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Spectral-Domain Optical Coherence Tomography Use in Macular Diseases: A Review

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Key Words
Optical coherence tomography · Macular disease · Medical retina

Abstract
The introduction of spectral-domain optical coherence tomography (SD-OCT) has improved the clinical value for assessment of the eyes with macular disease. This article reviews the advances of SD-OCT for the diagnostic of various macular diseases. These include vitreomacular traction syndrome, cystoid macular edema/diabetic macular edema, epiretinal membranes, full-thickness macular holes, lamellar holes, pseudoholes, microholes, and schisis from myopia. Besides offering new insights into the pathogenesis of macular abnormalities, SD-OCT is a valuable tool for monitoring macular disease.

Introduction

Ophthalmic imaging was revolutionized by optical coherence tomography (OCT). OCT derives from low-coherence interferometry. The first biomedical application of low-coherence interferometry was for the measurement of the length of the eye [1]. The next step was adding lateral scanning, and subsequently the introduction of OCT in 1991 [2–6] and its use in clinical practice since 1995 [3, 5, 7–23]. Various reviews have covered the technology and ophthalmic applications of OCT [24–31]. This article will review the progress in imaging macular disease by the introduction of high-resolution spectral-domain OCT (SD-OCT) [32, 33]. For the purpose of this review, we searched Medline (PubMed 1966 to September 2009) using the key words 'spectral domain optical coherence tomography' or 'Fourier domain optical coherence tomography'. This search resulted in 260 references, of which 103 were published in 2009.

Technique of SD-OCT

The OCT technique is an interferometric imaging technique that generates cross-sectional images by mapping the depth-wise reflections of low-coherence laser light from tissue. Spectral or Fourier domain OCT refers to Fourier transformation of the optical spectrum of the low-coherence interferometer. The optical spectrum output of an interferometer exhibits peaks and troughs, and the period of such a modulation is proportional to the optical path differences in the interferometer. Imaging of multilayer objects, such as the retina, results in various modulation periodicities representing the depth of each

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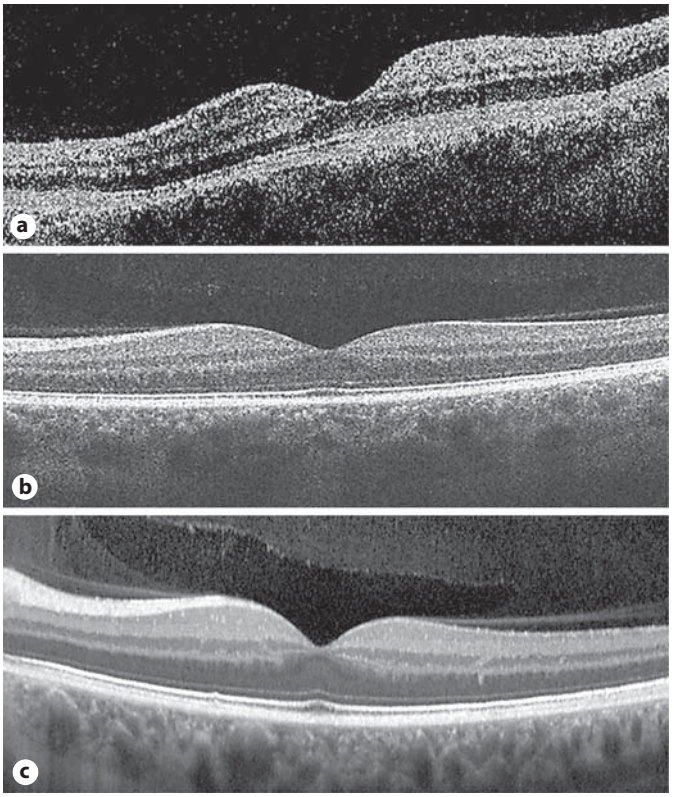

Fig. 1. OCT scan from the same healthy eye recorded with 1 TD-OCT [Stratus OCT (**a**)] and 2 SD-OCT instruments [Cirrus HD-OCT (**b**), Spectralis HRA + OCT (**c**)].

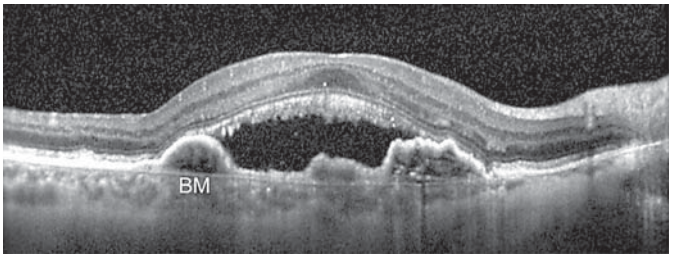

Fig. 2. SD-OCT scan of a patient with exudative age-related macular degeneration with pigment epithelium detachments. Note the thin hyperreflective band in the area of the RPE detachments representing Bruch's membrane (BM).

layer with amplitude of the spectrum modulation proportional to the reflectivity of the layer. From these signals, the A scan profile of the reflectivity in depth can be reconstructed. The most important advantage of the spectral domain technique over the conventional time domain OCT (TD-OCT) technique is the increase in scan speed. With the spectral domain technique imaging with 25,000–100,000 A scans/s is routinely possible. This is more than 100 times faster than with the time domain technique. Axial image resolution of OCT depends on the bandwidth of the low-coherence light source. Most OCT systems use superluminescent diodes with a bandwidth of about 20–50 nm allowing an axial resolution of 5–10 μm. The transversal resolution is limited by the optics of the eye and the number of A scans used to reconstruct a B scan [34], and the image depth is limited by the penetration of the laser light into the retinal tissue. Commercial OCT systems use light sources between 800 and 900 nm wavelength allowing good imaging of the retina, but limited visualization of the choroid. For imaging the choroid wavelengths above 1,000 nm have been used [34–37].

Currently, various SD-OCT instruments are commercially available: Cirrus™ HD-OCT, Carl Zeiss Meditec, Inc.; RTVue-100 Fourier-Domain OCT, Optovue Corporation; Copernicus OCT, Reichert/Optopol Technology, Inc.; Spectral OCT/SLO, Opko/OTI, Inc.; Spectralis™ HRA + OCT, Heidelberg Engineering, Inc.; Topcon 3D OCT-1000 (Color + OCT), Topcon; RS-3000 Retiscan, Nidek. All systems provide high-quality OCT line scans as well as special scan patterns for imaging the optic nerve fiber layer around the optic disk and for producing 3-dimensional OCT images. Segmentation of retinal layers allows reconstruction of thickness maps from these 3-dimensional OCT images [38–42]. Figure 1 shows the differences between a TD-OCT (Stratus™ OCT) and 2 SD-OCT instruments (Cirrus HD-OCT, Spectralis HRA + OCT) displaying scans from the same healthy eye. The OCT scan recorded with the Spectralis HRA + OCT has the best signal/noise ratio due to averaging 36 single OCT scans. This improves the signal/noise ratio by a factor of 6 as compared with a single OCT scan. Averaging of OCT scans requires compensation of eye movements during OCT recording by a real-time tracking system for eye movements. Currently, this feature is realized only in the Spectralis HRA + OCT.

SD-OCT versus TD-OCT in Normal Eyes

In healthy eyes, TD-OCT is able to image the retinal nerve fiber layer and the inner and outer plexiform layers. The outer retinal layers such as external limiting membrane, the junction of the inner and outer photoreceptor segments, and the retinal pigment epithelium (RPE) can

be visualized only in subjects without pathology and clear optical media.

SD-OCT imaging allows to distinguish the ganglion cell layer, the inner plexiform layer, the inner nuclear layer, the outer plexiform layer, the outer nuclear layer, the external limiting membrane, the photoreceptor inner segments (IS), the outer segments (OS), the RPE, and, in pathologic cases, Bruch's membrane (fig. 2).

Thickness Measurements

Before the introduction of SD-OCT, the only commercially available system was TD-OCT-3 Stratus (Carl Zeiss Meditec, Dublin, Calif., USA). For assessing retinal thickness, the Stratus OCT system uses only 6 radial lines with a total of 768 A scans to produce a thickness map with a diameter of 6 mm (27 A scans/mm^2). Since the density of measuring points is dependent on the distance from the center, only measurements inside the central 1,000-μm diameter area are based on a sufficient number of A scans (128 A scans). Nevertheless, measurements with this system have been the standard for many years and have been used in various clinical studies. The new SD-OCT instruments use a rectangular scan pattern resulting in a uniform density of A scans within the scan area. However, the number of A scans/mm^2 differs considerably between instruments and may be as high as 2,000 A scans/mm^2. After the introduction of new instruments, various studies have been published to compare retinal thickness measurements between instruments [42–51]. These studies have demonstrated that retinal thickness measurements are dependent on the segmentation of the inner and outer retinal borders. The segmentation of the inner retinal border shows no differences between instruments. All instruments identify the vitreoretinal interface as the inner retinal border. However, the segmentation of the outer retinal border differs considerably between instruments [42]. The Stratus OCT system images the outer retinal layers (RPE-photoreceptor complex) as two hyperreflective bands. The segmentation software of the Stratus OCT system uses the inner hyperreflective band for segmentation. The new SD-OCT systems image the outer retinal layers as 3 hyperreflective bands. The innermost of these hyperreflective bands has the lowest reflectivity. The bands may correspond to the external limiting membrane, the junction of the photoreceptor OS and IS and the RPE. Some SD-OCT systems use the second inner hyperreflective band as outer border of the retina; others identify the most outer reflective band as the outer border of the retina. These differences lead to differences in retinal thickness measurements of up to 70–80 μm. This implicates that the different OCT systems cannot be used interchangeably for the measurement of retinal thickness [42, 43, 52].

SD-OCT in Macular Diseases

SD-OCT has improved the visualization of intraretinal morphologic features allowing to evaluate the integrity of each retinal layer. Various macular diseases have been studied including age-related degeneration [16, 22, 53–57], diabetic retinopathy [30, 58–62], macular edema [63, 64], disease of the vitreomacular interface such as epiretinal membranes [20, 38, 65], full-thickness macular holes [13, 19, 66], pseudoholes, schisis from myopia or optic pits [59, 67–70], central serous chorioretinopathy [71], macular dystrophies [72], and juxtafoveolar retinal telangiectasis [73].

Age-Related Degeneration

In patients with age-related maculopathy, SD-OCT has demonstrated that the ultrastructure of drusen can be imaged in vivo [23, 53]. These ultrastructural characteristics may allow to distinguish subclasses of drusen and may allow to identify biomarkers for disease severity or risk of progression [57].

Studies in geographic atrophy have expanded our knowledge of the disease-specific retinal alterations as well as disease progression [16, 22, 74, 75]. SD-OCT provides adequate resolution for quantifying photoreceptor loss [76] and allows visualization of reactive changes in the RPE cells in the junctional zone of geographic atrophy [77]. In most eyes with geographic atrophy the inner retinal layers are unchanged, whereas the outer retinal layers show alterations in all eyes. Especially, the external limiting membrane seems to be disintegrated in the junctional zone and absent in areas of atrophy.

In exudative age-related macular degeneration, the main advantage of SD-OCT is the ability to image the macula in more detail as compared with TD-OCT. In single scans, the density of A scans is 3–14 times higher and the acquisition 45–100 times faster in SD-OCT than in TD-OCT. This results in an increased axial resolution, improved signal/noise ratio, and reduced eye movement artifacts with better delineation of contingent negative variation activity. Additionally, 3-dimensional scans allow visualization of the entire scanned area, resulting in a superior ability to detect intra- or subretinal fluid and

contingent negative variation activity over TD-OCT's radial line/fast macular thickness map scans [15, 23, 44, 55]. Since treatment decisions in exudative age-related macular degeneration usually rely on the presence of fluid accumulation in B scans, the higher number of B scans in 3-dimensional scans obtained with SD-OCT results in more sensitive detection of small pathologic findings (presence of intra- and/or subretinal fluid accumulation) leading to a higher detection rate of disease activity [55].

Diabetic Retinopathy

Numerous studies using TD-OCT have assessed the potentials of OCT for diagnosing macular edema in diabetic patients, comparing OCT imaging with gold standard tests such as stereoscopic fundus photography, fundus biomicroscopy, and fluorescein angiography. These studies demonstrated that OCT is a useful tool for diagnosing macular edema in diabetic patients, especially in eyes with borderline findings in the gold standard test [9, 29, 30]. Only a limited number of studies using SD-OCT for assessing diabetic macular edema have been published [45, 58–62, 78]. These studies have confirmed that macular thickness measurements in patients with diabetic macular edema differ significantly in magnitude between TD-OCT and SD-OCT systems [60]. OCT imaging in patients with diabetic macular edema has revealed several structural changes in the retina. These include epiretinal membranes, retinal swelling, cystoid macular edema, and subretinal fluid [79, 80]. SD-OCT has enabled us to analyze the integrity of the outer retinal layers in diabetic macular edema. These include the external limiting membrane, the photoreceptor IS, the OS, the RPE, and Bruch's membrane. First reports point towards the importance of the integrity of the external limiting membrane, the photoreceptor IS and the OS as a prognostic feature of visual improvement after treatment for diabetic macular edema [81].

Disease of the Vitreomacular Interface

Although conventional TD-OCT can visualize the vitreoretinal interface, the ability to image the posterior hyaloid membrane is very limited by the slow scan speed, limited sensitivity, and poor resolution. The increased axial resolution, signal/noise ratio and higher scan rate of SD-OCT have dramatically improved the visualization of the vitreomacular interface and posterior hyaloid membrane. Additionally, 3-dimensional scans enabled visualization and characterization of vitreomacular configurations [14, 20, 65]. These studies found that many eyes with vitreomacular traction have concurrent epiretinal membranes and eyes with idiopathic epiretinal membranes showed focal areas of attached vitreous. This suggests that there is a significant overlap between vitreomacular traction and idiopathic epiretinal membranes. The morphologic changes of the retina were dependent on the area of vitreous attachment. Eyes with more focal vitreomacular traction showed a foveal cavitation, whereas eyes with larger areas of vitreous attachment were more likely to have cystoid macular edema [14, 20]. Three-dimensional SD-OCT scans have improved the comprehensive evaluation of the vitreoretinal interface providing clinically significant additional information for clinicians. The 3-dimensional reconstruction enables meticulous surgical planning, with the potential for improved surgical outcomes.

Macular Holes

Anterior-posterior or tangential vitreomacular traction is involved in the formation of idiopathic macular holes. Eyes with a macular hole present intraretinal changes surrounding the hole, including cystic retinal edema and disruption of the photoreceptor layer. With SD-OCT alterations of the vitreomacular interface as well as of the photoreceptor layer have been described [13, 82–84]. Especially, the disruption in the junction between IS and OS of the photoreceptors has been described around macular holes [82, 83]. Imaging the IS/OS junction defect in macular holes with SD-OCT is a method of assessing structural integrity of the photoreceptors before and after macular hole surgery. Several studies have assessed the extent of the IS/OS junction defect as a prognostic feature of the visual outcome after macular hole surgery. However, the results of the studies are not conclusive [13, 19, 66, 84].

In various other macular diseases, SD-OCT has improved our understanding of intraretinal abnormalities. Alterations of the outer retinal layers imaged with SD-OCT have been demonstrated in various retinal diseases such as in vitelliform macular dystrophy [85], acute zonal occult outer retinopathy [86], occult macular dystrophy [87], in type 2 idiopathic perifoveal telangiectasia [88], and acute-stage Vogt-Koyanagi-Harada disease [89]. Inner retinal layer abnormalities have been described in early stages of chloroquine retinopathy [90], in X-linked retinoschisis [69], and in ocular albinism [91].

SD-OCT in Animal Models of Retinal Degeneration

The new SD-OCT technique allows to study changes of retinal integrity in a longitudinal way not only in human eyes but also in animal models of retinal degenera-

tion. So far, animal models of retinal degeneration have been studied at the structural level using imaging methods like fundoscopy and confocal scanning laser ophthalmoscopy and ex vivo histological approaches [92, 93]. Light and electron microscopy provide (ultra-)high structural resolution, but fixation procedures, dehydration preparatory to subsequent embedding and staining, as well as the process of cutting, flattening and mounting histological sections are potential sources for significant alterations of the vulnerable tissue [94, 95]. Ex vivo analysis of retinal tissue has certain limitations and should be interpreted carefully. In vivo analysis using SD-OCT has significant benefits for the detection of retinal changes like edema or focal neurosensory and/or pigment epithelial detachments, or RPE loss. In addition, SD-OCT provides the possibility to monitor dynamic changes in individual animals in a noninvasive longitudinal way [96]. Here, SD-OCT has the potential to complement the existing in vivo methods in vision research by providing histology-analog structural details on retinal structure and integrity. In addition, it could help to reduce the numbers of animals needed for such studies. This has ethical as well as economic implications.

Huber et al. [97] reported about the use of SD-OCT in mouse models of retinal degeneration. This group used *Rho15–/–, RPE65–/–,* BALB/c, C57/BL6/J, C3H *rd1/rd1*, and control C3H wild-type mice for imaging. Mice were anesthetized by subcutaneous injection of ketamine (66.7 mg/kg) and xylazine (11.7 mg/kg), and their pupils were dilated with tropicamide eyedrops before image acquisition. By applying hydroxypropyl methylcellulose on the eye, the refractive power of the air-cornea interface was effectively negated. A custom-made contact lens was used to reduce the risk of corneal dehydration and edema and acted as collimator. Mouse eyes were subjected to SD-OCT using the commercially available Spectralis HRA + OCT device. The laminar organization of the murine retina as determined in vivo by SD-OCT correlated well with ex vivo light microscopy studies. They presented evidence on the efficacy of a commercially available SD-OCT device in small animal retinal imaging and provide in vivo structural data on mouse models of retinal degeneration. This should facilitate further studies on dynamic changes of retinal structure through the natural course of the disease and help to monitor putative therapeutic effects of novel interventional strategies.

Conclusion

With the introduction of the spectral domain detection technique, the number of companies offering OCT instruments has expanded significantly. Today, more than 7 companies have introduced OCT instruments into the ophthalmic market. All of these instruments have a similar performance, with an imaging speed of 20,000–80,000 A scans/s and an axial resolution of 5–7 μm. Image quality of all SD-OCT instruments is sufficient to delineate as many as 10 retinal layers. Especially, the improved resolution of the outer retinal layers with SD-OCT as compared with TD-OCT imaging has a clinical significance. Various studies demonstrated that the integrity of the outer retinal layer is directly linked to visual prognosis [13, 19, 66, 81, 84]. The second important advantage of SD-OCT instruments is the possibility to obtain 3-dimensional scans allowing to image structural changes of the vitreoretinal interface and the retina in large areas. Since SD-OCT and image analysis is a fast evolving technique, further improvements of this technique are expected. New developments may include incorporation of adaptive optics into OCT instruments, polarization-sensitive OCT, Doppler flow OCT, and functional testing. Improvements in data analysis and image processing will generate new tools to analyze the structure and integrity of retinal morphology and function.

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