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Adaptive optics ophthalmoscopy: Application to age-related macular degeneration and vascular diseases

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A B S T R A C T

Adaptive optics (AO)-enhanced *en face* retinal imaging, termed here AO ophthalmoscopy (AOO) has reached a level of robustness which fuels its increasing use in research and clinical centers. Here we will review the contribution of clinical AOO to the understanding and monitoring of 1) age-related macular degeneration and 2) vascular diseases. The main contributions of AOO to the phenotyping of AMD are a better identification of drusen, a better delineation of the limits of atrophy, and the identification of novel features such as punctate hyperreflectivity and mobile melanin-containing clumps. Characterization of progression of atrophy is facilitated by time-lapse imaging. In vessels, AOO enables the observation and measurement of parietal structures and the observation of microscopic pathological features such as small hemorrhages and inflammatory cell accumulations.

1. Introduction

The first observation of the fundus of the eye in the nineteenth century led to the foundation of modern ophthalmology. Until recently, however, the retina itself could not be directly observed because it is translucent and hence faintly visible by fundus photography. It was the advent of techniques allowing a higher contrast such as optical coherence tomography (OCT) in the 1990s and then adaptive optics (AO)-enhanced ophthalmoscopy (AOO) in the 2000s that made neuroretinal structures directly observable in vivo. The first demonstration of the clinical interest of AOO was reported in 1997 in Liang, Miller and William's seminal work using an AO fundus camera (Liang et al., 1997) which allowed observation of cone photoreceptors. Since then, by achieving diffraction-limited resolution in clinically usable, robust systems, visualization of previously unseen structures such as individual photoreceptors and vessel walls can now be done in a routine fashion. Thanks to the convergence of technical maturity and better understanding of the contribution of AOO imaging, its use in research and clinical centers is expanding worldwide, in ophthalmology and beyond. AOO can contribute new and complementary information to other ophthalmic imaging techniques, and should form part of a comprehensive eye exam including in particular SDOCT (Kanagasingam et al., 2014) whose cross-sectional orientation makes it well-adapted to correlate with histology. Several reviews of AOO have been done previously (Roorda, 2010; Godara et al., 2010; Roorda and Duncan, 2015; Marcos et al., 2017). In the present review, we will focus on the contribution of AOO to the understanding of age-related macular degeneration (AMD) and vascular diseases, and suggest some perspectives for improvement in these areas. We will limit this review to en face fundus camera and scanning AOO systems, excluding adaptive optics optical coherence tomography (AO-OCT) which has not yet been applied to the same extent to AMD and vasculature in patients. Readers interested in AO-OCT may refer to several reviews (Jonnal et al., 2016; Pircher and Zawadzki, 2017).

2. AO ophthalmoscopy (AOO) technologies

High resolution imaging of the retina faces several challenges, including optical aberrations arising from the anterior segment and the limited reflectance of the retina. These challenges are tackled by AO which counteracts optical aberrations in real-time with a deformable mirror, whose shape is derived from wavefront measurements via a real-time control loop, in order to increase light throughput and resolution. AOO has been performed with flood illumination fundus

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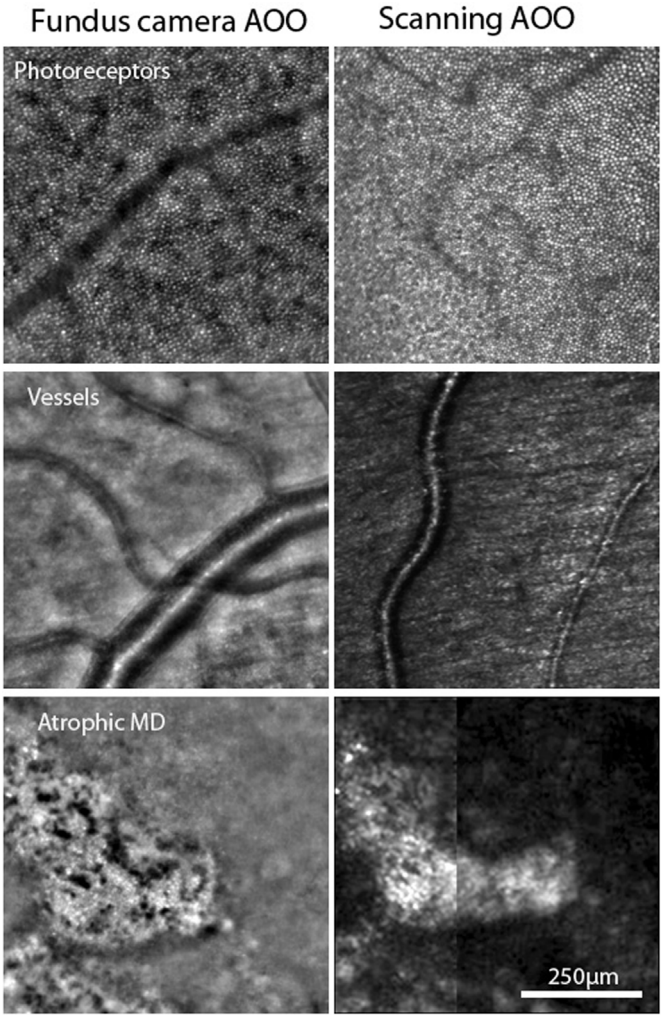

Fig. 1. Comparison of fundus camera (left column) vs bright field scan (right column) AOO, showing normal photoreceptors (top row), an artery (center row), and an atrophy zone during dry age-related macular degeneration (bottom row).

cameras, scanning laser ophthalmoscopes (SLO) and OCT (Jonnal et al., 2016; Pircher and Zawadzki, 2017). Fundus camera systems use flood illumination to capture a two dimensional en face image in a single shot using a two dimensional camera as detector. SLO systems scan point by point (or line by line) in a raster fashion over the retina and collect the backscattered light with a single-pixel detector. Fundus camera and scanning AOO systems yield different results (Fig. 1). Fundus camera images show inherently less motion-induced distortion than scanning systems, which is of interest in the case of poor fixation, at the cost of reduced contrast. The main advantage of SLO systems is the use confocal detection to reject light from out of focus layers and so achieve high axial resolution and contrast. SLO systems have also benefitted from alternative detection schemes (known as split detection, offset aperture or dark field) that capture multiply scattered photons that do not pass through the confocal pinhole. Eliminating the strongest signal, which tends to emanate from directionally dependent waveguided light from photoreceptor outer segments and the highly scattering nerve fibers and vessels, enables detection of more weakly reflective structures, for example photoreceptor inner segments (Scoles et al., 2014), retinal pigment epithelium (RPE) (Scoles et al., 2013; Rossi et al., 2013) and retinal ganglion cells (Rossi et al., 2017).

In the text that follows, for scanning AOO images we will call the directly backscattered light that passes through the confocal pinhole the “bright field” mode, and the multiply scattered light which is offset from the confocal pinhole the “dark field” mode. The ability to separate the different sources of contrast in these different modalities can provide clues as to the origin of the features we observe and hence their clinical signification.

3. Dry age-related macular degeneration

AMD is a leading cause of blindness in developed countries (Robman et al., 2015; Klein et al., 2011). Despite the identification of several genetic, molecular and environmental factors (Ardeljan and Chan, 2013; Ambati and Fowler, 2012), the pathophysiology of AMD remains debated and in its dry form there is currently no available treatment. Histopathological changes of dry AMD affect the outer retina, the RPE and the inner choroid (Sarks, 1976; Sarks et al., 1988; Bird et al., 2014). The dominant paradigm states that AMD results from cumulative damage affecting the interaction between the photoreceptors and the RPE cells related to genetically determined low grade subretinal inflammation (Guillonneau et al., 2017). Over decades, chronic, silent damage of the RPE/photoreceptor unit cumulates, which challenges the resilience of the outer retina; the sight-threatening complications of AMD can be considered as the clinical manifestation of an exhaustion of chronically activated compensatory mechanisms and hence an ultimate reduction of retinal resilience. Clinically, an early/intermediate phase moderately affecting vision is followed by a late stage at which sight-threatening complications are observed. Funduscopically, the canonical lesions of early/intermediate AMD are drusen and/or pseudodrusen, basal linear deposits (which are soft druse material, diffusely distributed in the space between the RPE-basal lamina and the sub-RPE space) and pigmentary changes. Loss of a continuous RPE layer signals the transition from early to late dry AMD. The disruption of the RPE monolayer (geographic atrophy) is indeed the key event leading to blindness, because it is temporally and spatially linked to loss of photoreceptors and to the advent of an absolute scotoma (Panorgias et al., 2013). Here, we will describe the most notable contributions of AOO to the phenotyping of AMD, and compare the knowledge about histology and pathophysiology of dry AMD to AOO. Most of the histology data presented here is from the Project MACULA developed by Christine Curcio and the University of Alabama of Birmingham (www.projectmacula.cis.uab.edu) (Curcio et al., 2017).

3.1. Early stage AMD

Drusen are composed of focal deposits of extracellular debris in contact with the RPE (Khan et al., 2016). Drusen are hallmarks of AMD. Each druse subtype bears a specific risk of evolution to late stages of AMD. Three main drusen phenotypes have been characterized: either under the RPE (soft drusen, hard drusen, and cuticular drusen) or over the RPE (subretinal drusenoid deposits (SDD, also called reticular pseudodrusen). Spaide, Curcio and co-authors have hypothesized that their different imaging and histologic characteristics are due to differences in location and biogenesis (Spaide and Curcio, 2010; Curcio et al., 2013; Spaide et al., 2010; Zweifel et al., 2010).

Fig. 2 illustrates the fundus camera AOO appearance of the different types of drusen by comparison with non-AO corrected near infrared (nIR) SLO images. Conventional drusen appear on AOO as subtle variations in the grayscale tones, with a variably hyperreflective center. Drusen are usually surrounded by a continuous or discontinuous hyporeflectivity and sometimes an incomplete dark ring. Some conventional drusen appeared more reflective than others, with a better contrast from the background areas (Mrejen et al., 2014; Querques et al., 2014). Cone photoreceptors are detected overlying conventional drusen and the cone density has been found to be moderately reduced over conventional drusen. The differences in reflectivity of conventional drusen may be due to differences in sub-RPE material reflectivity as these variations can be seen on SD-OCT as well, and also to variable degrees of depigmentation and thinning of the overlying RPE. These