Review Article

Optical coherence tomography angiography: Technical principles and clinical applications in ophthalmology

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Abstract:

Optical coherence tomography angiography (OCTA) is a functional extension of OCT that provides information on retinal and choroidal circulations without the need for dye injections. With the recent development of high-speed OCT systems and efficient algorithms, OCTA has become clinically feasible. In this review article, we discuss the technical principles of OCTA, including image processing and artifacts, and its clinical applications in ophthalmology. We summarize recent studies which qualitatively or quantitatively assess disease presentation, progression, and/or response to treatment.

Keywords:

Choroidal neovascularization, diabetic retinopathy, glaucoma, optic disc, optical coherence tomography angiography, retina

Introduction

Since its invention in the early 1990s, optical coherence tomography (OCT)[1] has become one of the most important imaging modalities in ophthalmology. OCT is a noninvasive imaging technology based on low-coherence interferometry. It generates high-resolution, cross-sectional images from backscattered light, enabling clinicians to assess structural changes in different retinal diseases. However, structural OCT cannot be used to monitor vascular changes because of the low contrast between capillaries and retinal tissue.

Given that many ocular diseases are associated with vascular abnormalities, the ability to visualize and quantify blood flow in the eye is of high importance to the global ophthalmic community. Conventionally, fluorescein angiography (FA) and indocyanine green angiography (ICGA) are used for qualitative clinical assessment of retinal and choroidal circulations, respectively. They require intravenous injection of contrast agents, which is time-consuming and can have potentially serious side effects.[2,3] Moreover, FA and ICGA provide two-dimensional (2D) images of ocular circulations, limiting depth perception and detailed investigation of the retinal and choroidal vasculatures.

Multiple noninvasive imaging technologies have been employed in the last few decades to visualize and quantify ocular circulations. Ultrasound color Doppler[4] and functional magnetic resonance imaging[5] have been previously used for research purposes. While they were able to provide good tissue penetration, they did not receive much clinical attention in ophthalmology due to poor resolution and measurement reproducibility. Other imaging modalities such as laser Doppler flowmetry and velocimetry, blue field entoptic technique, and laser speckle assessment have been used extensively to study vascular retinal physiology.[6] However, their clinical use has been limited by their complexity, poor reproducibility, and wide population variation.[7]

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Functional extensions of OCT have also been explored for vascular imaging of the eye. Doppler OCT (DOCT) uses the Doppler frequency shift resulting from the movement of red blood cells to quantify volumetric blood flow in large vessels, as well as for total retinal blood flow measurement.[8,9] However, DOCT is less suitable for investigating the retinal microvasculature. DOCT is sensitive to blood flow parallel to the OCT beam, whereas flow in the retinal microvasculature is mainly perpendicular to the OCT beam. OCT angiography (OCTA) is a more recent development.[10] It has the capability of producing high-resolution, 3D angiograms of the retinal and choroidal vascular networks. OCTA detects the motion of blood using intrinsic signals to capture the location of blood vessels. Despite its insensitivity to leakage and the relatively small field of view, the development of OCTA has the potential to improve our knowledge of the physiology and pathophysiology of the eye. In this review article, we discuss the history of OCTA as well as its technical principles and clinical applications.

Technical Principles and Image Processing

OCTA requires repeated scans at the same location to detect motion. Therefore, the development of OCTA was not possible during the era of slower speed time-domain systems. By the initial introduction of Fourier-domain OCT systems, the scanning speed of OCT improved by a factor 50, opening the door for more advanced OCT applications. OCTA was first described in some form in 2006 by Makita *et al.* using an 18.7 kHz spectral-domain OCT (SD-OCT) system.[11] With further improvement of OCT hardware and advancement in data processing techniques, higher quality OCT angiograms could be generated with less image artifacts.

Motion detection
OCTA identifies blood vessels by detecting the blood flow-induced change in the OCT reflectance signal. Flowing red blood cells causes more variation in the OCT signal between repeated scans than static tissue. Multiple approaches have been described for quantifying this change through assessment of the intensity, phase, or intensity and phase of the OCT signal. Studies also showed that the derived OCTA signal is related to the speed of flowing red blood cells, where faster flow results in greater flow signal, up to a saturation limit.

The aforementioned OCTA approaches were classically applied on the full OCT spectrum. In 2012, Jia *et al.* introduced an intensity-based technique to visualize the retinal and choroidal microvascular called split-spectrum amplitude-decorrelation angiography (SSADA).[12] The SSADA algorithm divides the OCT spectrum into narrower bands and then averages the intensity decorrelation detected in each band. This method significantly improved the signal-to-noise ratio, at the expense of axial resolution, which is less important when we construct *en face* angiograms of thick tissue slabs.

Commercially available optical coherence tomography angiography systems
A summary of the commercially available OCTA devices is provided in Table 1.

Image processing
The depth-resolved property of OCTA allows for constructing a 3D dataset representing the vascular portion of the scanned tissue. Accurate segmentation of the structural image is essential for optimal evaluation of retinal and choroidal vasculature. Fully automated segmentation algorithms can be highly efficient and accurate in a healthy retina. However, in the diseased eye, anatomical features are usually distorted and segmentation algorithms can fail, requiring manual correction by an expert grader. More recent advances in image processing tools have enhanced the efficiency of automated and semi-automated segmentation techniques in the presence of retinal pathology.[13] The more commonly used segmentation boundaries include internal limiting membrane (ILM), outer boundary of the nerve fiber layer (NFL), outer boundary of the inner plexiform layer, outer boundary of the inner nuclear layer (INL), outer boundary of the outer plexiform layer (OPL), retinal pigmented epithelium (RPE), and Bruch's membrane (BM).

The 3D flow data are usually presented as 2D images, comparable to conventional angiography. The flow signal in specific tissue layers or slabs could be compressed into one 2D *en face* image. These slabs are defined by two relevant segmentation boundaries. For instance, the inner retinal circulation is the flow signal between the ILM and outer boundary of OPL, while the normally avascular outer retinal slab is defined between the outer boundary of OPL and BM. Another method for presenting OCT angiograms is to use the conventional cross-sectional approach. Flow signal is color coded and overlaid on the structural OCT image. Displaying structural data along with the flow data in the same B-scan can be useful in providing detailed information on the depth of vascular abnormalities such as retinal or choroidal neovascularization (CNV).

Quantification of optical coherence tomography angiography
Quantification of OCTA is important for objective evaluation of retinal abnormalities. Vessel density and flow index are two commonly used metrics which can be obtained from the *en face* angiograms.[10,14-19] Vessel density is defined as the percentage area occupied by the blood vessels, while flow index is calculated as

Table 1: Summary of the commercially available optical coherence tomography angiography devices

Commercial name	Company	Algorithm used	OCTA approach	OCT spectrum	FDA approval
AngioVue™	Optovue, Inc.	SSADA	Intensity decorrelation	Split-spectrum	Approved
AngioPlex™	Zeiss	OMAG-C	Combined intensity and phase variance	Full-spectrum	Approved
SS-OCT Angio™	Topcon Corp.	OCTARA	Intensity ratio analysis	Full-spectrum	Pending
AngioScan	NIDEK CO., LTD		Combined intensity and phase decorrelation		Pending
SPECTRALIS® OCT Angiography	Heidelberg Engineering		Intensity decorrelation	Full-spectrum	Pending

FDA = Food and Drug Administration, OCTA = Optical coherence tomography angiography, OCTARA = Optical coherence tomography angiography ratio analysis, OMAG-C = OCT microangiography complex, SSADA = Split-spectrum amplitude-decorrelation angiography, SS-OCT Angio = Swept-source optical coherence tomography angiography

the average flow signal in the area of interest. Flow index carries information on both vessel area and blood velocity. However, it cannot be considered as a volumetric measurement of blood flow because of the saturation effect of the flow signal value with high flow velocity. Flow index was found to be more sensitive in detecting the metabolic and physiologic changes in retinal tissue.[19] However, vessel density was more useful for the diagnosis and monitoring of vascular pathology. Initial studies reported good repeatability and reproducibility of these metrics.[20]

Other metrics have been explored for quantification of vascular abnormalities in different eye diseases. Measurement of avascular area can serve as a valuable metric for objective evaluation of diseases characterized by capillary loss such as diabetic retinopathy (DR) and glaucoma.[10,21-23] Perfusion density mapping is another approach to assess abnormal flow regions.[24,25] It is a color-coded map demonstrating the vascular density in different areas of the scanned region. Attempts have also been made to quantify neovascularization area,[26,27] which is calculated as the sum of pixel areas representing the retinal or choroidal neovascular vessels. It can be helpful in monitoring neovascularization along the course of the disease or as a result of treatment.[28,29]

Quantitative parameters have the potential to provide new objective biomarkers for eye diseases, facilitating diagnosis, monitoring, and treatment. However, further investigations are needed for validation and reliability assessment of the new metrics.

Optical coherence tomography angiography image artifacts

OCTA, like any imaging technology, is affected by different types of artifacts [Figure 1].[30,31] Proper identification and understanding of these defects are essential to prevent inaccurate interpretation and wrong decision-making.

Weak optical coherence tomography signal

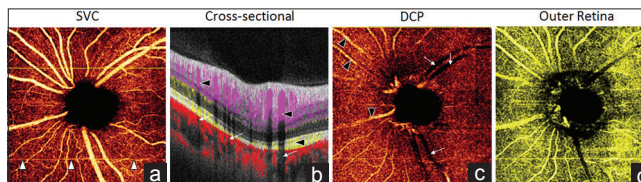The generation of structural OCT images depends on the backscattering of light from tissue structures. The

Figure 1: Image artifacts in a 4.5 mm × 4.5 mm optical coherence tomography angiography of the optic nerve head of a healthy individual. (a) *En face* optical coherence tomography angiography of superficial vascular complex. The yellow line corresponds to the cross-sectional optical coherence tomography angiography image in panel (b). (c) *En face* optical coherence tomography angiography of the deep capillary plexus. (d) *En face* optical coherence tomography angiography of an outer retinal slab extending from the outer boundary of the outer plexiform layer to the Bruch's membrane. A residual line artifact (white arrowheads) from microsaccadic eye motion can still be seen in the *en face* optical coherence tomography angiography images after registration and processing. Large vessels in the superficial vascular complex can cause two types of artifacts on the deeper layers as seen on the cross-sectional and *en face* images (b and c): projection artifacts with false positive flow signal (black arrowheads) and shadow artifacts with false negative flow signal (white arrows). Projection artifacts are usually more pronounced at the layers with high optical coherence tomography reflectance signal such as retinal pigmented epithelium (d)

OCT signal can be reduced globally by media opacity, pupil vignetting, and defocusing of the light beam. In such cases, low-quality images will be generated, obscuring inner eye components and producing unreliable flow information. Using light sources with longer wavelengths can theoretically overcome mild opacities. Proper OCT beam focusing and centering, as well as pupil dilation, can enhance the quality of an OCT scan. Focal OCT signal weakening or loss can also be encountered beneath large vessels or hyperreflective retinal lesions, obscuring flow signal and producing shadow artifacts [Figure 1b and c, white arrows].

Motion artifacts

OCTA relies on intrinsic motion contrast as the basis for detecting flow. Bulk tissue and saccadic eye movements can produce noise and motion artifacts, resulting in overestimation of the flow signal. Multiple approaches have been introduced to overcome motion artifacts. Motion correction technology is a technique that has been used in commercial OCT systems. In this method, two OCT volumes are acquired with perpendicular scanning directions and then registered and merged.[32] Eye tracking

is another potential solution. Variants of eye tracking have also been adopted on commercial OCTA systems.[33,34] Eye tracking systems work by detecting eye movement for real-time correction of motion artifacts. These methods can significantly reduce motion artifacts and improve the reliability of OCTA scans. However, residual defects can still be present as motion lines [Figure 1a, white arrowheads], vessel duplication, or vessel discontinuity. More advanced processing algorithms can help eliminate residual defects in OCTA images.[35,36]

Projection artifacts

Flowing red blood cells in more superficial vasculature cast time-varying shadows on the deeper retinal layers.[30] These flow projection artifacts lead to duplication of the superficial vascular pattern on deeper microcirculation, as well as the normally avascular outer retinal slab [Figure 1b-d, black arrowheads]. OCTA projection artifacts can lead to inaccurate measurement of flow index and vessel density of deeper retinal vasculature. Moreover, they impede the identification and quantification of CNV in the outer retina[27] or can even be mistakenly recognized as CNV.

Several solutions have been proposed to overcome OCTA projection artifacts. One method is to subtract the more superficial flow signal from the deeper *en face* angiograms, called the "slab-subtraction" method.[15,27,37] This approach can disrupt the continuity of vessels in the deeper vascular plexuses and potentially underestimate their vessel density. More recently, an algorithm called "projection-resolved" OCTA (PR-OCTA)[38] was developed to suppress the projected flow signal while preserving the natural continuity of ocular microvasculature, allowing for improved visualization and quantification of different retinal vascular layers in normal and diseased eyes [Figure 2].[23,38,39]

Clinical Applications

Normal vascular anatomy and physiology

FA and ICGA images are able to show 2D images of retinal and choroidal circulations, respectively.[40,41] However, no further details could be extracted because of their limited depth perception. With the introduction of OCTA, blood flow from different vascular beds within the retinal and choroidal circulations could be separately projected.[10,13,42] However, projection artifacts make it difficult to clearly visualize deeper retinal plexuses without the interference of projected flow from more superficial plexuses. Recently, the development of PR-OCTA[38] has allowed for exceptional *in vivo* visualization of detailed ocular vascular anatomy which was not achievable using other imaging modalities [Figure 2]. Four vascular plexuses can be identified in OCT angiograms of the human

retina, as well as the interplexus spaces containing the interconnecting vessels. This arrangement is consistent with histological studies on primates and human cadavers.[43] The four plexuses can be grouped into two retinal vascular complexes: superficial vascular complex (SVC) and deep vascular complex (DVC).

The SVC consists of the superficial vascular plexus (SVP) in the ganglion cell layer and radial peripapillary capillary plexus (RPCP) in retinal NFL (RNFL). The SVP originates directly from large retinal arteries and drains into retinal veins. It includes both macro- and micro-vessels. The SVP provides blood supply to the more superficial RPCP, as well as the deeper plexuses in DVC. The RPCP is a radially organized capillary plexus that runs parallel to NFL axons. It is believed that RPCP is responsible for blood supply to the dense NFL in the peripapillary region.

The DVC consists of the intermediate capillary plexus (ICP) above INL and deep capillary plexus (DCP) below INL. The ICP and DCP are relatively homogenous capillaries, responsible for nourishment of the deep layers of inner retina. Moreover, recent evidence suggests an overlap in function with the choroidal circulation to support the avascular outer retina.[44]

Visualization of choroidal circulation by OCTA is inherently more difficult than that of retinal circulation. Light scattering throughout the retinal layers and especially from the highly reflective RPE results in a decreased amount of light reaching the choriocapillaris (CC) and larger choroidal vessels. While commercially available SD-OCTA systems with
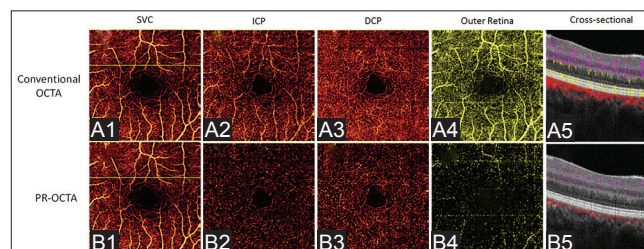
Figure 2: A comparison of optical coherence tomography angiography of the macula (3 mm × 3 mm) of a healthy individual without (a) and with projection-resolved optical coherence tomography angiography (b) projection-resolved optical coherence tomography angiography. Blood vessels of the superficial vascular complex (A1) cast projection artifacts onto the *en face* images of deeper layers, significantly interfering with the proper visualization of the normal anatomical features of intermediate capillary plexus (A2), deep capillary plexus (A3), as well as the avascular outer retina (A4). (A5) Cross-sectional optical coherence tomography angiogram at the position of the yellow line in (A1). Tail artifacts obstruct the normal avascular boundaries between retinal plexuses and produce false positive flow signal in the normally avascular outer retinal layers. Projection-resolved optical coherence tomography angiography significantly reduced the projection artifacts from the *en face* (B2–B4) and cross-sectional (B5) angiograms. Normal vascular architecture of the intermediate capillary plexus and deep capillary plexus can be appreciated, with minimal residual projection artifacts in the outer retina and on the cross-sectional image
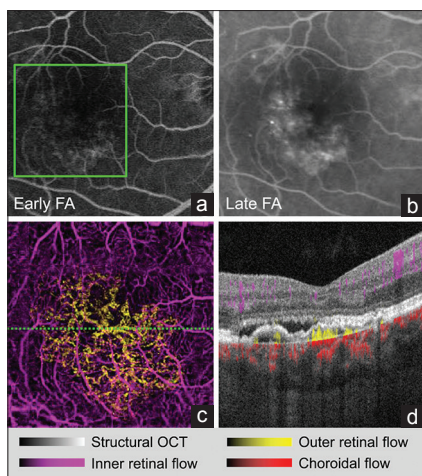
Figure 3: A case of central serous chorioretinopathy. Early-phase (a) fluorescein angiography image shows minimal leakage, with increasing hyperfluorescence staining in the late-phase (b). However, fluorescein angiography was not able to determine the source of the leakage; whether it was from the central serous chorioretinopathy or secondary choroidal neovascularization. (c) *En face* 3 mm × 3 mm OCT angiogram corresponding to the green box in Panel A. (d) Cross-sectional optical coherence tomography angiography corresponding to the green line in Panel C. optical coherence tomography angiography revealed abnormal flow signal in the outer retinal slab, beneath the retinal pigmented epithelium, consistent with Type 1 choroidal neovascularization

Figure 4: *En face* projection-resolved optical coherence tomography angiography images of the parafoveal retinal plexuses of two eyes with mild nonproliferative diabetic retinopathy. Avascular areas in each of the retinal vascular plexuses (a-c, e-g) were detected automatically (blue areas) from the *en face* projection-resolved optical coherence tomography angiography images, revealing capillary dropout lesions that could not be detected from the combined inner inner retinal angiogram (d and h)

840 nm light sources are able to provide visualization at the level of the CC,[31,45] OCTA systems at longer wavelengths can achieve deeper penetration and theoretically improve choroidal imaging. Jia *et al*.[10] and Choi *et al*.[46] used swept source OCTA (SS-OCTA) prototypes to image CC and choroidal vasculature. Their systems had central wavelengths of 1050–1060 nm. SS-OCTA was able to provide *en face* angiograms of CC and the larger choroidal vessels in Sattler's layer, which were consistent with the findings from histological and electron microscopic studies.[46]

The ability to reliably visualize and quantify flow in different retinal plexuses opens the door for a new era of *in vivo* investigation of vascular physiology. The vascular response to different physiologic changes has long been investigated in the retina of human and rats. OCTA has only recently been employed for noninvasive assessment of retinal vascular response to light stimulation[6] and increased blood oxygen content (systemic hyperoxia).[19] Wei *et al*.[18] observed retinal hyperemia in response to light stimulation using OCTA. Pechauer *et al*.[19] used a commercially available SD-OCTA system to assess the retinal autoregulatory hemodynamic response to hyperoxia. A significant decrease in both flow index and vessel density of the peripapillary region was observed. However, further investigations using the recent advancements in OCTA technology are needed to characterize these responses in individual vascular layers.
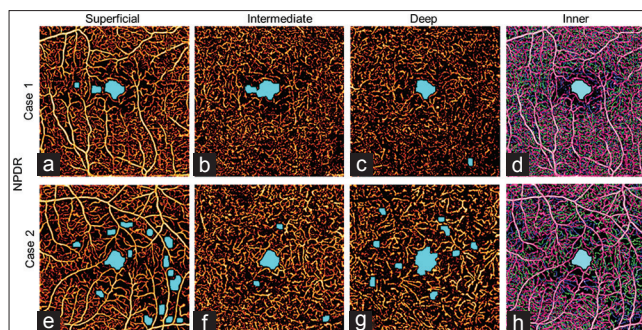
Choroidal neovascularization

CNV is the growth of new pathological blood vessels from the choroid which break into the retina. These vessels tend to leak or bleed, leading to vision impairment. CNV is associated with several eye diseases such as neovascular age-related macular degeneration (AMD), polypoidal choroidal vasculopathy (PCV), and central serous chorioretinopathy (CSC). CNV can be classified into three types depending on their extension. Type I CNV, the most common type, is located between BM and RPE. In Type II CNV, blood vessels cause disruption of RPE layer and extend into the subretinal space. Type III CNV or retinal angiomatous proliferation (RAP) is an advanced form of neovascularization, in which blood vessels extend all the way through retinal layers and form anastomosis between retinal and choroidal circulations.

Neovascular age-related macular degeneration

AMD is a leading cause of blindness in older patients in the developed world. Neovascular AMD is a less common but more devastating phenotype. It is characterized by CNV formation, leading to rapid and severe loss of central vision. Jia *et al*. first demonstrated the ability of OCTA to visualize and quantify Types I and II CNV in a small number of AMD patients.[15] *En face* OCT angiograms as well as composite B-scans were used to display abnormal blood vessels in the outer retinal layers [Figures 3 and 4].[31] Moreover, they provided quantitative assessment of the CNV by measuring CNV membrane area and the flow index within the CNV lesion. In a larger study, Palejwala *et al*. reported the ability of OCTA to detect nonexudative CNV.[47] Roisman *et al*. also demonstrated the capability of SS-OCTA to identify subclinical Type I CNV in intermediate AMD patients.[48] Automated CNV detection algorithms have been introduced with promising results in the efficient identification and quantification of abnormal vessels from outer retinal angiograms.[26,27]

OCTA has furthermore provided an opportunity to investigate the morphological characteristics of different types of CNV in AMD[49-51] and their response to treatment.[49,52-56] Short-term monitoring of CNV after anti-vascular endothelial growth factor (VEGF) injections revealed rapid and dynamic changes in the neovascular lesion. Regression of the CNV was detected 1–2 days after injections and continued over the following 2 weeks.[28] Significant exacerbation of the CNV was then detected 4–6 weeks after injections, which was associated with re-accumulation of subretinal fluid. OCTA scans at 2-week intervals could be useful in aiding CNV management by anti-neovascular therapy.[28]

The depth-resolved nature of OCTA allows for the accurate assessment of the CNV extension into retinal tissue, with unique advantages in distinguishing early Type 3 versions of the CNV from other lesion types. OCTA has been used to identify the connection between neovascularization in the outer retina and the DCP in the inner retina, which was too small to be visualized by the conventional approaches.[53,57-59] Liang *et al.* also reported high correlation between the clinical activity of the disease and the presence of CNV, but not the morphology, on OCTA.[60] More recent studies on a larger number of patients reported good sensitivity and specificity of OCTA in CNV detection in AMD.[61,62] OCTA has also been used to evaluate subretinal fibrosis secondary to exudative AMD. The abnormal vascular network inside the fibrotic tissue and surrounding architectural abnormalities were detected in most patients.[63-65]

Polypoidal choroidal vasculopathy

PCV is characterized polyp-like aneurysmal dilatations of choroidal vessels, associated with serous and hemorrhagic detachments of the RPE, which can lead to subretinal fibrosis.[66] Inoue *et al.* first demonstrated the usefulness of OCTA in a small series of PCV patients.[67] Polypoidal lesions, as well as abnormal branched vascular networks, were detected on the *en face* and cross-sectional OCT angiograms of the outer retinal slab.[68] Pachy vessels and loss of CC were also detected beneath the abnormal branched vascular networks.[67] Although OCTA provides flow-based anatomical and pathophysiological information that enhances our understanding of the disease,[68,69] improvements are still required to be used solely as a diagnostic instrument for PCV.[67,70,71]

Central serous chorioretinopathy

CSC is a chorioretinal disease characterized by increased permeability of the CC. This leads to serous fluid leakage and accumulation between the outer segment of the photoreceptors and RPE, resulting in detachment of the neurosensory retina, as well as focal lesions in the RPE.[72] CNV is an uncommon but sight-threatening complication of CSC that requires treatment. OCTA allows for the visualization of blood flow abnormalities and the associated structural changes in CSC [Figure 3].[29,31,62,73-75] In a study by Feucht *et al.*,[76] no changes were observed in the inner retina, outer retina, or CC in the acute stage of the disease. However, alterations in choroidal flow were detected in some eyes.[76] In chronic CSC cases, focal choriocapillary ischemia surrounded by an area of hyperperfusion was apparent on OCT angiograms.[29,77,78] McClintic *et al.*[29] demonstrated the ability of OCTA to monitor the response to treatment in a case of chronic CSC. The OCT angiograms revealed loss of several peripheral vascular loops within the neovascular lesion, resulting in reduction in the CNV area.[29]

Nonneovascular age-related macular degeneration

Nonneovascular AMD is the more common and less severe form of AMD. It is characterized by drusen deposition without CNV formation. A common feature in advanced stages of nonneovascular AMD is geographic atrophy (GA), which is characterized by loss of photoreceptors, RPE, and CC. However, the primary insult responsible for GA is still unknown.[79] The simultaneous presentation of structural and flow information using OCTA can be of great value in developing a better understanding of disease evolution. However, OCT angiograms should be interpreted with caution in cases of GA. The degeneration of the RPE and CC allows for deeper light penetration into the choroid, allowing visualization of the larger choroidal vessels that should not be misinterpreted as CNV. Using OCTA, choroidal flow impairment was detected within the atrophy area,[80,81] and more interestingly, beyond the margins of GA.[10,82,83] These findings suggest that CC alterations may precede the atrophy in photoreceptors and RPE.[10] Alterations in superficial and deep retinal plexuses have also been reported in different stages of disease progression.[82,84]

Diabetic retinopathy

DR is a retinal microvascular complication of diabetes mellitus, which leads to progressive vision loss. It is characterized by capillary occlusion, hyperpermeability, and retinal neovascularization.[85] Early detection and proper treatment of DR can significantly reduce the risk of vision-threatening retinopathy.[86] *En face* OCT angiograms are able to visualize the enlargement of the foveal avascular zone (FAZ),[87-89] retinal capillary dropout,[10,21,90] microaneurysms,[87,91] and retinal neovascularization.[10,87,92] FAZ changes were observed not only in DR eyes but also in diabetic patients with no evidence of DR.[89,93] Moreover, FAZ area was significantly correlated with increasing severity of the disease,[94,95] as well as visual acuity findings.[96] Capillary loss was also apparent on the OCT angiogram of the inner retina, with good correlation with FA findings.[21] Automated quantification of avascular area

using PR-OCTA was able to detect capillary abnormalities in individual retinal plexuses that were not visible in the combined inner retinal angiograms [Figure 4].[23] Moreover, capillary perfusion density maps, as derived from OCTA measurements of vessels density in retinal plexuses, might be helpful in clinical evaluation and grading of DR patients.[25]

Vascular occlusions

Retinal vein and artery occlusions are common causes of acute unilateral painless vision loss. OCTA has the ability to provide pathologic details of both superficial and deep retinal vascular complexes, which is not possible with FA.[97,98]

Retinal vein occlusion

Different vascular features can be recognized in OCT angiograms of retinal vein occlusion. Enlargement of FAZ area can be observed in both superficial and deep retinal plexuses, which is correlated with best-corrected visual acuity.[96,99] OCTA also provides highly detailed visualization of the extension of ischemia and capillary dropout in the SVC.[100] Moreover, vascular congestion and microvascular abnormalities can be identified in the DVC.[101] Venous-venous shunting and cystoid macular spaces have also been detected on OCT angiograms of different retinal vascular layers.[102,103]

Retinal artery occlusion

Obstruction of the central or a branch retinal artery can lead to ischemia and coagulative necrosis in the corresponding region of retina. These regions appear on structural OCT cross-sections as areas of increased thickness and reflectivity, leading to shadowing and weakened signal in the deeper layers of the outer retina and choroid.[104,105] *En face* OCT angiograms can be used to visualize the boundaries of capillary nonperfusion areas in the retinal superficial and deep vascular plexuses and how they change over time.[105-108]

Paracentral acute middle maculopathy

Paracentral acute middle maculopathy is a recently described condition presenting as an acute-onset paracentral scotoma. It is characterized by ischemic necrosis of the middle retinal layers (INL/OPL/outer nuclear layer).[109] Decreased perfusion in the DVC (intermediate capillary plexus and DCP) was suggested to be the cause for these lesions.[104] OCTA provides a comprehensive tool to investigate the vascular aspect of the disease, which has not been possible before. *En face* OCT angiograms showed a significant decrease in vessel density of retinal DVC as compared to the unaffected eye.[110,111] Meanwhile, no significant changes were observed in the SVC.[112] These findings provide support to the previously proposed theory that the DVC is responsible for the disease.

Macular telangiectasia

Macular telangiectasia Type 1

Qualitative assessment of *en face* OCT angiograms revealed focal capillary telangiectasias in the DVC but not in the superficial layers.[113] Meanwhile, global and focal capillary loss was observed in both the SVC and DVC. In addition, irregular FAZ with abnormal capillary invasion was also seen in OCTA images of the SVC. Quantitatively, capillary density was found to be significantly lower in the diseased eyes than the fellow eye or eyes from a control group.[113] Moreover, visual acuity correlated with capillary density measurements in both the SVC and DVC, demonstrating the great potential of OCTA for objective clinical assessment of macular telangiectasia Type 1 (MacTel 1).[113]

Macular telangiectasia Type 2

Characteristic OCTA findings can be seen in different stages of MacTel 2. In the earlier nonproliferative phase of the disease, mild telangiectatic changes in the DVC, with normal SVC and avascular outer retina, can be seen.[114] These vascular changes were usually associated with structural abnormalities in retinal layers. A variable degree of ellipsoid zone loss and an abnormal deposition of pigmented clumps were usually observed on cross-sectional OCT.[115,116] With increasing disease severity, dilatations in the SVC were detected with abnormal anastomotic connections between the SVC and DVC.[117] Temporal enlargement of the FAZ and capillary dropout were also detected in both retinal vascular complexes.[118] Vascular ingrowth into the FAZ, as well as dilated feeder and draining vessels, was commonly seen in OCT angiograms of the SVC. A lamellar or full-thickness macular hole was sometimes present in the more advanced cases of MacTel 2.[119,120]

The proliferative phase of the disease is characterized by abnormal vascular invasion into the outer retinal layers, in addition to severe telangiectatic changes and capillary loss in the inner retina. Subretinal neovascularization is a common complication in MacTel 2. It appears on cross-sectional OCT images as subretinal hyperreflective elevated lesions corresponding to the area of ellipsoid zone disruption.[121] On OCTA, subretinal neovascularization was seen as abnormal flow signal in the normally avascular outer retinal slab.[122] OCT angiograms were also able to identify the connecting vessels between these neovascular lesions and choroidal circulations.[114] Zhang *et al*. showed decreased retinal vascular caliber and their anastomosis, as well as disappearance of miocroaneurysms, following treatment.[114]

Inherited retinal dystrophies

Accurate diagnosis of inherited retinal dystrophies (IRDs) has always been a challenge, even with the current

genetic testing techniques. Recent advancements in ocular imaging modalities, including OCTA, can be useful in diagnosis and tracking progression, as well as monitoring the response to gene therapy.[123] Using OCTA, Battaglia Parodi *et al.* investigated the vascular abnormalities associated with early-stage retinitis pigmentosa.[124] A significant impairment of capillary density was detected in retinal circulation, with earlier and more severe capillary loss in the DVC, temporal to the macula. In addition, FAZ area measurements revealed significant enlargement in DVC but not SVC. On the other hand, no abnormalities were revealed in the CC.[124] These findings alleged that early vascular abnormalities in RP are localized in the DVC with relative sparing of SVC and CC.[123,124] On the contrary, OCTA findings in choroideremia demonstrated more extensive damage in CC than retinal circulation.[10] Meanwhile, RPE degeneration was found to be more extensive than CC abnormalities,[24] suggesting that RPE loss might be the primary insult with subsequent loss of CC and relatively late impairment of retinal circulation. OCTA was also used to investigate vascular changes in Stargardt disease. Pellegrini *et al.* detected widespread loss of CC within the area of dark atrophy, with residual lobules at the margins where RPE was completely lost.[81] In addition, in another study by Battaglia Parodi *et al.*, they reported vascular impairment in the superficial and deep retinal vascular complexes, with enlarged FAZ in SVC.[125] Moreover, Patel *et al.* demonstrated the capability of OCTA in morphologic characterization and quantification of CNV-complicated IRDs, despite the highly distorted retinal architecture.[126] In summary, OCTA findings in different IRDs along with other imaging modalities can be of great value in diagnosis, severity evaluation, progression tracking, as well as enhancing our understanding of the pathophysiology. Further studies are needed to correlate the vascular changes with functional outcomes and evolving therapeutic strategies.

Inflammatory diseases

Conventionally, fundus autofluorescence, FA, or ICGA is used to assess inflammatory disease activity and the response to treatment. Despite its small field of view and insensitivity to leakage, OCTA provides depth-resolved images to help localize the inflammatory process, as well as allows for objective assessment of retinal and choroidal circulations. Decreased parafoveal vessel density was detected in patients with retinal vasculitis, even in those who had only peripheral vasculitis on FA.[127,128] de Carlo *et al.* investigated the retinal and choroidal OCTA findings in a series of birdshot chorioretinopathy patients.[129] Marked disruption of RPE and depletion of CC were detected at the birdshot lesions. Retinal vascular abnormalities were also detected. Abnormal telangiectatic vessels, dilated capillaries, and increased intercapillary space were observed in the parafoveal region.[129] Reduced capillary density was also detected, more prominently at the DVC.[130] These changes were diffusely distributed and spatially independent from CC and RPE lesions.

Using OCTA, lesions of serpiginous choroiditis showed loss of CC in the inside, with higher flow signal at the edges.[131] The loss of flow signal can be attributed to depleted blood flow, atrophic CC, or signal attenuation from the overlying lesions.[131] Meanwhile, higher signal at the margins could be either due to disrupted RPE above the capillaries or increased blood flow resulting from an active inflammatory process.[131] In addition, OCTA was able to detect the characteristic trizonal pattern in acute zonal occult outer retinopathy lesions.[131] In toxoplasmosis, the most common infectious retinochoroiditis in humans, OCTA can show the early capillary dropout lesions at the retinal SVC and DVC, as well as decreased vessel density of CC in later stages when the choroid is involved.[132] Furthermore, OCTA can be of great value in detecting neovascular lesions in inflammatory diseases.[131,133,134]

Radiation maculopathy

Radiation maculopathy is a common complication of radiation treatment of ocular or orbital malignancies, resulting in variable degree of vision impairment.[135] Ionizing radiation has been suggested to produce preferential damage to endothelial cells of the retinal microvasculature, leading to capillary occlusion.[136] Clinical examination reveals signs of retinal vascular disease, including microaneurysms, neovascularization, vitreous hemorrhage, hard exudates, cotton wool spots, and macular edema.[137] Horgan *et al.* suggested an expansion of the Finger classification by grading macular edema which can be detected by structural OCT before the onset of clinical signs.[138,139] More recently, Veverka *et al.* demonstrated the sensitivity of OCTA to radiation maculopathy by early detection of subclinical microvascular ischemia.[140] Widening of the FAZ and capillary dropout in both the superficial and deep retinal vascular complexes has been detected in eyes with established diagnosis of radiation maculopathy, as well as in patients receiving radiotherapy without ophthalmoscopic or OCT evidence of maculopathy.[141,142] In more advanced stages of the disease, changes in the FAZ and morphology of the microvasculature can be observed. OCTA findings were more pronounced at the FAZ in all stages of the disease, suggesting that capillaries adjacent to the FAZ might be more sensitive and susceptible to damage by radiation.[143] Prospective studies using OCTA are needed for a better understanding of the pathophysiology and time course of microvascular alterations in radiation maculopathy.

Glaucoma

Primary open-angle glaucoma

Visual field (VF) testing is essential for clinical evaluation of glaucoma. However, it has poor reproducibility and is only sensitive to relatively late stages of glaucoma where functional impairment is already evident. Structural OCT measurements of RNFL and ganglion cell complex can provide more reliable and objective parameters for glaucoma assessment. However, they are still not sensitive enough to detect early glaucoma and only moderately correlate with VF loss.[144,145] There is a growing body of evidence suggesting that vascular alterations are a major contributor in the pathophysiology of primary open-angle glaucoma (POAG).[146,147] OCTA demonstrated its ability to visualize and reliably quantify optic nerve head (ONH) vasculature.[14,148] Jia *et al.* reported a decrease of 25% in flow index of ONH in glaucomatous patients, with 100% sensitivity and specificity and strong correlation with VF pattern standard deviation (PSD).[17] Subsequent studies confirmed the ability of OCTA ONH perfusion parameters in detecting glaucoma and their association with structural and functional glaucomatous damage [Figure 5].[149-152]

The glaucomatous loss of retinal ganglion cells and their axons in NFL is also associated with a reduction in perfusion.[153,154] Liu *et al.* were the first to use OCTA to demonstrate vascular changes in the peripapillary retina.[22] A significant reduction in peripapillary flow index and vessel density was reported in glaucomatous patients. The changes were found to be highly correlated with structural OCT changes,[155,156] as well as functional VF PSD and mean deviation (MD).[22] Moreover, the correlation of glaucoma stage[157] with peripapillary OCTA measurements was higher than VF PSD or MD.[22] OCTA parameters could differentiate glaucoma suspects from both healthy subjects and confirmed glaucoma
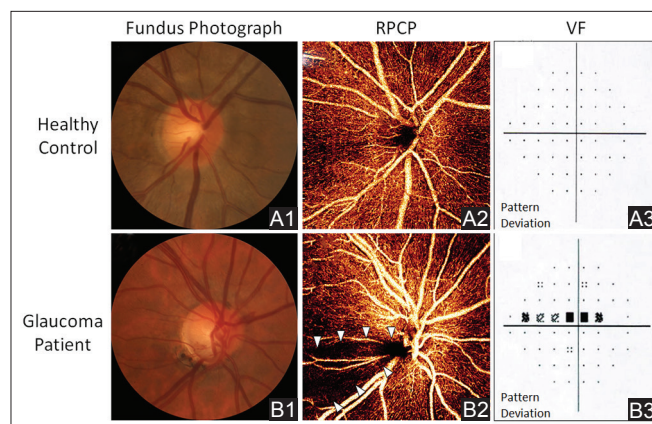
patients.[155,158] In addition, sectoral analysis of the retinal peripapillary region identified a significant association of microvascular impairment with VF defects.[159,160]

Changes in the lamina cribrosa have long been suggested to be associated with the pathophysiology of glaucoma.[161-164] Suh *et al.* used both SD-OCTA and structural SS-OCT to investigate the peripapillary microvasculature of glaucomatous patients with and without lamina cribrosa defects.[165] Vessel density in the peripapillary region was found to be lower in the group with lamina cribrosa damage. Moreover, a spatial correlation was observed between the regions of the lowest microvascular impairment and the location of lamina cribrosa defects.[165] These findings highlight the possible causal relationship between lamina cribrosa defects and retinal microvasculature abnormalities.

Primary angle-closure glaucoma

Retinal perfusion in primary angle-closure glaucoma (PACG) has been studied and reported by Jiang and Sun using OCTA.[166] Compared to a control group, PACG eyes that have just recovered from an acute attack showed significantly decreased vessel density in the peripapillary regions, despite having normal RNFL thickness. In addition, peripapillary retinal perfusion was compared between POAG and PACG eyes with similar VF defects. The decrease in vessel density in PACG was found to be more evenly distributed throughout the peripapillary region. On the other hand, POAG eyes showed significantly lower perfusion in the inferotemporal region, which corresponds to the frequent superonasal VF damage in POAG.[167]

Jiang and Sun also compared retinal and ONH perfusion between normal eyes and PACG eyes of different levels of intraocular pressure (IOP) control (well-controlled and poorly controlled).[166] They reported significantly reduced ONH, peripapillary, and parafoveal vessel density in PACG eyes. However, the decrease was greater in the peripapillary region than the parafoveal region. Moreover, poorly controlled IOP eyes showed significant reduction in ONH and peripapillary vessel density, but not in the parafoveal retina. These observations indicate that optic nerve perfusion is more significantly impaired by elevated IOP.[166]

Multiple sclerosis

Detection of NFL loss using OCT is a well-documented structural parameter in multiple sclerosis (MS) patients with and without optic neuritis.[168,169] OCT findings showed high correlation with functional measurements and were predictive of the clinical visual outcome.[168] Furthermore, OCTA measurements in MS patients detected retinal vascular impairment. Wang *et al.* reported significant decrease of ONH flow index in MS

Figure 5: The right eyes of a healthy subject (a) and primary open-angle glaucoma patient (b). Focal capillary dropout in the infratemporal area is apparent in the *en face* optical coherence tomography angiography of the radial peripapillary capillary plexus of the glaucoma patient (B2, white arrowheads). The optical coherence tomography angiography lesions matched with the visual field defect (B3)

patients with a history of optic neuritis compared to healthy controls or MS patients without ON.[16] On the other hand, no significant changes were observed in the parafoveal region.[16] These findings demonstrate the usefulness of OCTA in studying vascular abnormalities associated with MS.

Current Limitations and Potential Solutions

OCTA has many advantages over the traditional angiography techniques. However, it has certain technical restrictions. One limitation is the relatively small field of view of current commercial OCTA systems, which restricts imaging to the posterior pole. This limits its usefulness in diseases such as DR, which can affect the peripheral retina more severely in some patients. The field of view limitation will ease with the development of higher speed OCT systems capable of wide-field OCTA scans without sacrificing sampling density. The development of automated image stitching algorithms will allow for more efficient montaging of multiple scans of adjacent areas to produce even wider OCT angiograms of the retina. Other limitations include artifacts that interfere with image interpretation–flow projection, shadow, motion, and signal strength variation. Improvement of processing algorithms will be needed to reduce these artifacts and improve the reliability of vessel density, vessel area, and flow measurements.

The 3D nature of OCTA allows for more comprehensive visualization and quantification of ocular microvasculature. However, accurate segmentation is required for proper interpretation of ocular pathologies. Improvements in the accuracy of automated segmentation, as well as detection and quantification of pathologies, will make OCTA easier and more efficient to use in clinical settings.

Conclusion

OCTA has distinct advantages over FA and ICGA in the evaluation of retinal and optic nerve diseases. It provides noninvasive simultaneous 3D structural and blood flow information, allowing for comprehensive evaluation of disease presentation and progression. In addition, the ability to quantify angiographic information allows for objective monitoring of treatment response. Because OCTA is a novel imaging modality, it is still unclear how we should use it in the disease management. However, it has already improved the visualization of pathologies that were previously difficult to assess, such as capillary dropout in different retinal plexuses in glaucoma and DR, occult and nonexudative CNV, and the rapid dynamics of CNV flow response to anti-VEGF therapy. More clinical experience and research are needed to establish the use of OCTA findings for clinical decision-making. With the expected technological improvements in the near future, we believe OCTA will become an important tool in standard eye care.

Conflicts of interest
Oregon Health & Science University (OHSU), Yali Jia and David Huang have a significant financial interest in Optovue, Inc., a company that may have a commercial interest in this technology. These potential conflicts of interest have been reviewed and managed by OHSU. David Huang receives patent royalties from Carl Zeiss Meditec, Inc. Other authors do not have financial interest in the subject of this article.

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