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An overview of optical coherence tomography angiography and the posterior pole

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Abstract: Optical coherence tomography angiography is a relatively new, noninvasive technology that has revolutionized imaging of the retinal and choroidal microvasculature. This technology is based on the detection of movement or changes that represent moving red cells in sequential optical coherence tomography scans. As with other established imaging technologies, it has unique benefits as well as certain disadvantages, which include a limited field of view and vulnerability to imaging artifacts. However, software and hardware improvements are continually evolving to mitigate these limitations. Optical coherence tomography angiography has been used to gain a better understanding of microvascular changes across a spectrum of ocular diseases including diabetic retinopathy, age-related macular degeneration, glaucoma, and retinal vein occlusions. In this article, we review algorithms and techniques commonly utilized in optical coherence tomography angiography systems and compare optical coherence tomography angiography to fluorescein angiography, the current gold standard for imaging the retinal vasculature. In addition, we provide an overview of important optical coherence tomography angiography findings in a variety of ocular diseases. Although the clinical role of this technology is still poorly defined, optical coherence tomography angiography has the potential to become an invaluable tool in the diagnosis and monitoring of vascular pathologies.

Keywords: age-related macular degeneration, diabetic retinopathy, optical coherence tomography angiography, retinal imaging, retinal segmentation, retinal vein occlusion

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Introduction

Optical coherence tomography (OCT) is a technology that has revolutionized the field of ophthalmology. Introduced in the early 1990s, it has firmly established itself as one of the most prominent and useful imaging modalities over the last several decades. Using noninvasive low-coherence interferometry, OCT provides high-resolution two-dimensional (2D) images of the retinal structure *in vivo*.[1,2] Along with developments in OCT technology such as spectral-domain OCT, improvements in acquisition speed and hardware have facilitated advanced imaging applications such as OCT angiography (OCTA), which would not have been possible with the original OCT technology, time-domain OCT.[3]

In general, OCTA images blood flow through detecting changes in reflectivity, thought to be related to red blood cell movement, facilitated by scanning the same location over time. Since it was first demonstrated in living patients,[4] this promising concept has undergone significant improvements culminating in Food and Drug Administration (FDA) approval of the first commercial OCTA device in 2016.

Despite its infancy, OCTA has all the makings of a paradigm-changing technology for noninvasive ocular imaging. Since it is based on flow motion detection, there is no need for contrast dye injections that can be associated with rare but serious adverse reactions that range from nausea to full

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anaphylaxis.[5,6] In addition, fast acquisition times allow OCTA imaging to be acquired in seconds compared to the 10–30 min required by traditional gold standard imaging such as fluorescein angiography (FA).[7] Importantly, OCTA also offers the unique opportunity to resolve the individual retinal plexuses and thereby study the differential involvement of each capillary layer in a number of ocular and systemic diseases.[8,9]

The goals of this OCTA review article are to provide a brief overview of the various algorithms and techniques utilized in the OCTA devices currently available on the market and to discuss recent and notable OCTA findings in several diseases of the posterior pole.

Principles and techniques

Noninvasive imaging of ocular perfusion using Doppler OCT was first introduced in the mid 1990s.[10] While it was a revolutionary concept, this technology suffered from inherent drawbacks including an inability to detect blood flow perpendicular to the OCT beam as well as vulnerability to sample motion.[11] As a result, other OCT software algorithms for angiographic imaging were developed over the following decades, including split-spectrum amplitude-decorrelation angiography (SSADA) and optical microangiography (OMAG). These algorithms exploit differences in OCT signal phase, intensity, or a combination of the two in order to generate the angiograms.

SSADA is the algorithm currently utilized in the OCTA device RTVue XR Avanti manufactured by Optovue, Inc. (Fremont, CA, USA), which detects the differences in OCT signal intensity to represent flow.[12] As with other OCTA techniques, SSADA relies on the comparison of sequential OCT B-scans for the detection of blood flow. Static tissues are highly correlated, whereas moving erythrocytes cause changes in reflectance between consecutive scans and are therefore highly decorrelated. Uniquely, SSADA splits the spectrum of light into multiple spectral bands, calculates the decorrelation of each band separately, and then averages the results. This leads to an increased signal-to-noise ratio and the ability to produce angiograms using only two consecutive OCT B-scans.[3,13] As a result, SSADA has an axial resolution that is approximately three times lower than standard OCT (approximately 15 μm),[11,14] but also has a decreased susceptibility to bulk motion.

OMAG is another algorithm that is implemented in the AngioPlex system by Carl Zeiss Meditec AG (Jena, Germany). This approach analyzes both the amplitude and phase differences in the OCT signal to generate the angiograms. One distinct advantage is the use of the entire spectrum without loss of axial resolution, but it has the disadvantage of requiring more than two sequential scans to generate the angiogram.[15–17]

Briefly, OCTA ratio analysis (OCTARA) is a separate algorithm developed by Topcon Corp (Tokyo, Japan), which uses a ratio method that is not based on amplitude decorrelation. Notably, this approach also does not require splitting of the full spectrum, resulting in preservation of axial resolution.[18,19] This algorithm is paired with swept-source OCT (SS-OCT) in the Topcon DRI-OCT Triton SS-OCT system.

Artifact

An important limitation of OCTA is its unique susceptibility to imaging artifacts, which have been characterized by Spaide and colleagues.[20] These artifacts include motion artifacts, a result of microsaccades and breathing, and projection artifacts, where flow in the superficial retinal vasculature is projected onto the underlying structures. Projection artifacts appear as long flow tails underneath the superficial vessels on cross-sectional OCTA images and can give the appearance of flow in areas where there should be none.[21] These artifacts can often be magnified by hyperreflective material such as hard exudates or pigment migration.[22]

In general, platforms have integrated real-time eye tracking systems, such as FastTrac™ (Carl Zeiss Meditec AG (Jena, Germany)). and SMARTTrack™ (Topcon Corp.), that compensate for eye movement and blinking,[19,23] a concept that was introduced over a decade ago.[24] Optovue, Inc. instead utilizes a two-level approach with their DualTrac™ software, which incorporates eye tracking along with an orthogonal registration algorithm called motion correction technology (MCT).[23] Their use of SSADA also mitigates effects of movement in the axial direction from microsaccades and pulsations during the cardiac cycle due to the lower axial resolution and subsequent higher signal-to-noise ratio.[20]

Projection artifact in commercial OCTA systems has typically been addressed using a slab-subtraction

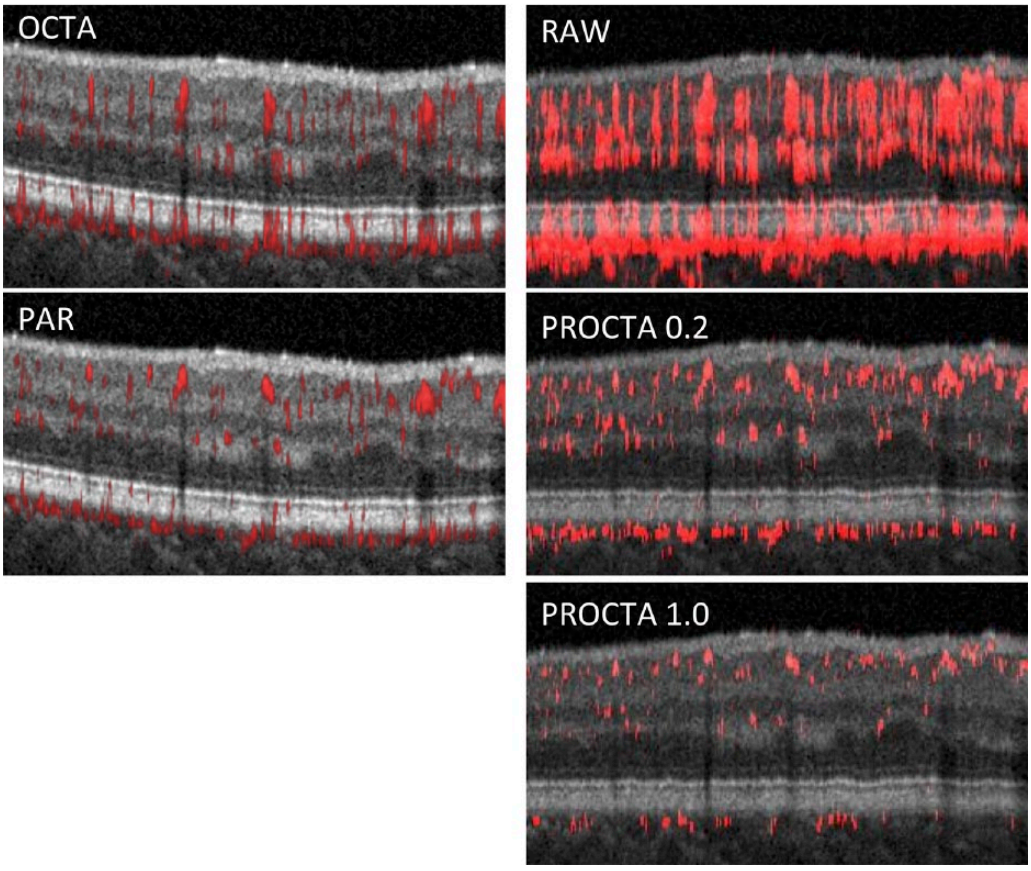

Figure 1. Projection artifact and correction with projection artifact removal (PAR) and projection-resolved OCTA (PR-OCTA). (Top left) Optovue AngioVue OCTA B-scan and (top right) OCTA B-scan with raw angiographic overlay. Note the significant projection artifact visible as long tails of apparent flow projecting from areas of real flow located superficially. (Middle left) default PAR. (Middle right and bottom right) PR-OCTA with increasingly stringent removal of projection artifact (α=0.2 and 1.0).
OCTA: optical coherence tomography angiography.

algorithm.[19,25,26] This technique subtracts the superficial vascular pattern from the outer retina, thereby removing projection artifact but often causing an undesirable negative artifact.[21] More recently, a new algorithm called projection-resolved OCTA (PR-OCTA) was introduced by Zhang and colleagues.[27] This algorithm interprets high decorrelation-value peaks as real vessels while removing lower decorrelation-value signal as projection artifact and has successfully been used to study the retinal vasculature in healthy and diseased eyes.[21,28–30] Larger values of an empiric parameter, α (range between 0 and 1), result in a higher threshold for decorrelation values for interpretation as flow and therefore less artifact. Subsequently, Optovue, Inc. incorporated their own proprietary three-dimensional (3D) projection artifact removal (PAR) technique into their AngioVue software. PAR is distinct from PR-OCTA and has also been shown to be effective in mitigating projection artifact in healthy eyes[31] (Figure 1).

Segmentation

OCTA has sparked interest in the retinal capillary layers because of its unique ability to optically section the distinct networks. More recently, studies using segmentation schemes to separate the inner retinal circulation into three layers have become commonplace (Figure 2). This approach is based on histologic reports that have demonstrated the existence of four distinct capillary planes in the perifoveal retina[32] that form three capillary plexuses: the superficial capillary plexus (SCP), middle capillary plexus (MCP), and deep capillary plexus (DCP). The SCP is found in the nerve fiber and ganglion cell layers, the MCP is located between the inner plexiform layer (IPL) and inner nuclear layer (INL), and the DCP is

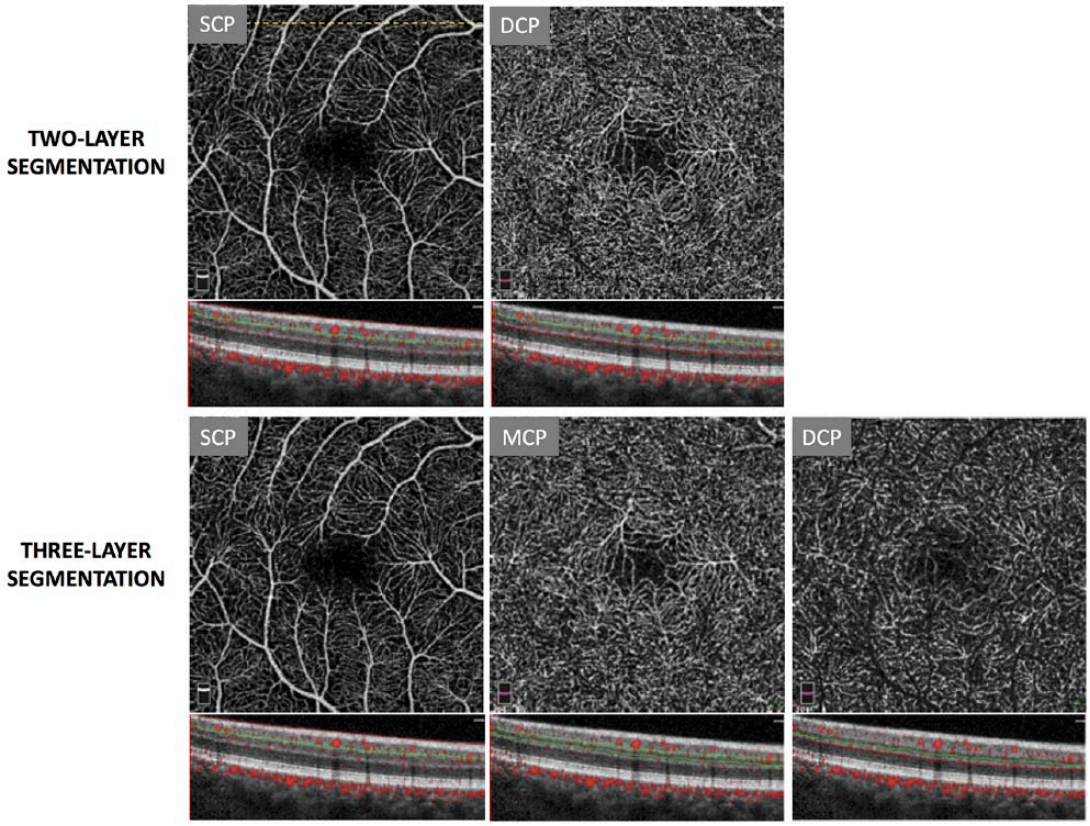

Figure 2. Inner retinal segmentation schemes in a healthy eye using the Optovue OCTA system. The top row displays en face images and B-scans from default segmentation of the inner retina into the superficial capillary plexus (SCP) and deep capillary plexus (DCP). The dashed line demarcates the location of the B-scans used in the figure. The bottom row displays en face images and B-scans from inner retinal segmentation into the SCP, middle capillary plexus (MCP), and DCP using manufacturer-recommended custom boundaries. Figures are created with images using default Optovue Projection Artifact Removal (PAR; AngioVue Analytics Version 2017.1.0.151).
OCTA: optical coherence tomography angiography.

present between the INL and outer plexiform layer (OPL). OCTA has successfully and consistently been used to visualize these three capillary layers,[8,21,31,33,34] leading to deeper insights into their structure and connectivity. For example, while there has been debate regarding previously proposed theories of parallel or serial connections between the layers,[28,35] Nesper and colleagues[36] have found evidence supporting a hybrid model of connectivity using OCTA.

Other common predefined OCTA segmentation slabs include the outer retina, which is normally an avascular area with any apparent flow being the result of pathology or projection artifact,[28] and the choriocapillaris. OCTA offers a rare opportunity to visualize the choriocapillaris *in vivo*, as it is more difficult to study in detail using FA and indocyanine green angiography (ICGA).[37] However, image quality of the choriocapillaris remains limited by low lateral resolution as well as susceptibility to projection artifact and shadowing artifact from overlying pathology such as large drusen.[20,38]

While automated segmentation is a helpful starting point, manual adjustment of the segmentation lines is often necessary to correct for segmentation errors that are relatively common in the setting of retinal pathology.[39]

Comparison to FA

Major advantages of OCTA over FA include its quick imaging time, noninvasiveness, and lower cost.[14,40] However, FA is a well-established imaging modality that is still the gold standard for multiple conditions including choroidal neovascularization

(CNV) and retinal neovascularization (NV).[41–43] Benefits of this technology include a wide field of view, visualization of flow from retinal arterioles to venules, and accurate identification of exudates or leakage (which OCTA is unable to detect).

The field of view in FA (50°, 120°, or 200°) is significantly larger than the 3 × 3 mm^2 area (~7°) traditionally used in OCTA.[44] However, these larger fields of view have lower resolution than 3 × 3 mm^2 OCTA scans, making identification of microvasculature dysfunction in conditions such as diabetes more difficult.[45,46] In addition, with developments in OCTA hardware and software, larger imaging areas up to 12 × 12 mm^2 have become possible with commercial OCTA systems. Techniques like extended field imaging using 20 diopter lenses, as well as image montaging, can increase the field of view even further while preserving detail to become comparable if not superior to that of FA.[40,47,48] Furthermore, OCTA has been found to be superior to FA for visualization of the deeper retinal microvasculature.[49,50]

Study of posterior pole disease

Diabetic retinopathy

Numerous OCTA measures including vessel density, perfusion density, and vessel diameter index have been developed and studied for diabetic retinopathy (DR). Changes in these measures of vascular function have almost universally been shown to correlate with increasing severity of DR and worsening visual acuity, thereby suggesting a promising role for OCTA in the monitoring of disease progression.[9,33,45,51–54] In addition, OCTA parameters such as foveal avascular zone (FAZ) area have been reported to be enlarged in diabetic eyes prior to the development of clinically apparent DR, thereby indicating value as a potential screening tool.[55] Of note, the derivation of many of these measures requires the use of third-party software such as ImageJ (developed by Wayne Rasband, National Institutes of Health, Bethesda, MD, USA) or MATLAB (MathWorks, Natick, MA, USA).

OCTA has been found to be superior to FA in delineating the microvasculature, allowing an improved visualization of capillary dropout and changes in the FAZ.[56] However, while Ishibazawa and colleagues have reported that OCTA can be useful in identifying microaneurysms and retinal perfusion deficits, La Mantia and colleagues[57] have shown FA to be more effective in visualizing microaneurysms relative to OCTA. This is more consistent with other OCTA reports[58,59] and can be explained by the relative insensitivity of OCTA to slow flow[60] (Figure 3).

Additional benefits of wide-field OCTA are still being explored by numerous researchers. Sawada and colleagues[61] and Hirano and colleagues[40] have directly compared wide-field OCTA to FA, showing a high sensitivity and specificity of OCTA for retinal nonperfusion areas (NPAs) and retinal NV. Both studies utilized 12 × 12 mm^2 SS-OCTA scans, although the study by Hirano and colleagues was enhanced with extended field imaging to offer an even greater field of view. In the report by Sawada and colleagues, the sensitivity and specificity of OCTA for NPA were 0.98 and 0.82, respectively, with the sensitivity and specificity for NV being 1.0 and 0.97, respectively. Hirano and colleagues reported a sensitivity and specificity of 0.96 and 1.0 for NPA and a sensitivity and specificity of 0.79 and 0.96 for NV, respectively. Separately, Schaal and colleagues[62] compared widefield OCTA imaging to color fundus photography and reported an increased detection rate for intraretinal microvascular abnormalities with OCTA.

Age-related macular degeneration

OCTA is an effective tool for the identification of CNV associated with neovascular age-related macular degeneration (AMD),[26,63] although reported sensitivities and specificities of OCTA have varied.[64] This may be due to differing study distributions of type 1 and type 2 CNV, which appear to be more readily apparent on OCTA than Type 3 CNV and polypoidal complexes.[64]

Given its high level of image detail, OCTA has been advantageous in the study of the structure of CNV and its changes in response to antiangiogenic agents. Different morphologic appearances of CNV have been described, including ‘medusa’ and ‘sea-fan’ forms, which generally consist of smaller vessels radiating from a larger feeder vessel.[65] These larger vessels remain stable despite changes in lesion size with antiangiogenic treatment.[64]

Multiple studies have been conducted to identify OCTA biomarkers for CNV activity. Souied and colleagues found that active CNV lesions

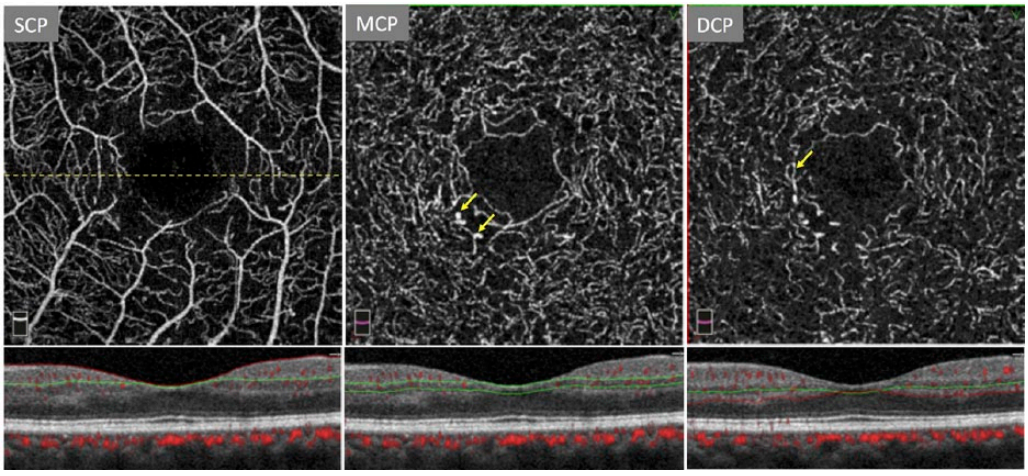

Figure 3. Three-layer segmentation in a patient with proliferative diabetic retinopathy. The dashed line denotes location of B-scan used in the figure. Note the enlarged foveal avascular zone (FAZ). Arrows mark vascular abnormalities such as microaneurysms and dilated capillary loops. Figure created with images using default Optovue Projection Artifact Removal (PAR; AngioVue Analytics Version 2017.1.0.151).
DCP: deep capillary plexus; MCP: middle capillary plexus; SCP: superficial capillary plexus.

requiring treatment were more likely to have a combination of high-risk features including a well-defined shape (lacy-wheel or sea-fan shaped), branching of many small capillaries, the appearance of anastomoses and loops, the presence of a peripheral arcade at the vessel termini, and the presence of a hypointense halo surrounding the lesion on OCTA.[66] In their study of type 1 CNV, Al-Sheikh and colleagues[67] similarly found that branching of small vessels and the presence of peripheral arcades were more prevalent in active *versus* quiescent lesions and also reported that fractal dimension (a measure of complexity of CNV lesions) was significantly different between active and quiescent lesions. Other OCTA indicators of long-term growth of type 1 CNV lesions include the presence of a network of tiny capillaries at the border of the CNV lesion, as well as a lack of mature dilated feeder vessels.[68]

The ability of OCTA to analyze lesions three-dimensionally may be important in the study of neovascular AMD as well. Recent work by Nesper and colleagues[69] demonstrated the novel use of 3D volume-rendered PR-OCTA in the characterization of complex CNV lesions. After examining parameters such as the number of CNV flow layers, they found that increasing complexity of the lesions was associated with poor treatment response to antiangiogenic agents. Further investigation using OCTA could potentially lead to the development of accurate predictors of treatment response in CNV and could validate the use of similar 3D approaches in the study of other diseases.

Prior to the availability of OCTA, imaging of subclinical NV (defined as asymptomatic CNV prior to the development of exudation) in dry AMD using ICGA was limited by cost, invasiveness, and an overall limited understanding of the significance of these lesions. More recently, de Oliveira Dias and colleagues[70] found that 21.1% of patients with subclinical CNV found on baseline OCTA imaging demonstrated exudation within 1 year, compared to 3.6% of those eyes without subclinical NV at baseline. In general, eyes with subclinical CNV had an approximately 15 times greater risk of exudation than those eyes without NV. As a result, this noninvasive and time-efficient technology may be critical as a tool for screening and monitoring subclinical CNV (Figure 4).

OCTA has also been used to study drusen-associated atrophy and geographic atrophy (GA) in dry AMD. Imaging of the choriocapillaris is inherently more difficult due to factors including its location beneath the highly reflective retinal pigment epithelium (RPE).[71] However, OCTA reports have consistently demonstrated significant impairment of choriocapillaris perfusion in areas of GA, as well as diffuse choriocapillaris dysfunction outside the margins of atrophy.[72,73] Interestingly, using OCTA, Pellegrini and colleagues[74] found that the choriocapillaris is still present in regions of RPE loss in GA, but is rarefied.

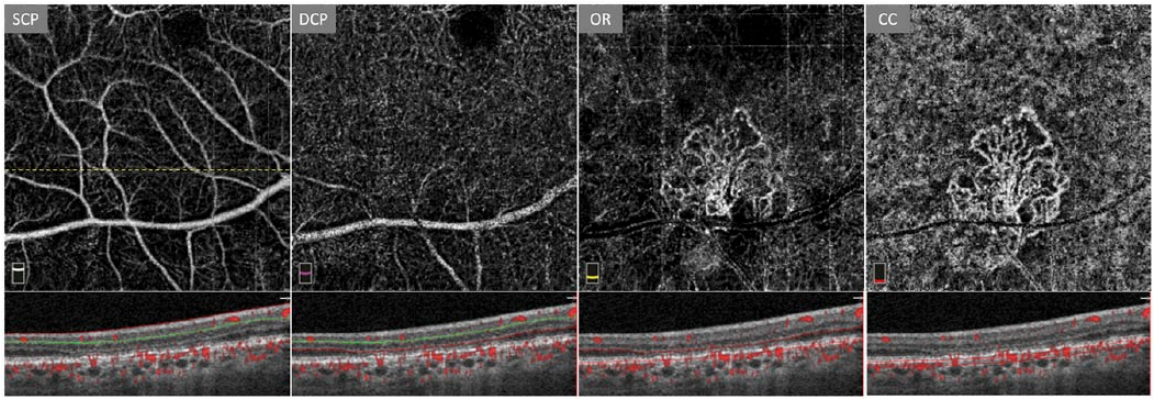

Figure 4. Default segmentation of an eye with age-related macular degeneration displaying a subclinical choroidal neovascular membrane in the outer retinal slab (OR). Dashed line indicates location of B-scan used in the figure. Note the lack of edema or exudate as well as the overlaid angiographic flow signal within the boundaries of the B-scan. Figures are created with images using default Optovue Projection Artifact Removal (PAR; AngioVue Analytics Version 2017.1.0.151).
CC: choriocapillaris; DCP: deep capillary plexus; SCP: superficial capillary plexus.

Retinal vein occlusion

Retinal vein occlusion (RVO) has been a highly active area of research using OCTA. Reports have shown significant changes in vascular measures such as fractal dimension and vessel density in eyes with RVO compared to healthy eyes, as well as correlations with increasing severity of RVO.[75] Other parameters such as FAZ area have been found to be enlarged in RVO (as well as in fellow unaffected eyes) compared to healthy controls on OCTA,[76] and changes in these markers have been demonstrated to be associated with worsening visual acuity.[77,78] Derivation of the aforementioned parameters requires postacquisition image analysis using third-party software such as ImageJ and Matlab.

While FA is still the gold standard imaging modality for RVO,[79,80] OCTA has been found to be comparable to FA in identifying capillary nonflow and changes such as dilations and telangiectasias.[81] Dysfunction of retinal peripheral perfusion on FA has also been shown to be significantly associated with changes in OCTA quantitative parameters.[82] Using OCTA to resolve the different capillary plexuses, Adhi and colleagues[76] identified more severe perfusion deficits at the level of the DCP in central and branch RVO, which is consistent with the data from other studies.[83,84] Another interesting finding is that FAZ areas are significantly enlarged only at the level of the DCP in branch RVO compared to nonaffected fellow eyes[78] (Figure 5).

OCTA has also demonstrated possible utility in the clinical setting as an imaging modality for the follow-up of treatment of RVO. In their study, Sellam and colleagues[85] used OCTA in RVO patients before and after intravitreal antivascular endothelial growth factor injections and found that significant decreases in retinal fluid, capillary disruption, and capillary cysts could be visualized post intervention.

Glaucoma

Although the exact pathophysiologic process of glaucoma is unknown, there is convincing evidence that vascular dysfunction contributes to the progression of the disease.[86–89] For that reason, OCTA has been a popular tool for the study of the microvasculature in glaucoma, with the majority of these reports examining the peripapillary region. Generally, these studies have found vascular dysfunction in glaucomatous eyes compared to healthy controls.[90–93] Optic disk flow index, the average decorrelation signal in OCTA, has previously been shown to have high sensitivity and specificity for glaucoma and to be highly correlated with visual field pattern standard deviation.[94] Peripapillary perfusion deficits have also been shown to be associated with structural changes in glaucoma on OCTA.[93] Those OCTA studies examining vascular changes in the macula have identified similar dysfunction in retinal blood flow and perfusion.[95–98]

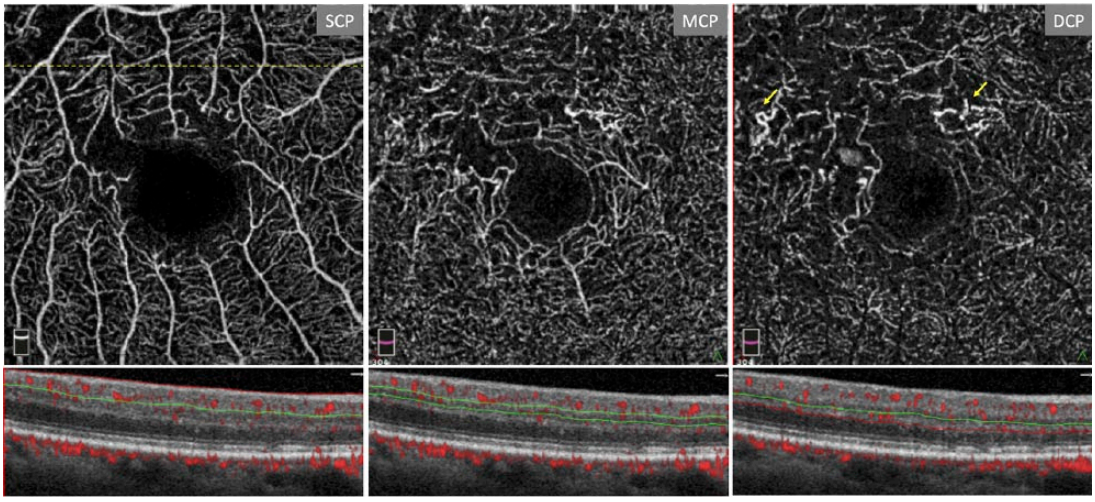

Figure 5. Three-layer capillary segmentation of a case of long-standing superotemporal branch retinal vein occlusion (BRVO) of the right eye. The dashed line indicates location of B-scan used in the figure. Enlargement of the foveal avascular zone (FAZ) is visible. Arrows demarcate capillary abnormalities. Note that these abnormalities and capillary dropout appear to be more severe in the deeper capillary layers. Figures are created with images using Optovue Projection Artifact Removal (PAR; AngioVue Analytics Version 2017.1.0.151).
DCP: deep capillary plexus; MCP: middle capillary plexus; SCP: superficial capillary plexus.

OCTA reports have suggested that quantitative OCTA parameters such as vessel density could eventually be used for the diagnosis of glaucoma. Takusagawa and colleagues[96] demonstrated a high area under the receiver operating characteristic curve (AUC) of 0.961 using superficial macular vessel density for glaucoma, consistent with a similar report by Richter and colleagues[95] who identified an AUC of 0.83 for the macular microvasculature. However, there has been some controversy as to the area of choice as Rao and colleagues[99] found that peripapillary and inside the optic disk vessel densities had higher AUC than macular vessel density.

One important unresolved question in the field relates to whether vascular changes precede structural changes or whether loss of the retinal ganglion cells and their decreased metabolic need leads to the reduced blood flow observed with OCTA.[100] In their longitudinal OCTA study, Shoji and colleagues[101] demonstrated that the average rate of decline in macular vessel density over the course of at least 1 year was significantly higher in glaucomatous eyes than healthy or glaucoma suspect eyes. Interestingly, these authors found no significant decline in ganglion cell layer thickness in any of the three groups over the same time period. However, they could not definitively conclude that vascular changes preceded structural changes because it is possible that neural structural changes might occur earlier in the course of glaucoma and thus would not be captured in their population of mainly moderate-severity glaucoma. Further carefully detailed longitudinal and multimodal structure and function studies involving OCTA will be required to settle this chicken-or-egg debate.

Acute macular neuroretinopathy, paracentral acute middle maculopathy, and disorganization of the retinal inner layers

OCTA offers an exciting opportunity for further investigation into acute macular neuroretinopathy (AMN), paracentral acute middle maculopathy (PAMM), and disorganization of the retinal inner layers (DRIL), which manifest on OCT as disruption of the retinal architecture, given their postulated relationship with inner retinal ischemia. However, due to the rarity of these entities as well as the difficulties of segmentation in these conditions, the quality of evidence of the OCTA studies discussed in this section is relatively low and consists mainly of small descriptive studies and case reports.

AMN is a rare retinal disease that classically presents with initial OPL and outer nuclear layer (ONL) hyperreflectivity on spectral domain-OCT. These

changes are followed by eventual disruption of the outer segment/RPE lines correlating to hyporeflective lesions on infrared (IR) imaging and further progression to long-term findings such as thinning of the ONL.[102] PAMM is a similar but distinct condition and presents with middle retinal involvement manifesting as initial IPL and INL hyperreflectivity followed ultimately by INL thinning.[103]

AMN and PAMM are both thought to be associated with retinal capillary ischemia, although there is still controversy over the specific plexuses affected. Fawzi and colleagues[102] originally postulated that DCP ischemia was responsible for the adjacent lesions of AMN, which has since been demonstrated in several studies.[104,105] Choriocapillaris nonperfusion has also been reported in AMN,[106,107] although these findings are potentially confounded by choriocapillaris artifact as well as the use of larger OCTA scan sizes with limited density and resolution of the retinal capillaries.[108] More recently, Casalino and colleagues[109] have reported focal DCP involvement correlating with AMN lesions as well as decreased global choriocapillaris flow. While MCP and DCP nonflows have been hypothesized to cause PAMM,[110] there have been disagreements due to reports of perfusion abnormalities in the SCP and DCP.[111]

OCTA imaging is particularly difficult in AMN and PAMM given focal thinning and hyperreflectivity of the retinal layers, which can, respectively, lead to segmentation errors and exacerbation of projection artifact and can potentially explain the previously reported conflicting findings. Using PR-OCTA to mitigate these artifacts, Chu and colleagues[112] have shown that AMN is associated with DCP ischemia, while PAMM is associated with MCP and DCP ischemia with occasional SCP perfusion deficits. Improved software algorithms are needed to lead to better consensus in the field regarding inner retinal blood flow changes in AMN and PAMM.

DRIL is a retinal biomarker first described by Sun and colleagues[113] that also appears to be associated with inner retinal ischemia.[114] DRIL is defined as the absence of distinguishable boundaries between the ganglion cell–IPL junction, INL, and OPL and is usually reported in eyes with macular edema.[113,115,116] Moien and colleagues[117] have used OCTA with a two-layer segmentation scheme and found enlargement of the FAZ as well as ischemia in the superficial, deep, and full retina in eyes with DRIL. Using PR-OCTA as well as a three-layer segmentation scheme, Onishi and colleagues[30] were able to further localize these perfusion deficits to the SCP or MCP in addition to underlying DCP ischemia present in areas of DRIL.

The complexity of perfusion deficits at multiple capillary levels on a 3D basis in these entities emphasizes the importance of OCTA and algorithms such as PR-OCTA in the study of macular ischemia at the capillary level.

Posterior uveitis. OCTA has been shown to be a useful research tool and potential clinical adjunct in inflammatory eye disease. FA can provide valuable information about active areas of inflammation in retinal vasculitis by displaying vessel wall staining and leakage, but this leakage may prevent visualization of the adjacent vasculature that may therefore only be assessed with OCTA.[118] In addition, OCTA can help identify complications such as inflammatory CNV, which mostly affects the macula and can lead to severe vision loss.[119] While dye-based imaging is often helpful for identification of these neovascular membranes, there is also overlap with inflammatory lesions.[118,119] Additional OCT imaging may be useful as it can show subretinal hyperreflective tissue that is consistent with CNV, but can also be seen with other conditions like fibrosis.[118]

The highly detailed images and depth-resolved quantitative data regarding retinal perfusion contributed by OCTA provides information that may not be possible with other imaging modalities. For example, a case report by Pichi and colleagues[120] was the first to report NV within a foci of retinochoroiditis secondary to *Bartonella henselae* with OCTA that was not seen on FA. With their cohort of uveitic eyes, Kim and colleagues[121] used a two-layer segmentation scheme to show that parafoveal vessel density and fractal dimension in the SCP and DCP were lower in uveitic eyes compared to healthy eyes. In the same study, these authors found that uveitic eyes with macular edema had significantly lower DCP vessel densities (with no significant difference in SCP vessel densities) compared to uveitic eyes without edema, thus potentially implicating DCP ischemia in the development of cystoid macular edema.

OCTA has been helpful in the study of conditions such as birdshot chorioretinopathy (BSCR). de

Carlo and colleagues[122] used OCTA to study eight eyes of patients with BSCR and identified abnormalities such as inner retinal telangiectatic vessels and increased intercapillary space. These areas of decreased SCP perfusion have been found to correlate with central retinal thinning,[123] raising the possibility that ischemia could contribute to ganglion cell damage and the macular thinning that has been observed in BSCR,[118] although prior studies have shown that the majority of thinning is in the outer retina.[124] In a patient with BSCR complicated by retinal NV and vitreous hemorrhage, Sarraf and colleagues found more profoundly impaired vessel densities in the DCP than the SCP compared to age-matched normal eyes, indicating that both ischemia and inflammation may contribute to the development of retinal NV in BSCR.[125]

Value of OCTA beyond the role of FA and ICGA. Given the ease and noninvasive nature of OCTA imaging in relation to conventional angiography, OCTA can be used to study changes in the retinal vasculature in conditions and procedures where angiographic imaging would not traditionally be indicated. For example, multiple authors have examined changes in the FAZ in vitreomacular interface disorders such as macular holes and epiretinal membranes (ERM). In their retrospective study, Baba and colleagues[126] reported that superficial FAZ area was significantly reduced in eyes following pars plana vitrectomy (PPV) with internal limiting membrane (ILM) peeling, as well as in relation to unaffected companion eyes. This decrease in superficial FAZ area was significantly associated with a higher central foveal thickness (CFT), suggesting that the process of closing the macular hole results in a movement of macular tissue centrally. These quantitative changes are consistent with subsequent studies,[127,128] although a report by Kim and colleagues[127] interestingly demonstrated an additional significant association between the FAZ area and 6-month postoperative best-corrected visual acuity (BCVA) that was not previously described (possibly due to differences in baseline subject characteristics or follow-up periods). This could indicate that eyes with smaller FAZ may have more neural tissue filling in the macular hole, thus leading to improved central visual outcomes.[127]

In their study of FAZ changes following PPV with ERM and ILM peeling, Yoon and colleagues[129] found that preoperative FAZ area was significantly smaller than in unaffected fellow eyes and that preoperative FAZ area was highly negatively correlated with CFT. Following the intervention, postoperative FAZ area was significantly increased and CFT was significantly decreased compared to preoperative measurements, providing further evidence that ERMs cause substantial foveal architectural changes that are somewhat restored by surgery. These changes in FAZ area and CFT are consistent with the results of other studies.[130,131]

Importantly for ERM patients, preoperative parameters involving the FAZ area may also be predictive of vision postoperatively. For patients with a unilateral idiopathic ERM, the preoperative FAZ area interocular ratio has been found to be significantly correlated with the degree of aniseikonia following surgical intervention.[132] The authors postulated that this ratio compensates for variability in the FAZ area between individuals and is an indicator of centripetal contraction, which may lead to the changes in INL thickness that have been shown to be significantly associated with metamorphopsia. Postoperative FAZ area (along with CFT) has also been shown to be negatively correlated (CFT is positively correlated) with postoperative LogMAR BCVA, suggesting that restoration of the normal foveal morphology is important for the recovery of visual acuity.[131] These quantitative OCTA measures should be studied further as they may provide valuable prognostic information for surgical interventions in the future.

Future directions and conclusion

OCTA is an innovative game-changing technology that has already contributed to a greater understanding of the vascular pathologies of a variety of retinal disease. However, a clearly defined role for OCTA in the clinic is yet to be determined, and there are numerous steps that must be taken to reach that point. While normative data for healthy and diseased eyes in multiple ocular diseases have been published, more extensive databases, including racial and sex databases, are needed for the various OCTA parameters. In addition, given the increasing number of OCTA systems, cross-platform agreements are needed for sublayer segmentation.[19] Advances in software and hardware are necessary to better correct for motion and projection artifacts. The utility of SS-OCTA systems, which promise faster imaging with greater field of view and enhanced visualization of deeper retinal structures, still needs to be validated.

Since its inception, OCTA has evolved into the promising tool it is today and is continuing to improve at an incredible rate. It is positioned to establish itself as the first-line angiographic imaging modality over the course of the next decade, revolutionizing the field of ophthalmology much as the technology of OCT has done over the past few decades.[133]

Conflict of interest statement

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