Optical Coherence Tomography Angiography: Principles and Application in Retinal Diseases

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Abstract

The non-invasive imaging technology of optical coherence tomography angiography (OCT-A), has been claimed to potentially revolutionize the management of patients suffering from retinal disease. Its use in retinal diseases such as diabetic retinopathy (DR), age related macular degeneration (AMD), and retinal vein occlusion (RVO) has been expanding significantly over the last years. However, as any other imaging technique, limitations and artifacts need to be considered for its correct interpretation. Further studies are needed to assess the diagnostic properties of OCT-A as a patient management tool for retinal diseases. To what extent the potential of OCT-A will translate into daily medical routine still needs to be established.

Introduction

Optical coherence tomography (OCT) is a non-invasive imaging technique designed to obtain cross-sectional in-depth images of biological tissues. Since OCT has been introduced into ophthalmology by Huang et al in 1991, it has revolutionized the management of patients suffering from retinal diseases. Optical coherence tomography uses low-coherence interferometry to measure backscattered light reflected from samples in order to generate high resolution images. Advances have been made throughout the past years i.e. in terms of image acquisition speed (ranging from spectral-domain, to time-domain and swept-source OCT) causing less interference by motion artefacts and resulting in enhanced image resolution and quality. This has ultimately led to the development of the so called “in vivo optical biopsy”. Optical coherence tomography thereby contributed to a better understanding of vascular morphology of the retinal and choroidal anatomy while prompting an opportunity to combine structural and functional information. The newest advancement that has been based on OCT, so-called optical coherence angiography (OCTA) allows non-invasive retinal and choroidal angiography by the analysis of differences in OCT signals caused by blood flow. Principles of Optical Coherence Tomography Angiography

Fluorescein angiography (FFA) and Indocyanine green (ICG) have been considered gold standard techniques in the diagnosis of diseases affecting retinal and choroidal vasculature for the past years. However, both are invasive procedures and may therefore cause adverse events or in rare cases even serious life threatening allergic reactions. Unlike FFA and ICG, OCT-A has the advantages of being a non-invasive and dye-free imaging method that offers a faster acquisition time and reproducibility. It has first been introduced by Jia and colleagues in 2012 and has had a great impact in ophthalmology ever since by the unprecedented visualization of retinal and choroidal vascular layers. Optical coherence tomography angiography is based on ultra-high speed sequential acquisition of B-scans of the exact same retinal area. It assesses changes within OCT signals (so called signal decorrelation) what allows to detect moving blood cells within a static background. The flow of red blood cells in a vascular network is visualized by the analysis of the difference in the reflected OCT signal between static and non-static tissue from one scan to another. Since OCT-A is based on the principle of multiple scans on the same retinal location, it requires high speed image acquisition processes. Various algorithms such as split spectrum amplitude decorrelation angiography (SSADA), optical microangiography (OMAG), OCT-A ratio analysis (OCTARA), and phase variance are available among OCT-A devices that allow the creation of motion contrast. Acquisition protocols, acquisition speed, and segmentation techniques also vary in between manufacturers. The angiograms are usually obtained within three to six seconds, and by the reconstruction of volumetric data, en face and cross-sectional images mapping retinal and choroidal vasculature are created. Depending on the software, segmentation algorithms allow the depiction of vascular structures in the retinal capillary plexus and in the choriocapillaris within a field of view ranging from 3 × 3 to 12 × 12 mm. This segmentation is based on the architectural morphology of the tissue observed in the structural OCT.

Limitation and Artefacts

Unlike FFA, that depicts the superficial vascular plexus, OCT-A can evaluate deeper capillary structures, providing a more precise location and depth of a pathology. However, limitations such as i.e. a limited field of view, artifacts that may lead to misinterpretation, or the inability to evaluate speed flow and leakage should be considered when analysing the scans. Since OCT-A currently has a maximal field of view of 12×12 mm, pathology within the peripheral retina may be missed. There is a constant trade-off between field of view and imaging quality. In terms of diabetic retinopathy, this stands out as a particular issue since changes in peripheral microvasculature are not thoroughly assessed through OCT-A. Future high-speed scanning protocols will...
hopefully be able to provide wider retinal coverage with an increased sample density, and thus high-definition images. Low signal strength is another limitation for OCT-A. A reduced blood flow may not reach the threshold necessary to allow differences in contrast and OCT signal. Thus, not being identifiable through the imaging software. A decorrelation signal that is below threshold values will therefore be indistinguishable from its background\textsuperscript{21,22}. This could raise a particular concern when assessing for example fibrotic choroidal neovascularization (CNV) or microaneurysms which, due to a slower blood flow, may not be depicted\textsuperscript{22}. Although an increase in time intervals in between scans might improve detection of these slow flow subjects, there is a counter effect due to increased background noise detection and motion artifacts. Additionally, as with standard SD-OCT, an increase in background noise due to cataracts or vitreous opacities, also decreases signal strength and image quality\textsuperscript{17}. Motion artifact is also considered as an important limitation for OCT-A. Although the aim of OCT-A is to identify changes in consecutive images of the same location, movements as discrete as eye saccades and pulsation of choroidal vessels may cause artifacts and lead to misinterpretations. Algorithms such as the SSAD have been presented as efficient strategies to improve signal-to-noise ratio of flow detection. They help reduce bulk motion noise in the axial dimension, while the retinal and choroidal flow signal are generally in a transverse dimension\textsuperscript{11}. Nevertheless, transverse motion from fixation changes is not accessed by these techniques. Motion correction technology has been included into software in an attempt to reduce decorrelation and gaps within the created image. Another significant artifact includes the so called “projection-” or “tailing artifact”\textsuperscript{19,20}. Through the penetration of the OCT light source across the retina into deeper tissues, structures such superficial retinal blood vessels, are crossed. Blood flow or any other change in light scattering within these superficial vessels may therefore cause variation of amplitude and phase that translates into a signal difference in deeper structures of the retina. Thus, these projection artifacts may cause duplication of superficial vessels on deeper tissue, thereby interfering with the correct interpretation of blood flow. Different software algorithms have been introduced to address these artifacts by suppression of the projected image from the superficial retina. However, extra caution is required for an accurate examination of deeper retinal and choroidal layers. Segmentation artifacts are critical when interpreting OCT angiograms. Segmentation allows to visualize the superficial and the deep retinal plexus as well as the choriocapillaris\textsuperscript{23}. However, pathological conditions that alter the anatomy of the retinal architecture have a direct effect on automated segmentation strategies, potentially causing them to fail. For instance, in patients suffering from high myopia involving staphyloma current automated techniques regularly lead incorrect segmentation. In patients suffering from age related macular degeneration (AMD), intra- or subretinal fluid may also cause inaccurate automatic segmentation, ultimately leading to incorrect interpretation of CNV in terms of its location and morphology. Figure 1 shows an example of an error of automatic segmentation on a patient with AMD where the superficial plexus is wrongly segmented, particularly in the areas with pigment epithelium detachments (PED). Therefore, many OCT-A systems allow manual segmentation correction. However, not only is this time-consuming, but also raises concerns regarding feasibility in daily medical routine, reproducibility and accuracy.

The inability to depict vessel leakage is another issue that has been discussed as a disadvantage of OCT-A compared to FFA and ICG, which are both able to show hyper-fluorescence caused by leakage [20]. However, details of the microvasculature in FFA and ICG may be obscured by leakage. Optical coherence tomography angiography on the other hand, has the ability to locate depth of a specific pathology but is unable to identify active leakage, pooling or staining.

Figure 1: Optical coherence tomography angiography (Carl Zeiss Meditec, Dublin, CA) and corresponding segmentation B-scan showing an automatic segmentation error. The segmentation scan does not follow the contour of the pigment epithelium detachment as it displaces the retina, thus causing an error in the segmentation of the superficial plexus.
Applications in Medical Retina

Among the various potential applications of OCT-A in Medical Retina, we would like to highlight its role in the management of the most common retinal diseases, such as age related macular degeneration, retinal vein occlusion and diabetic retinopathy. In particular, we aim at discussing the assessment of retinal vascular parameters, i.e. choroidal neovascularization (CNV) in AMD, myopic degeneration and central serous chorioretinopathy (CSCR), macular oedema and ischaemia in RVO, and the foveal avascular zone (FAZ) in DR.

Optical coherence tomography-angiography allows to delineate and locate CNV. In an observational retrospective study by De Carlo et al. investigating 72 eyes, the sensitivity and specificity of CNV detection was 50% and 91% respectively, when compared to FFA as ground truth [24]. In Figure 2, we show an example of an OCT-A scan delineating a CNV of a patient suffering from AMD. In 2015, Coscas and colleagues evaluated 80 eyes of wet AMD patients and reported a correspondence of 90 to 95% between OCT-A and traditional imaging techniques [25]. Similarly, Bonini et al. evaluated OCT-A for the detection of CNV in patients with chronic CSCR and reported a sensitivity and specificity of 100% for both [26].

OCT-A is able to detect CNV before the development of (sub-)retinal oedema, which has not yet been possible by the use of invasive imaging or OCT. Although OCT-A allows delineation of asymptomatic vascular lesions, the assessment of the activity status of a CNV membrane is not possible. In fact, Roisman and colleagues [27] raised a discussion of whether the detection of asymptomatic/non-exudative CNV may lead to an overtreatment with anti-vascular endothelial growth factor (anti-VEGF) therapy. Given that early detection and treatment of CNV is crucial in terms of visual prognosis but that the benefit of anti-VEGF at this stage has not been investigated yet, more research is warranted. Other studies also discussed the benefits of identifying CNV membranes at an early stage to understand their natural course and proposed an OCT-A based protocol for the management of CNV [27,28]. Cole et al raised a discussion about OCT-A clinical trial endpoints for patients with wet AMD, which was divided in qualitative and quantitative features of CNV membranes [29]. Further studies are still needed to evaluate the significance of each of these characteristics in terms of natural course of the disease and prognosis. An emphasis should be given on the importance of validated systematic approach that allows reproducibility among graders, different algorithms and devices.

Due to the fact that OCT-A is non-invasive, it has been claimed to be an optimal tool to monitor the course of retinal diseases, allowing quantitative and qualitative evaluation of the CNV morphology. Saying this, an important use case may be the management of patients suffering from wet AMD that need repeated intravitreal injections (IVI) of anti-VEGF. Muakkassa et al investigated CNV membranes...
Diabetic retinopathy is characterized by microvascular abnormalities that lead to capillary occlusions and non-perfusion as well as increased vasopermeability and neovascularization. The management of patients suffering from DR has benefited by the use of OCT-A in several aspects. Although OCT-A offers only a limited field of view (maximally 12x12 mm) and is not able to depict leakage, it has been shown to detect retinal capillary abnormalities, capillary distortion, neovascularization and enlargement of the FAZ. As already mentioned, compared to FA, the capillary vasculature is not obscured by leakage of retinal and choroidal vessels in OCT-A. In a study conducted by Ishibazawa et al, microaneurysms were detected via OCT-A as dilated saccular or fusiform capillaries and identify the origin of them within the retinal layers. However, it has been claimed that the sensitivity for microaneurysms (MA) detection is higher through FFA since blood flow velocity within MA may be sub-threshold for the detection by OCT-A.

La Mantia et al evaluated macular perfusion of diabetic patients using FFA and swept source optical coherence tomography angiography (SS-OCTA) and demonstrated a good agreement in FAZ diameter and area amongst the two imaging techniques. Although early signs of diabetic retinopathy i.e. microaneurysms still seems to be better identified through FFA, OCTA-A can be promising tool for macular flow assessment. In 1984, Bresnick et al first demonstrated the enlargement of the foveal avascular zone.
(FAZ) through fluorescein angiography in diabetic patients, which supports the importance of capillary occlusion or drop out in the pathogenesis of the disease\(^6\). De Carlo et al\(^{27}\) and Takase et al\(^{48}\) suggest that OCT-A could be a useful screening tool as it is able to detect microvascular changes in the macula and the FAZ even before the onset of DR and MA are clinically visible. Its ability to precisely evaluate the area of non-perfusion as well as the irregularity in microvasculature, also showed to be a great advantage of the OCT-A systems.

Neovascularization is considered a hallmark for proliferative diabetic retinopathy (PDR)\(^{46}\). Different from intraretinal microvascular abnormalities (IRMAs), NV are characterized as loops in a vascular network on the surface of the retina that invades the vitreous cavity. They can be identified in slit lamp fundus examination and show profuse leakage in late phases of a FFA\(^47\). The segmentation done in OCT-A shows an advantage over FFA in terms of allowing clinicians to locate the NV and identify a flow signal protruding above the internal limiting membrane. Figure 3 illustrates a case of proliferative diabetic retinopathy where a neovascularization of the optic disc is cleared demonstrated via OCTA. Moreover, Ishibazawa et al. demonstrated in their study the use of OCT-A to evaluate vascular changes in new vessels at the disc (NVD) relative to flow volume after anti-VEGF therapy\(^42\). Therefore, OCT-A also rises as a potential follow-up tool for managing patients with DR due to its advantages of being non-invasive, reproducible and fast.

**Conclusion**

To conclude, OCT-A has proven to be a promising tool to complement the diagnosis and management of retinal diseases. Although scans need to be interpreted carefully due to the intrinsic limitations and artifacts of this technology, OCT-A has emerged as one of the major advances in medical retina. Different scanning strategies and enhanced software are constantly being introduced to improve this imaging modality, which will ultimately broaden its scope of use and establish protocols for its application as part of the routine eye care examination.

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