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Review article

Photoacoustic imaging of the eye: A mini review

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ABSTRACT

The eye relies on the synergistic cooperation of many different ocular components, including the cornea, crystalline lens, photoreceptors, and retinal neurons, to precisely sense visual information. Complications with a single ocular component can degrade vision and sometimes cause blindness. Immediate treatment and long-term monitoring are paramount to alleviate symptoms, restore vision, and cure ocular diseases. However, successful treatment requires understanding ocular pathological mechanisms, precisely detecting and monitoring the diseases. The investigation and diagnosis of ocular diseases require advanced medical tools. In this mini review, we discuss non-invasive photoacoustic (PA) imaging as a potential research tool and medical screening device. In the research setting, PA imaging can provide valuable information on the disease progression. In the clinical setting, PA imaging can potentially aid in disease detection and treatment monitoring.
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Contents

1. Introduction and background

The eye is divided into the anterior and posterior segments (Fig. 1a) [1]. Prominent anterior segment structures include the cornea, iris, pupil, crystalline lens, and ciliary body. Prominent posterior segment structures include the vitreous body, retina,

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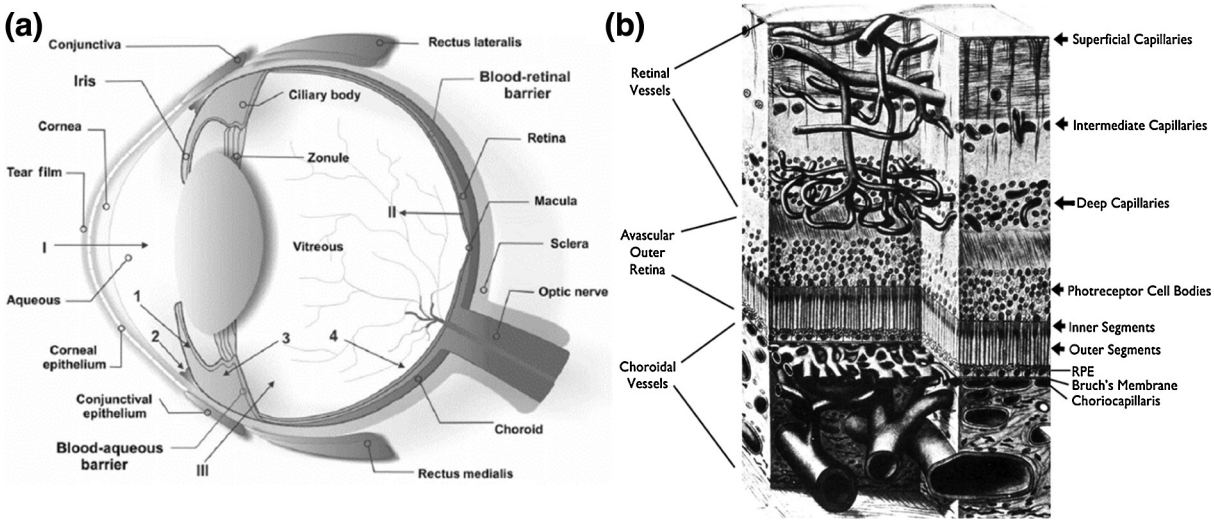

Fig. 1. (a) Schematic of normal ocular anatomy, I is anterior chamber, II is retinal pigment epithelium, III is vitreous. (b) Illustration of the retinal and choroidal vascular systems that nourish the retina in the posterior segment. RPE: retinal pigment epithelium.
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choroid, and optic nerve. All of these structures work together in a coordinated manner to provide visual information to the brain. However, before visual information is sent to the brain, it undergoes processing by structures in both the anterior and posterior segments. First, the cornea and lens form images on the retina [2], while the iris simultaneously adjusts pupil size to control the amount of light that reaches the retina. Second, retinal photoreceptors convert light into electrical signals [1], while pigment in the retinal pigment epithelium (RPE, mainly containing melanin) absorbs unnecessary light [3]. Third, retinal neurons modulate electrical signals and send them to brain for further processing.

Retinal and RPE processing of visual information consumes large amount of energy and oxygen [4]. Two delicate vascular circulation systems, the retinal and choroidal circulations, collectively support the retina (Fig. 1b) [5]. In a healthy eye, the retinal circulation mainly delivers oxygen and nutrients to the inner retinal tissues and the choroidal circulation mainly nourishes photoreceptors [6].

Eye diseases compromise, and even disable, normal functions of ocular components, which can threaten vision. Studies have demonstrated that variations in retinal blood oxygen saturation (sO_2) and RPE melanin concentration play an important role in several prevalent blinding ocular diseases. The sO_2 has been shown to be abnormal in diabetic retinopathy (DR) [7–9], glaucoma [10,11], and retinal venous occlusion [12,13]. Additionally, RPE melanin loss and lipofuscin accumulation have been shown to contribute to the progression of age-related macular degeneration (AMD) [14–16]. The ability to precisely detect aberrant retinal sO_2 values and RPE melanin concentrations can be important for improving investigations and diagnoses of ocular diseases.

In the past decades, large efforts have been made to quantitatively measure sO_2 and melanin concentration in the eye. Multi-wavelength fundus photography has been tested for a long time to measure retinal sO_2 [17–19] and has the advantage of being a non-contact technique. However, multi-wavelength fundus photographs often provide inaccurate measurements because of light scattering within retinal tissues and the RPE pigmentations [20]. Invasive methods, including fluorescence lifetime imaging and oxygen-sensitive microelectrode measurements, have been used to measure the partial pressure of oxygen in retinal tissue [21,22], but these methods are only suitable for laboratorial animal studies. Visible-light optical coherence tomography (vis-OCT) was recently used to successfully quantify retinal and choroidal sO_2 in rodents [23–25]. This non-contact technique has the benefits of accurately measuring sO_2 [26] and providing images with high depth resolution [23]. Therefore, vis-OCT has the potential to provide retinal and choroidal sO_2 measurements in the clinical setting. However, measurements made with vis-OCT have not yet been verified at many other different anatomical sites. This must be done before vis-OCT is tested in the clinical setting.

Measurements of RPE melanin have mostly been obtained during *in vitro* experiments. The most direct method to calculate melanin concentration involves manually counting melanin granules on high-magnification micrographs [27]. A less direct *in vitro* method involves measuring optical absorption of solubilized free melanin granules [28,29]. However, the invasive nature of these *in vitro* techniques prevents them from being used in clinical settings. Instead, spectroscopic fundus photography and near-infrared autofluorescence (NIR-AF) imaging are used to measure RPE melanin concentration *in vivo* [30–32]. Spectroscopic fundus photography uses mathematical optical models to estimate melanin optical density. However, over-simplified optical models used in spectral fundus photography calculations result in inaccurate melanin concentration measurements. The NIR-AF technique measures melanin concentration using the coincidence between the strong AF and NIR-excited melanin emission signals [32]. Unfortunately, a rigorous model that describes the relationship between AF and melanin has not yet been developed. Therefore, better non-invasive methods to measure retinal/choroidal blood sO_2 and RPE melanin concentration are still needed.

Blood and melanin both have high optical absorption coefficients within the visible light spectral range (Fig. 2) and optical absorption can be used to measure their concentrations [33]. Photoacoustic (PA) imaging has been shown to precisely and non-invasively measure optical absorption properties [34–40], and have already been used to measure both blood sO_2 and melanin concentration in the ear [41–44], brain [45,46], esophagus [47,48], colon [47,48], and epidermis (melanin only) [49,50]. Therefore, PA

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