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EDITORIAL

Optical coherence tomography angiography: a non-invasive tool to image end-arterial system

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Optical coherence tomography angiography (OCTA) is a relatively novel technology for *in vivo* imaging of vascular network. It uses moving erythrocytes as contrasting mechanism and avoids the use of intravenous dyes. A depth-resolved 3-dimensional image set can be generated within seconds using the technique of OCTA. Therefore, it possesses a great potential for widespread application in ophthalmic angiography. Herein we discuss the most common technologies behind OCTA and the scope of future technical improvement. We provide a perspective on advantages and disadvantages of OCTA over conventional fluorescein angiography and indocyanine green angiography. Lastly, current literature on the clinical application of OCTA in common ocular diseases including neovascular age-related macular degeneration, diabetic retinopathy, retinal artery and vein occlusion, and glaucoma are reviewed.

OCT has been a routinely used imaging modality in ophthalmology for the past 2 decades. Its ability to generate high-resolution (1-10 μm), depth-resolved, cross-sectional images noninvasively has made OCT an ideal tool to decipher structural information of the eye.

Recently, development of OCT angiography (OCTA) has added a new dimension of functional vascular network imaging to the existing capabilities of

OCT allowing it to image end-arterial system without the need of a dye injection.

Current gold standard investigations for ophthalmic angiography include fluorescein angiography (FA) and indocyanine green angiography (ICGA). Both investigations require injection of intravenous dye, which is time-consuming and carries the risk of allergic reaction. Fluorescein dye injection is a relative contraindication in certain systemic conditions such as pregnancy and renal impairment. Since fluorescein dye cannot diffuse through intact blood-retinal-barrier, it serves as an excellent tool for imaging retinal lesions. On the other hand, ICGA enables imaging of the deeper choroidal circulation below the retinal pigment epithelium. However, both FA and ICGA generate 2-dimensional images of the retinal or choroidal circulation. This poses difficulty in localizing the depth and extent of lesions, especially in the presence of dye leakage or retinal hemorrhages.

Swept source OCT (SS-OCT) uses a tunable swept laser, which enables the measurement of interference at different optical frequencies or wavelengths sequentially over time.[1] No spectrometer or line camera is needed for the Fourier transformation. This increases the imaging speed up to 300,000 axial scans per second and allows a deeper penetration of the sampling beam. It provides an axial resolution of 8 microns with transverse resolution of 20 microns. SS-OCT offers several potential advantages over SD-OCT, including increased sensitivity through the full imaging depth, deeper penetration, decreased fringe washout, better axial resolution over a broad imaging range, and higher detection efficiencies. Being a longer length, it has potential to image choroid much better than conventional SD-OCT[1].

OCTA is non-contact as well as non-invasive, and avoids dye-related complications such as anaphylaxis. Image acquisition is fast with one scan set of volumetric information obtained within seconds. OCTA generates a 3-dimensional image set so that vascular plexuses at different depths can be visualized from internal limiting membrane up to choroid.

OCT angiogram is reconstructed from a series of OCT b-scans taken in a very short time frame. A substantial number of OCTA methods have been proposed so far. In brief, these methods capitalize on the changes in phase and/or amplitude between OCT signals backscattered from moving erythrocytes and that from static tissue background in consecutively collected OCT b-scans. The most commonly used methods in ophthalmic OCTA can be broadly classified into 3 categories, i.e. complex OCT signal based, e.g. optical microangiography (OMAG) [2]; OCT signal amplitude based, e.g. amplitude decorrelation [3] and speckle variance; and OCT signal phase based, e.g. phase variance. Of note, two commercially available OCTA systems have now been approved by the Food and Drug Administration of the United States (US-FDA). The AngioVue system (Optovue, Inc, Fremont, CA) uses the split-spectrum amplitude-decorrelation angiography (SSADA) algorithm, while the AngioPlex system (Carl Zeiss Meditec Inc, Dublin, CA) employs the OMAG algorithm. Direct comparisons among OCTA methods is currently very limited and there is no consensus on whether any one is more superior [4]. However, since the OMAG algorithm has a unique ability of

mathematically mapping the backscattered optical signals from moving particles into one image, and static signals onto a second image simultaneously, this technique may provide better results since it uses the signal to the fullest extent. In addition, we also expect the development of new algorithms that combine merits of various methods to achieve better image quality [4]. Evolution of OCT devices is also making an impact on the OCTA improvement. As reported by Novais et al, Swept-source OCT appeared to demarcate lesion better compared to spectral domain OCT in evaluating choroidal neovascularization (CNV) [5].

Currently, literature on clinical applications of OCTA in determining endpoints in therapeutic clinical trials is lacking. Research is underway for the quantitative analysis of the information obtained by OCTA. This may be useful in providing more information on the effect of therapy on the disease process. Large prospective studies comparing OCTA with FA/ICGA in various disease entities are also required. There are ever increasing number of publications of OCTA in ophthalmic imaging in the last 2 years. In the index editorial, we will focus on the use of OCTA in common ocular diseases which may have large impact on the future of this technology.

Neovascular age-related macular degeneration (AMD): Jia et al first reported OCTA was able to detect and quantify choroidal neovascularization (CNV) in 5 eyes with AMD [6]. De Carlo et al showed a sensitivity of 50% (4 of 8) and specificity of 91% (20 of 22) when they compared OCTA and FA's ability to detect CNV. This relatively low sensitivity was attributed to small sample size and presence of large retina hemorrhage [7]. Researchers also demonstrated the usefulness of OCTA in evaluating changes of CNV in response to

treatment [8,9]. However, both studies were of small sample size and did not evaluate whether features on OCTA could predict response to treatment.

Diabetic retinopathy (DR): In a prospective pilot study, Ishibazawa et al demonstrated OCTA clearly depicted retina microvascular status in DR [10]. Changes in foveal avascular zone (FAZ) were described with OCTA in 113 eyes from 65 patients by Di et al [11]. An automated algorithm for quantification of capillary nonperfusion using OCTA was shown to detect DR reliably compared to FA [12]. Most recently Bradley et al reported moderate agreement between OCTA and FA's grading of diabetic macular ischemia [13].

Retina artery occlusion (RAO) and retina vein occlusion (RVO): OCTA features of RAO and RVO have been described in observational studies [14,15]. Of note, Nobre Cardoso et al used a standardized grading protocol to systemically compare OCTA to FA, and showed good agreement between the two in discerning vascular features in RVO [15].

Glaucoma: Angiography is not routinely performed in glaucoma. Jia et al proposed a novel measurement of optic disc perfusion using OCTA, which detected reduced perfusion in early glaucoma patients with 100% sensitivity and specificity [16]. The same group also demonstrated reduced peripapillary retina perfusion in glaucomatous eyes [17]. Using OCTA, Wang et al showed reduction in disc flow index correlated with glaucoma severity [18].

OCTA features have also been described for central serous chorioretinopathy (CSC), dry AMD and other less common chorioretinal diseases showing abnormalities in superficial retinal, deep retinal and choroidal vasculature.

Among patients with CSC, it may be possible to have a higher detection rate of CNV compared to conventional dye-based FA [19]. Recognition of CNV in central serous retinopathy on FA is often challenging and likely to be missed, resulting in permanent photoreceptor and retinal pigment epithelial damage. Thus, OCTA may be useful in changing management practices and preserving vision in such patients. In addition to posterior segment imaging, OCTA has been adapted for anterior segment imaging and showed consistent and comparable results to ICGA [20].

There are certain limitations of the existing OCTA system. As OCTA is essentially a snapshot of the vascular network at one point of time, dynamic information such as leakage is absent. Therefore, we are unable to differentiate between quiescent and active lesions on OCTA. Secondly, OCTA is dependent on erythrocytes movement as contrast mechanism. If blood flow is slower than detection threshold, e.g. in some microaneurysms and fibrotic CNV, it will not be visualized with OCTA. Thirdly, image acquisition area for current generation of OCTA systems is relatively small, ranging from 2x2 mm up to 12x12mm. However, wide-field OCTA covering more than 60º of the retina while maintain high definition and resolution has now become available [21]. Introduction of swept-source OCT with faster scanning speed has allowed for a wider field of view as demonstrated by Choi et al [22]. Montaging of multiple OCTA images is another strategy used to increase field of view. Fourthly, OCTA image artifact can arise from a few sources. Loss of fixation, patient movement and blinking all can cause motion artifacts. Projection

artifacts are observed when large retina vessels casting a shadow on deeper layers of the retina and choroid [23].

OCTA is a novel angiographic imaging tool that has evolved rapidly in recent years. It is quick, non-invasive, dye-less and able to generate depth-resolved 3-dimensional images of the vascular network. Although majority of the current literature on OCTA in ophthalmic imaging were observational case-control studies, they consistently showed OCTA provided accurate detection and quantification of changes in the corneal, retinal and choroidal vasculature in common ocular diseases. In the future, OCTA can be improved with new algorithms that maximize signal-to-noise ratio and new OCT devices with faster scanning speed to expand the field of view may become commercially available. In order for OCTA to gain wider acceptance and routine use, large scale prospective studies are required to establish a normative database and to evaluate the sensitivity and specificity of OCTA compared to current standard FA and ICGA. The next step in determining the usefulness of OCTA may be evaluation of its clinical applications in assessing therapeutic effects of various treatment strategies in retinal and choroidal diseases. It remains to be seen how useful this technology is in clinical decision-making in conditions such as diabetic macular edema and CNV in AMD. Nonetheless, OCTA offers a non-invasive option of angiography that is valuable in the armamentarium of clinicians and researchers.

Declaration of Interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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