What Is New In Retinal Imaging?

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Abstract

Background: Ophthalmology is the most technology-driven specialty among all the medical specialties. Advances in retinal imaging have proven fundamental to many paradigm shifts in our understanding and treatment of ocular disease.

Methods: Literature review.

Discussion: This article provides an overview of current, state-of-the-art retinal imaging technologies, as well as highlights many emerging imaging technologies that we believe are likely to transform the provision of eye care.

Conclusions: The second decade of the 21st century is an exciting time to be an ophthalmologist, and especially a retinal specialist. However, studies of diagnostic accuracy are more prone to bias than many other forms of clinical research. With the likely imminent proliferation of ocular imaging techniques, standardized and robust methods for their clinical validation will be essential, with reporting of results according to standards for reporting of diagnostic accuracy recommendations.

Keywords: retina imaging; ocular imaging techniques; Optical coherence tomography.

Introduction

Ophthalmology is the most technology-driven specialty among all the medical specialties. Advances in retinal imaging have proven fundamental to many paradigm shifts in our understanding and treatment of ocular disease. This article provides an overview of current, state-of-the-art retinal imaging technologies, as well as highlights many emerging imaging technologies that we believe are likely to transform the provision of eye care in the 21st century.

Topographic Imaging of the Fundus

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Wide-field Imaging

Conventional fundus imaging, whether performed with a fundus camera or a Scanning Laser Ophthalmoscopy (SLO), typically generates images with a 30 to 50 degree external field of view, corresponding to approximately 5% to 15% of the retinal surface area. The Optos p200 system (Optos, Dunfermline, Scotland), through the use of a large ellipsoid mirror with 2 focal lengths (allowing wide scanning angles) and a SLO, provides image capture with a 200 degrees internal field of view (approximately equivalent to 135 to 150 degrees external field of view).1

Limitations include artifacts due to eyelashes and eyelids, which obscures superior and inferior field. As only two colors are used, red and green laser, the color of the retina appears strange. As the 3D structure of the retina is not captured, this can lead to misinterpretations.

Conventional imaging allows optimal visualization of the posterior pole; however, a large area of the peripheral retina is not captured, even with 7-field fundus photography. Optos produces color images of the retina using a green laser light (red-free light) (532 nm) and red laser light (633 nm).

Wide-field imaging in diabetic retinopathy has shown its utility in diagnosing more new vessels compared to conventional 2-field and 7-field imaging (Figure 1).2

Wide-field could be useful in diabetic retinopathy screening as it uses a non-mydriatic camera. Wide-field angiography facilitates treatment of proliferative diabetic retinopathy with targeted laser photocoagulation. Ultra Wide-field Angiography (UWFA) has been shown to demonstrate abnormality in a variety of retinal conditions, including diabetic retinopathy, retinal vein occlusion, sickle cell retinopathy, uveitis, and pediatric retinal disease.3, 4

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the retina is being shown as 2D image, there is some distortion or difference in measurements in central and periphery. This is being dealt by newer software algorithm.

**Adaptative Optics**

In the past two decades, optical coherence tomography (OCT) has become an essential tool in ophthalmology. Its ability to image detailed ocular structures noninvasively in vivo with high resolution has revolutionized patient care by revealing a lot about the structural unknown. Axial resolution of available OCT devices has improved up to 5-7 microns; however, the lateral resolution still remains up to 20 microns. Poor lateral resolution does not allow the visualization of photoreceptors layers.

Ability to obtain high lateral resolution images of the human retina by OCT is limited by the presence of defects, or aberrations, in the optical system of the eye (i.e., the cornea and lens). In addition to exhibiting lower-order monochromatic aberrations such as defocus and astigmatism, normal eyes also exhibit higher-order monochromatic aberrations such as coma, trefoil, and spherical aberration. The combined effects of these aberrations limit the quality of images obtainable for the diagnosis and management of retinal disease. In short, the transverse (lateral) optical resolution of fundus cameras and SLO devices is limited by the presence of astigmatism and higher-order aberrations in the optical system of the eye.

Wavefront sensors based on the Hartmann–Shack principle, originally developed for astronomical purposes, have now been adapted for use in the human eye. The adaptive optics devices first developed for ophthalmic use were conventional fundus cameras modified to incorporate wavefront sensing and correction. These systems typically focus a laser beam on the retina at a location of interest. The light reflected from the retina is then distorted by the optical system of the eye before returning to the wavefront sensor. Information obtained from the wavefront sensor is then used to alter the shape of the deformable mirrors and compensate for the aberration. This process continues in a closed loop until the ocular aberrations have been reduced to near diffraction-limited levels; at this point, a flash from a separate incoherent light source is triggered by the wavefront sensor, illuminating the retina as an image is captured by the digital fundus camera. Adaptive optics components have also been incorporated into confocal SLO systems, offering the advantage of increased contrast, cross-sectional imaging, and the measurement of dynamic changes such as blood flow.

A successful combination of OCT and adaptive optics could potentially demonstrate; therefore, the narrowest point-spread function of all in vivo retinal-imaging techniques. However, a number of technical challenges remain, in particular, the reductions in image quality that occur as a result of chromatic aberrations when large-bandwidth light sources are used.

Clinical application of adaptive optics has been explored recently. Using adaptive optics, Song et al show increased cone and rod spacing in areas in eyes with Stargardt’s disease that appear normal in conventional images, suggesting that photoreceptor loss precedes clinically detectable retinal pigment epithelial disease. Jacob et al reported decreased cone density in eyes before damage of outer retina structures, which may be the first sign of disease and can be used as biomarker for monitoring. Limited field of imaging, long image acquisition time, unavailability of validated automated algorithms make this system a research tool.
rather than a clinical tool at the present. However, ongoing research in exploring its clinical application in vision restoration will make this imaging modality essential (Figure 2).

**Multicolor Imaging**

Each laser with particular wavelength provides information about particular layer of the retina. The shorter wavelength blue laser provides details of superficial retinal structures such as epiretinal membranes, retinal folds, the retinal nerve fiber layer and macular pigments. The medium wavelength green is highly absorbed by hemoglobin and provides details of vascular abnormalities of blood vessels such as microaneurysms and exudates. The longer wavelength infrared laser penetrates the deepest providing images of the retinal pigment epithelium (RPE) and the choroid and is particularly useful for imaging deeper lesions such as choroidal rupture, drusen and choroidal nevi. However, obtaining three kinds of images in a single subject could be a very difficult task especially for the elderly or uncooperative subjects. Multicolor imaging can be obtained by using multiple laser wavelengths including blue, green and infrared simultaneously to selectively capture and provide information of different retinal structures from a single image during a single examination. Multicolor imaging helps in easier and earlier detection of various pathologies such as age-related macular degeneration (AMD) and diabetic retinopathy when compared to a conventional color photograph (Figure 3).

**Spectral Imaging: Measurement of Retinal Oxygenation**

Spectroscopy is the study of the interaction between any form of matter and radiated energy. In biological systems, the combination of spectroscopy with conventional imaging techniques – “spectral imaging” – allows determination of the spatial distribution of spectroscopic data. In clinical settings, the application of spectroscopic principles has been of particular use for oximetry, the measurement of oxygen saturation in a patient’s blood.

Spectral imaging devices typically employ one of three different approaches: (1) multispectral imaging; (2) hyperspectral imaging; and (3) imaging spectroscopy. This technique is dependent on assumptions about the relationship between light transmittance through the blood and its oxygen (according to the Lambert-Beer law). In retinal oximetry, direct measurement of light transmittance through the retina is not possible, and therefore, measurements of light reflected from the retina at different wavelengths typically are substituted.

Knowledge about the oxygen saturation is important in retinal vascular occlusions and diabetic retinopathy. Its application has been shown in eyes with glaucoma, as well in dystrophies. Increased oxygen saturation of the retinal venules in advanced-treated primary open-angle glaucoma eyes may indicate reduced metabolic consumption of oxygen in the inner retinal tissues. Despite significant progress made in recent years, there is currently no consensus on the optimal method for measurement of oxygen saturation in the retinal vasculature. Most spectral imaging devices provide relative, rather than absolute, measurements of oxygen saturation. In addition, all devices depend to a certain extent, on biophotonic assumptions that may not hold true for in vivo imaging. Hence, validation and reproducibility are still being worked upon. Future prospects for oximetry include integration with a scanning laser ophthalmoscope and its applicability in predicting systemic disease from retinal oxygen saturation values.

**Intraoperative Optical Coherence Tomography**

Various intraoperative OCT systems are now available, including microscope-mounted portable iOCT system (Bioptigen Envisu SDOIS; Bioptigen, Research Triangle Park, NC, USA), Rescan 700 OCT® (Zeiss), Haag-Streit’s intraoperative OCT system. Use of hand held OCT by Bioptigen® as intraoperative OCT is cumbersome; however, integrated intraoperative OCT by Zeiss provides a scan through the microscope as well as heads up display. Its intraoperative applications include membrane peeling, assessment of retinal layers, vitreomacular interface changes. This technology has expanded the image-guided patient management. Limitation of this technology includes adoption and widespread utilization and cost. Further improvement is required for optimized feedback platforms, and more definitive value for individualized surgical care with image guidance.
Hand Held OCT

Spectral-domain OCT systems (Bioptigen Envisu SDOIS; Bioptigen, Research Triangle Park, NC, USA) with handheld imaging probes connected to a table-top console by a 1.3-m-long cable is a device which has now been used widely in settings such as neonatal intensive care units, pediatric eye clinics, animal research laboratories, and intraoperative imaging examinations. It has been proven particularly useful in neonatal populations for the study of ocular development and for diseases such as retinopathy of prematurity.

Wide Field OCT

Wide field OCT up to 12mm scan is now available with the Avanti RTVue-XR® (Optovue, Inc., CA, USA). Montaged images of four radial optical coherence tomography scans through the fovea with scan length up to 36mm has been reported. Wide field OCT provides detailed information of the lesions, which are present away from the arcade. These are very useful imaging modalities for conditions like choroidal tumors, peripheral lesions such as retinoschisis.

Optical Coherence Angiography

An important focus of current OCT research is the generation of 3-dimensional maps of the retinal and choroidal vasculature, known as optical coherence tomography angiography (OCTA). A number of techniques for OCA currently are under development. In essence, these all involve high speed, sequential acquisition of OCT A-scans or B-scans at the same retinal locus and then assessment of differences in the scans that occur as a result of blood flow. Primarily OCTA works on three principles: phase based, amplitude based, and combination of both.

After acquisition of OCA image sets, it is possible to generate 3-dimensional renderings of the vasculature or 2-dimensional fundus images with color coding of the vessel depth. The available devices provide prefixed en-face sections at the level of superficial retina, inner retina, and outer retina. The swept source OCT devices also provide en-face sections at different choroidal vascular layers. In the recent past, the literature is flooded with OCTA findings in various diseases. OCTA does provide a better delineation of foveal avascular zone in diabetic retinopathy; ischemic areas in venous occlusion; choroidal neovascular complex.10,21 Recently, the quantitative assessment of ischemic areas in diabetic retinopathy as well as measurements of CNV complex is also reported.22

Several limitations of OCTA include no functional or leakage information, artifacts, limited field of view and inaccurate segmentation. OCTA is based on the blood flow, so OCTA is not able to image vessels that have no flow or that have flow that is slower than the detection threshold of the OCTA.

Photoacoustic Ophthalmoscopy

No ophthalmic imaging modality exists that can directly measure the absorption of light by retinal tissues. Assessment of optical absorption profiles at multiple wavelengths may improve the accuracy of retinal vascular oxygen saturation measurements. Through recent advances in microscopy, utilizing the photoacoustic effect, it has become possible to acquire optical absorption profiles in the context of noninvasive ophthalmic imaging – photoacoustic ophthalmoscopy (PAOM).23,24

A photoacoustic microscopy in which a laser is used to irradiate a target tissue and induces ultrasonic pressure waves as a result of specific optical absorption. These pressure waves then can be recorded using a high-resolution ultrasonic transducer, and images can be generated. Through the integration of OCT technology with a laser scanning, optical-resolution PAM, Jiao et al. have recently reported the use of PAOM in small animals.24 Photoacoustic ophthalmoscopy offers the first possibility for direct measurement of light absorption by retinal tissues. The development of photoacoustic imaging techniques may greatly extend the scope of future retinal imaging; however, at present, the technology remains at an early stage in the development process.
MOLECULAR IMAGING

Contrast Agents

In recent years, the use of more novel nanoparticles increasingly has been explored. Due to the phenomenon of localized surface plasmon resonance, gold nanoparticles are capable of scattering or absorbing large amounts of light when illuminated. As a result, gold nanoparticles are particularly well suited for use as contrast agents in optical imaging.25

There are a number of reasons, gold nanoparticles have potential for use as contrast agents with OCT:

1. Gold nanoparticles have the property of localized surface plasmon resonance;
2. Gold nanoparticles can be fabricated so that their light-scattering properties attain a peak at the near-infrared wavelengths typically used by OCT systems;
3. Gold nanoparticles can be conjugated readily with targeting ligands. They are water soluble and potentially biocompatible.

More recently, the creation of a new form of nanoparticle, “gold nanoshells” – has reigned interest in gold nanoparticles as contrast agents for clinical imaging.26 Gold nanoshells can be designed and synthesized to demonstrate light-scattering peaks in the near-infrared region commonly utilized by ophthalmic imaging systems such as OCT. In addition to spherical gold nanoparticles and gold nanoshells, gold nanorods and gold nanocages have also been investigated as contrast agents for optical imaging in preclinical settings.

The unique and tunable optical properties of many nanoparticles, along with their size and capacity for cellular targeting, make them strong candidates for use as contrast agents in retinal imaging. Using these agents in combination with techniques such as OCT may ultimately allow visualization of many retinal structures (e.g., Müller cells) and cellular processes (e.g., apoptosis) in clinical practice.

Targeting Ligands

Targeting ligands commonly are based on macromolecules such as peptides, antibodies, or proteins and are aimed at molecular imaging of:

1. Retinal ganglion cells (RGCs);
2. The RPE;
3. Endothelial cells;
4. Leukocytes.

The most advanced of these areas is the molecular imaging of RGCs. Fluorescently labeled Annexin V is administered via intraocular or intravenous injection and binds specifically to phosphatidylserine on apoptosing RGCs (during apoptosis, this molecule is translocated from the inner to the outer plasma membrane, rendering it accessible to extracellular targeting ligands). Considerable safety and toxicology testing already has been performed; however, early phase clinical trials are expected to commence in the near future.

References