater axial resolution of Stratus OCT (particularly when compared to stereoscopic fundus photography) has allowed improved characterization of the structural changes that occur in macular oedema. In diabetic macular oedema, for example, distinct patterns of morphologic change may be seen on OCT: diffuse retinal thickening, cystoid macular oedema, serous retinal detachment, and vitreomacular traction (retinal vascular diseases are also commonly accompanied by epiretinal membrane formation) (Figure 4).[15–17] In addition to these qualitative assessments, measurements of retinal thickness provided by time domain OCT have become important criteria for determining eligibility for clinical trials, as well as being adopted as anatomic end points in these trials.[18]

In recent years, driven by the seminal findings of the PrONTO study for neovascular AMD, OCT has also been rapidly adopted for the management of patients with choroidal vascular disease.[19,20] In the PrONTO study, OCT-derived criteria were used both for determination of eligibility, and for re-treatment decisions (eg presence of subretinal fluid), in patients receiving intravitreal ranibizumab. In 2007, the following OCT-derived guidelines, for the treatment of neovascular AMD, were suggested by Brown and Regillo: (1) initial monthly treatment, until no intraretinal, subretinal, or sub-RPE fluid; (2) consideration of fluorescein angiography if visual acuity changes do not correlate with anatomic improvements; (3) re-treatment based on qualitative inspection of all six high-resolution Stratus OCT scans with re-treatment for any recurrence of intraretinal, subretinal, or sub-RPE fluid.[21] These guidelines or variations, thereof, have been quickly adopted by retina specialists worldwide, greatly increasing the utilization of OCT in the management of patients with choroidal vascular disease.

Limitations of time domain OCT

Although it is clear that OCT successfully addresses many of the limitations of fluorescein angiography, the use of OCT in choroidal vascular diseases has also highlighted many of the limitations of time domain OCT. OCT-derived retinal thickness values are obtained by automated detection (segmentation) of the inner and outer retinal boundaries. Unfortunately, however, this automated detection frequently fails in patients with retinal disease, particularly in patients with choroidal vascular disease.[22] Moreover, even if boundary detection is correct, many specific disease components are not quantified by OCT (eg subretinal fluid, pigment epithelium detachments). To ensure the accuracy of retinal thickness measurements, and to allow quantification of other morphologic parameters, manual segmentation of OCT images is often performed in dedicated image reading centres.[23–25]

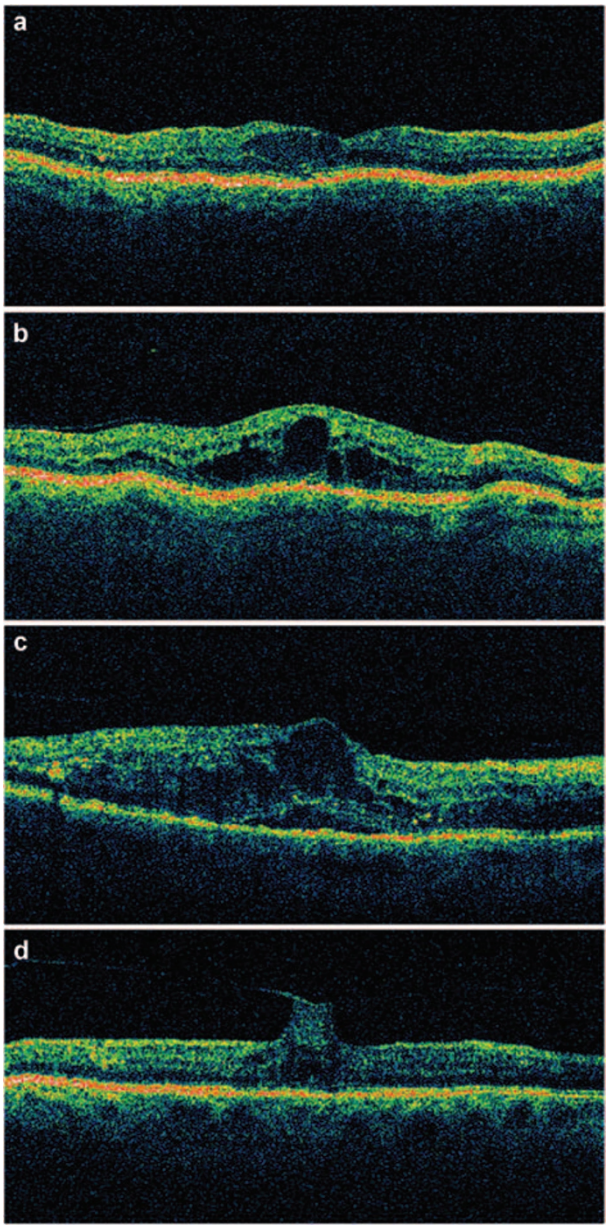

Figure 4 Patterns of structural change on optical coherence tomography (OCT) in patients with diabetic macular oedema. OCT B-scans show sponge-like retinal thickening (a), cystoid macular oedema (b), serous retinal detachment (c), and vitreomacular traction with peaking of the retinal surface (d).

Time domain OCT systems are also limited by their requirement for a mobile reference mirror—a requirement that limits their image acquisition speed.[26] Consequently, typical time domain OCT scanning protocols capture <5% of the macula in a single image set and significant interpolation is required to construct retinal thickness maps. As a result, time domain OCT scanning protocols often miss small lesions that fall between the scanned lines, and any segmentation errors that occur may often be propagated across large areas. Fortunately, these limitations have been largely overcome in recent years with the latest generation of commercial OCT technology—'spectral domain' OCT.

Spectral domain OCT

In spectral domain OCT systems, the use of spectral interferometry and a mathematical function (Fourier transformation) removes the need for a mobile reference mirror, and allows images to be acquired 50–100 times more quickly than in time domain systems (typically over 20 000 A-scans per second).[27–29] The high speed of spectral domain OCT allows significantly greater coverage of the macular area using raster scanning protocols (eg 128 B-scans, with each B-scan consisting of 512 A-scans). The greater speed of spectral domain OCT also reduces the frequency of eye motion artefacts and allows the creation of three-dimensional reconstructions of the retina. In addition, by summing the intensity values in each A-scan, the dense scanning of spectral domain OCT allows generation of 'projection' images that appear superficially similar to fundus photographic images. These projection images contain invariant landmarks that can be aligned with standard fundus photographic images, facilitating direct comparison with these images and allowing more precise registration for inter-visit comparisons.[30]

The rapid scanning of spectral domain OCT also allows averaging of multiple B-scan images to be readily performed, reducing speckle noise and allowing greater visualization of fine structures—in particular, the structures of the outer retina and choroid.[31] Although spectral domain OCT has a higher sensitivity than time domain OCT, spectral domain image quality changes as the scan moves vertically on the screen. By adjusting the spectral domain OCT device to maximize its sensitivity at the choroid, and through the use of B-scan averaging, extremely high-quality images may be obtained. Such imaging allows clear visualization of outer retinal structures such as the external limiting membrane, and enhanced visualization of the architecture of fibrovascular tissue in neovascular AMD (Figure 5).[32–34]

Current limitations and future directions

Although it represents a significant advance, spectral domain OCT also has a number of limitations. As with time domain OCT, the transverse resolution of spectral domain OCT is limited by the optics of the ocular system and, as a result, spectral domain OCT does not allow visualization of individual cells.[35] In addition, the functional data provided by spectral domain OCT

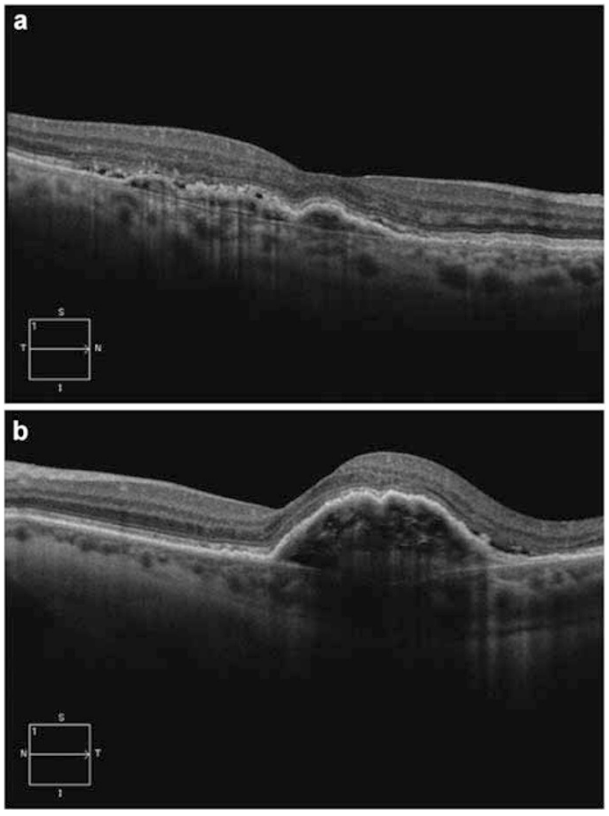

Figure 5 Evaluation of neovascular age-related macular degeneration (AMD) using 'enhanced depth' spectral domain optical coherence tomography (Cirrus HD-OCT, Carl Zeiss Meditec, Dublin, CA, USA)—(a) and (b).

remains rudimentary at best. Furthermore, better segmentation software is still required to facilitate precise quantitative subanalysis of dense raster scan data sets.[36] Not surprisingly, future OCT technologies will likely address these limitations. Prototype Doppler OCT systems allow measurement of retinal blood flow by the assessment of light reflectivity changes in retinal blood vessels over short time periods.[37] 'Swept-source' OCT systems allow significant increases in imaging sensitivity and speed (eg $>300\,000$ A-scans per second), through the use of a tunable laser,[38] whereas polarization-sensitive OCT may prove to encode much of the information provided by FAF.[39] Finally, the use of adaptive optics in OCT devices may increase the transverse resolution of OCT systems and provide cellular level detail.[40]

Conclusion

In recent years, retinal imaging with OCT has become central to the treatment of patients with chorioretinal disorders. Using current, commercially available, technology, it is now possible to obtain high-quality cross-sectional images of the choroid—such imaging may represent the next frontier in our understanding of retinal disease pathogenesis. Furthermore, the applications of OCT in chorioretinal vascular disease are likely to grow with functional extensions of this technology in the near future (eg Doppler OCT may lead to a new wave of categorizing retinal vascular disorders on the basis of blood flow). Such advances, in association with improvements in other imaging techniques, are likely to dramatically enhance our management of patients with chorioretinal disease.

Conflict of interest

Dr Sadda is a co-inventor of Doheny intellectual property related to optical coherence tomography that has been licensed by Topcon Medical Systems, and is a member of the scientific advisory board for Heidelberg Engineering. The Doheny Image Reading Center also receives research support from Carl Zeiss Meditec and Optovue Inc.

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