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Optical Coherence Tomographic Angiography Imaging in Age-Related Macular Degeneration

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ABSTRACT: Optical coherence tomographic angiography (OCTA) is emerging as a rapid, noninvasive imaging modality that can provide detailed structural and flow information on retinal and choroidal vasculature. This review contains an introduction of OCTA and summarizes the studies to date on OCTA imaging in age-related macular degeneration.

KEYWORDS: Age-related macular degeneration, OCTA, neovascularization

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Introduction

Age-related macular degeneration (AMD) is a leading cause of irreversible vision loss worldwide and has a profound impact on the quality of life of many individuals. It is classified into 2 main types: nonexudative (also known as "dry" or "non-neovascular") and exudative ("wet" or "neovascular"). Dry AMD is characterized by drusen, retinal pigment epithelium (RPE) changes, and, in advanced forms, geographic atrophy—confluent areas of regressed drusen and RPE atrophy. Wet AMD is characterized by the development of neovascularization under the retina or RPE that results in leakage of fluid and hemorrhage in the intraretinal, subretinal, or sub-RPE space. Severe vision loss occurs primarily due to 2 processes: geographic atrophy in advanced nonexudative AMD and choroidal neovascularization (CNV) in exudative AMD culminating in fibrosis.

Advancements in imaging over the past 15 years have revolutionized the diagnosis and treatment of AMD. Imaging is especially critical at 2 junctures in the course of the disease: (1) monitoring for the development of CNV and leakage (signifying the progression to exudative AMD) and (2) monitoring the response to anti–vascular endothelial growth factor (anti-VEGF) therapy in exudative disease. Since 1961, the criterion standard for retinal vascular imaging has been fluorescein angiography (FA).[1] Traditional FA uses a fluorescent dye to visualize the retinal and choroidal vasculature. Clinically, FA images are essential in assessing the presence and extent of abnormal vascular permeability and provide the clinician with vital cues regarding the transformation from nonexudative to exudative AMD.[2] Its greatest utility is in showing dynamic changes in fluorescent patterns, such as leakage, staining, and pooling, as well as dye transit time to the eye. However, FA provides only a limited 2-dimensional (2D) depth resolution of the retinal and choroidal vasculature and poorly visualizes vessels that may be obscured by fluid, hemorrhage, pigment, RPE detachments, fibrosis, or other areas of hyperfluorescence.[2,3] Neovascular patterns under the RPE are difficult to evaluate as well. Therefore, given that changes to the retinal and choroidal vasculature are inferred as opposed to directly visualized, FA images require an experienced clinician to interpret. In contrast to FA, indocyanine green angiography (ICGA) uses a dye that does not usually leak from neovascular membranes, so it can be used to provide a more detailed image of the choroid and in particular neovascular membranes beneath the RPE, as well as in the AMD variants idiopathic polypoidal choroidal vasculopathy (IPCV) and retinal angiomatous proliferation (RAP). Both procedures involve invasive injections of dyes that can cause adverse effects ranging from nausea and vomiting to anaphylactic reactions and very rarely death.

In the past decade, optical coherence tomography (OCT) has established itself as an essential imaging modality in the diagnosis and management of AMD.[4] Optical coherence tomography is currently the primary method to monitor for structural changes, such as neovascular membranes, fibrosis, intraretinal and subretinal fluid, and pigment epithelial detachments. Exudation manifests as intraretinal and subretinal fluid and retinal thickening on OCT. Sequential OCT imaging enables clinicians to monitor response to anti-VEGF therapy in exudative AMD by following intraretinal and subretinal fluid and retinal thickening as well as pigment epithelial detachments. Optical coherence tomography is easier and faster to acquire than FA, does not require invasive injections, and provides cross-sectional and en face images of retinal and choroidal features. However, it does not provide detailed visualization of the neovascular membrane itself, and oftentimes, it can be difficult to distinguish CNV from subretinal fibrosis, fibrotic

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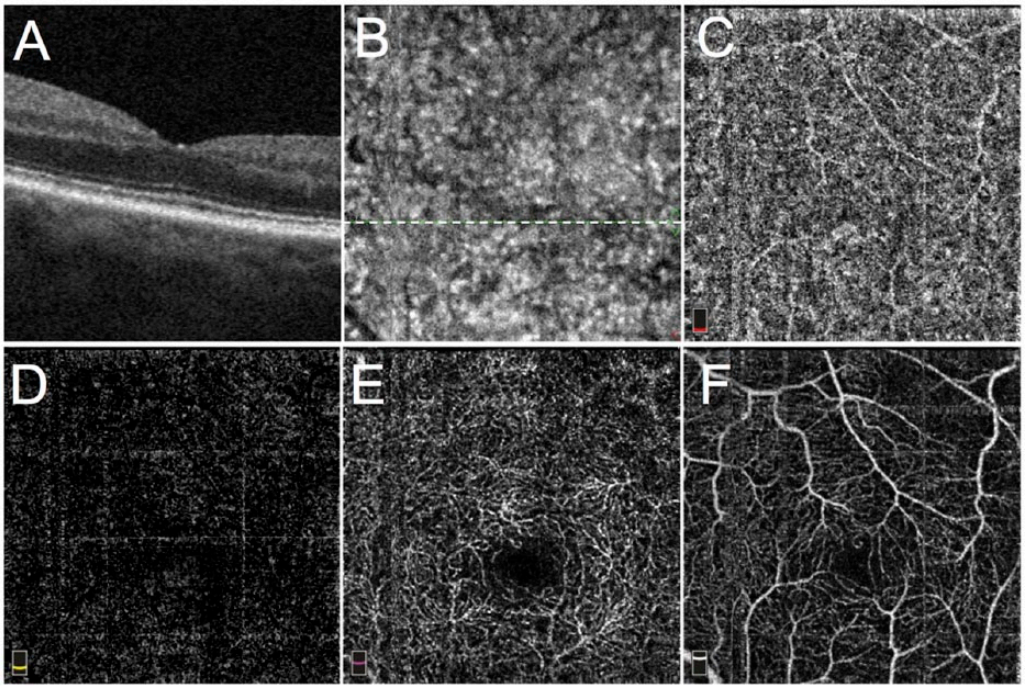

Figure 1. Optical coherence tomographic (OCT) angiography in a healthy right eye of a 74-year-old man: (A) spectral domain OCT B scan through the fovea (corresponding to the white dotted line in B), (B) en face structural OCT, (C) 3 × 3 mm spectral domain OCT angiogram of the choriocapillaris centered on the fovea (acquired using RTVue XR Avanti; Optovue Inc., Fremont, CA, USA) with split-spectrum amplitude-decorrelation angiography software, (D) OCT angiogram of the outer retina showing absence of blood flow, (E) OCT angiogram of the deep capillary plexus, and (F) OCT angiogram of the superficial capillary plexus.

pigment epithelial detachments, hemorrhage, drusenoid material, or adjacent retinal tissue, RPE, and the Bruch membrane due to similar reflectivities.[5]

Optical Coherence Tomographic Angiography

In recent years, a new imaging modality known as optical coherence tomographic angiography (OCTA) has been developed to simultaneously obtain structural images of the retina as well as assess blood flow within the retinal and choroidal vasculature without the use of intravenous agents.

Optical coherence tomographic angiography provides vascular imaging via motion contrast processing of decorrelation signals. Decorrelation signals are generated by variable signal intensities and amplitudes obtained from sequential B scans in a single area of the posterior segment.[6] After bulk axial movement has been eliminated via software, the remaining differences in signals and amplitudes of sequential B scans are thought to represent the flow of erythrocytes within vasculature. Finally, signal differences are processed by various algorithms to create a functional vascular map of the retina and choroid.

Thus far, 3 broad categories of imaging algorithms have been used: (1) phase based, (2) amplitude based, and (3) complex algorithm based (combination of phase based and amplitude based).[6] The most common algorithm in use with the current spectral domain OCTA (SD-OCTA) machine is split-spectrum amplitude-decorrelation angiography (SSADA). The SSADA algorithm, developed by Huang and colleagues,[6] optimizes the signal-to-noise ratio of flow detection to provide a higher quality image. In SSADA, bulk motion noise is significantly reduced in the axial direction, whereas flow signal remains preserved in the transverse direction, resulting in higher resolution OCTA images.[1] Using the SSADA OCTA algorithm, Huang and Bailey et al were able to demonstrate the presence of distinct superficial and deep capillary networks within the retina, as well as the absence of vascular flow in the foveal avascular zone, indicating minimal noise artifact.[6–8]

Given that OCTA technology is inherently OCT based, OCTA images are depth resolved on a micrometer scale.[9] Optical coherence tomographic angiograms can further be manually or automatically segmented with preprogrammed software to highlight individual layers of the retina, choriocapillaris, and choroid (Figure 1). The user can either analyze en face images extending from the inner limiting membrane to choroid or use automated views to locate a vascular or structural lesion within the retina.[2]

Optical coherence tomographic angiography requires higher imaging speeds than most existing clinical OCT models. The most commonly used OCTA system is the prototype RTVue XR Avanti SD-OCT with AngioVue software (Optovue Inc., Fremont, CA, USA). This system uses an 840-nm wavelength light source and obtains 304 × 304 A scans at a rate of 70 000 scans per second. The software can obtain scans ranging in size from 2 × 2 mm to 8 × 8 mm.[10]

Given that retinal capillary vessels have an average diameter of approximately 6 to 8 μm, it is important to assess the image

resolution of OCTA systems.[9] Axial resolution of OCT angiograms is determined by the bandwidth of the accompanying light source, and increasing bandwidth translates to improved image resolution. Currently, the axial resolution for an 800-nm system is approximately 7 to 10 μm, and the resolution for a 1200-nm system is approximately 10 to 20 μm. Therefore, with the 840-nm light source in the current RTVue system, image resolution is within an acceptable range of 7 to 10 μm.

To preserve adequate image resolution, the OCTA systems must forgo a larger scan size. The largest scan size obtainable with the available technology is 12 × 12 mm. However, at this size, there is a clinically significant decline in image resolution. Therefore, the most commonly used scan size is 3 × 3 mm with the current SD-OCTA technology.[2] When compared with FA and indocyanine green (ICG) images, this smaller scan size may represent a potential limitation of the OCTA technology.

In an effort to improve the axial and lateral resolution of images, and thereby to increase the scan size, a new prototype has been developed by the Massachusetts Institute of Technology known as swept source OCT (SS-OCT). In addition to using a vertical cavity surface-emitting laser, a 1060-nm wavelength light source, the SS-OCTA system also has a higher imaging speed. The SS-OCT obtains 500 × 500 A scans at a rate of 400 000 scans per second in approximately 3.8 seconds.[10] Although the standard SD-OCTA system allows posterior segment imaging just greater than 1 mm in depth, the SS-OCTA system has an imaging range of approximately 2.44 mm.[11,12] As a result, this system allows for improved view of the choroidal vasculature in addition to improved image quality. Yet, the most commonly used scan sizes are 3 × 3 mm or 6 × 6 mm. Therefore, even with the current advances in technology, the inability to visualize larger areas of the retina and choroid may still pose a disadvantage for clinical use.

Another significant drawback to the OCTA system is the potential for various forms of artifact. Bulk motion artifact, due to poor fixation or an uncooperative patient, results in horizontal or vertical white lines on imaging.[2] Because signals from consecutive B scans are used to map retinal and choroidal vasculature, any movement that exceeds the maximum detectable velocity, determined by time interval between sequential B scans, has the ability to create motion artifact.[13] Another type of artifact is referred to as a "projection" artifact in which more superficial retinal vasculature is projected onto deeper layers of the retina and choroid, resulting in the appearance of "ghost vessels."[2] Furthermore, projection artifacts of the choriocapillaris and choroid can also result from simple attenuation and scattering from the RPE layer.

Although faster scanning speeds may overcome the motion artifact, it is possible that at these higher scanning speeds, OCTA may not be able to adequately capture slow flow states, such as those seen in microaneurysms or fibrotic CNV. The slowest detectable flow rate is set by the time interval between 2 consecutive B scans. As a result, OCTA technology requires a significant trade-off between overall acquisition time, elimination of bulk motion, and comprehensive vascular imaging.

Overall, the current OCTA technology is promising and certain limitations encountered in the current system are being actively addressed through small research studies. In general, OCTA provides vascular imaging in different layers of the retina and choroid that is not possible with current FA/ICG images. The elimination of exogenous dye for image acquisition and the faster image collection times are significant benefits for clinical practice. Yet, despite these advantages, one must remember that as a new technology, OCTA is limited in clinical use by the lack of large studies demonstrating the accuracy of current segmentation technology and the overall reproducibility of data.[1,14] Furthermore, OCTA can only provide information regarding vascular flow at a single time point and cannot demonstrate dynamic vascular leakage, as is possible with FA and ICG.

OCTA in Nonexudative AMD

More than 80% of patients with AMD have the nonexudative form, which is characterized by the presence of drusen, RPE abnormalities, and geographic atrophy (Figure 2). Because patients with mild nonexudative AMD can maintain reasonably good visual acuity, there is much interest in improving the early detection of CNV before it distorts the retinal architecture and leads to vision loss.

The presence of CNV in 1 eye is a known risk factor for progression to wet AMD in the fellow eye. Huang and Bailey et al have used SD-OCTA (RTVue XR Avanti AngioVue) to screen eyes with nonexudative AMD at risk of developing exudative AMD based on having exudative AMD in the fellow eye.[15] Study participants had exudative AMD in one eye and nonexudative AMD in the fellow eye based on the presence of drusen and retinal pigment epithelial changes. Of the 32 eyes with nonexudative AMD, 2 were found to have a vascular membrane on OCTA that did not show leakage on FA nor the presence of intraretinal or subretinal fluid on OCT. In both patients, the vascular membrane appeared in the sub-RPE space on en face OCT angiograms, consistent with type I CNV. In one of the eyes, the CNV was located within a pigment epithelial detachment. Although one of the patients was lost to follow-up, the other was monitored for 8 months without any treatment. On follow-up angiograms, there was a 20% increase in CNV flow area but no evidence of fluid or leakage on OCT and FA.

In a similar study, Rosenfeld and colleagues[16] followed 11 patients with asymptomatic intermediate, nonexudative AMD (defined as the presence of many medium-sized drusen [63-125 μm] or at least 1 large drusen [>125 μm] or noncentral geographic atrophy) in one eye and type I neovascular AMD in the fellow eye using a modified Zeiss 1050-nm SS-OCT prototype. In 3 of the 11 eyes, ICGA showed a central macular

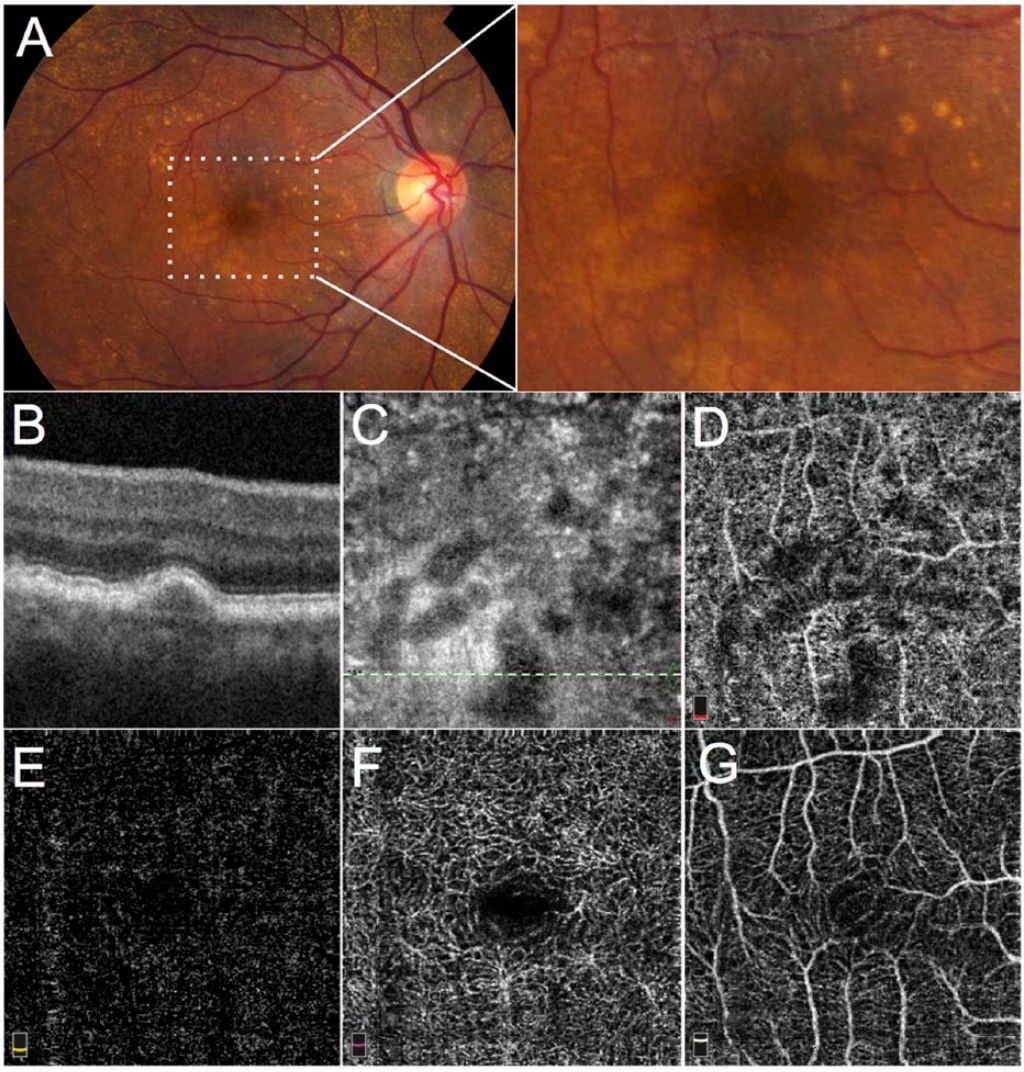

Figure 2. Optical coherence tomographic (OCT) angiography in nonexudative age-related macular degeneration in the right eye of an 80-year-old woman, with exudative AMD in the fellow eye (not shown). (A) Color fundus photograph showing numerous drusen, enlarged to approximate area of following OCT angiograms; (B) SD-OCT B scan through a drusen (corresponding to the white dotted line in B); (C) en face structural OCT showing dark areas corresponding to drusen; (D) 3 × 3 mm spectral domain optical coherence tomographic (SD-OCT) angiogram of the choriocapillaris showing shadowing artifact and/or flow impairment in areas under the drusen; (E) OCT angiogram of the outer retina showing absence of choroidal neovascularization; (F) OCT angiogram of the deep capillary plexus appears uninvolved; and (G) OCT angiogram of the superficial capillary plexus appears uninvolved.

plaque. Fluorescein angiography of these 3 eyes showed areas of early focal hyperfluorescence with late staining and no leakage, consistent with nonexudative AMD. Standard OCT B scans through these areas showed elevations of the RPE normally consistent with typical drusen without evidence of fluid. However, on SS-OCTA, there was evidence of blood flow within the presumed drusen. These lesions could be classified as type I CNV based on the en face images and corresponded with the location of the plaques seen on ICG. Others have previously described subclinical CNV lesions that are detected as staining plaques on ICGA and give the appearance of drusen but are not associated with leakage on FA or intraretinal or subretinal fluid on OCT.[17] Eyes with these so-called nonexudative CNV lesions have no clinical signs of exudative AMD, and it remains unclear whether their presence represents a precursor to exudative AMD. Gass[18] has proposed that early CNV networks have minimal or no exudation due to low flow and that exudation results from increases in blood flow with time. Additional longitudinal studies of nonexudative CNV are necessary to discern the natural history of these vascular lesions.

Mastropasqua and colleagues[19] used SD-OCTA (RTVue XR Avanti AngioVue) to compare superficial and deep retinal vascular plexus densities and choroidal thickness in patients with early (defined as having medium drusen [63-125 μm] but without pigmentary abnormalities) and intermediate AMD as well as normal eyes. Vessel density was quantified as the percentage of a 3 mm × 3 mm region centered on the foveal avascular zone occupied by vessels. They found a significant reduction in choroidal thickness and superficial and deep retinal vessel densities between patients with AMD and healthy

controls but no significant difference in these measurements between early AMD and intermediate AMD patients.

OCTA in Exudative AMD

Exudative AMD accounts for about 10% to 15% of AMD cases but is responsible for 90% of cases with vision loss.[20,21] The appearance of leakage and fluid from CNV defines the progression from nonexudative to exudative AMD. With the recent development of effective anti-VEGF agents for the treatment of exudative AMD, there is a critical emphasis on correctly classifying the stage of AMD and type of CNV present.[22]

CNV has been classified into 3 different types: type I CNV, type II CNV, and type III CNV. In type 1 CNV, vessels arising from the choroid penetrate the Bruch membrane and invade the subretinal pigment epithelial space (Figure 3). In type II CNV, vessels also originate from the choroid but infiltrate between the RPE and retina. Type III CNV, also known as RAP, is thought to arise from downward proliferation of the deep plexus layer of retinal vessels to the RPE (Figure 4). There has been growing interest in studying the characteristics of CNV lesions in neovascular AMD using OCTA.

Huang and Bailey et al imaged treatment-naive exudative AMD patients using SS-OCTA (prototype with 1050-nm laser) and segmented 3-dimensional (3D) angiograms into 3 slabs: inner retinal layer (containing the internal limiting membrane to the outer plexiform layer), outer retinal layer (containing the outer plexiform layer to the Bruch membrane), and choroidal layer (below the Bruch membrane).[23] Optical coherence tomographic angiograms of patients with exudative AMD show structural details of CNV lesions with great depth resolution, and viewing them on cross section identifies their exact position, enabling classification as type I, type II, or type III CNV. In their limited sample of 5 patients with exudative AMD, they found that larger CNV networks had higher blood flow than smaller lesions and that type II CNV had higher blood flow than type I CNV or combined type CNV. In 1 eye with subretinal hemorrhage overlying the CNV, the hemorrhage did not obscure the view of the CNV. In all eyes with wet AMD, there were prominent deep choroidal vessels and loss of choriocapillaris. In addition, in some of these eyes, OCTA images showed diminished perfusion of the choriocapillaris and deeper choroid under the CNV. As they propose, this may be evidence of a role of choroidal circulation abnormalities and outer retinal ischemia in the pathogenesis of CNV and AMD, as a growing body of literature has hypothesized.[24–26]

Sarraf and colleagues[27] described the morphologic characteristics of type I CNV lesions on OCTA (RTVue XR Avanti AngioVue). In their study of 33 eyes with AMD, all had previously been treated with anti-VEGF (mean number of injections received was 15.3). They described 2 distinct appearances of type I membranes: a "medusa" form (about 55% of the lesions) with vessels radiating in all directions from a large main feeder vessel and a "seafan" form (about 25% of lesions) where most of the smaller vessels radiated from one side of a large feeder vessel. The remaining vascular membranes lacked distinct smaller vessels. Lesions were quantified by measuring area, width of the largest caliber vessel, and density of vessels. Overall, there was no correlation between the morphologic pattern of the lesions and the presence of RPE detachment, the presence of RPE atrophy, or the number of anti-VEGF injections received. Notably, there was also no significant change in the area and vessel density of type I CNV lesions at baseline and at follow-up imaging after further anti-VEGF therapy, although qualitatively there appeared to be attenuation of some of the finer vessels in some of the eyes after anti-VEGF injections. The authors posit that the lack of change in morphology after anti-VEGF injections likely reflects the chronicity of the lesions. Like Huang and colleagues,[23] they also found that in

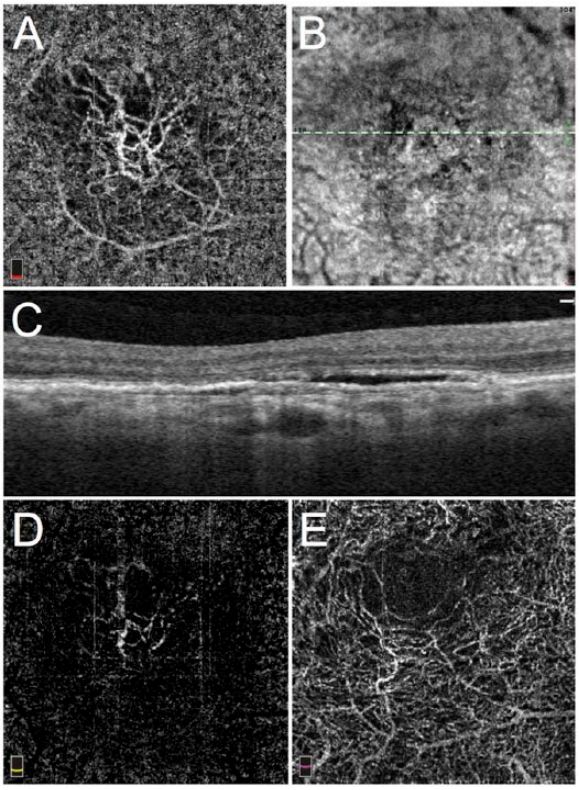

Figure 3. Type I choroidal neovascularization (CNV) in exudative age-related macular degeneration in the right eye of a 67-year-old woman, status post 9 ranibizumab injections and 13 aflibercept injections. (A) 3 × 3 mm spectral domain optical coherence tomographic (SD-OCT) angiogram of the choriocapillaris showing a neovascular membrane centrally; (B) en face structural optical coherence tomography (OCT) of the same area showing patchy hyperreflectivity, with hyporeflectivity corresponding to subretinal fluid; (C) OCT B scan through area of CNV and subretinal fluid (corresponding to the white dotted line in B). Fluorescein angiography (not shown) confirms occult membrane without a classic component. Width of OCT B scan is equivalent to width of angiograms in (A), (D), and (E). (D) OCT angiogram of the outer retina. Small net seen in this image is due to elevation of part of the subretinal pigment epithelium membrane into the outer retina slab segmentation. (E) OCT angiogram of the deep capillary plexus appears normal.

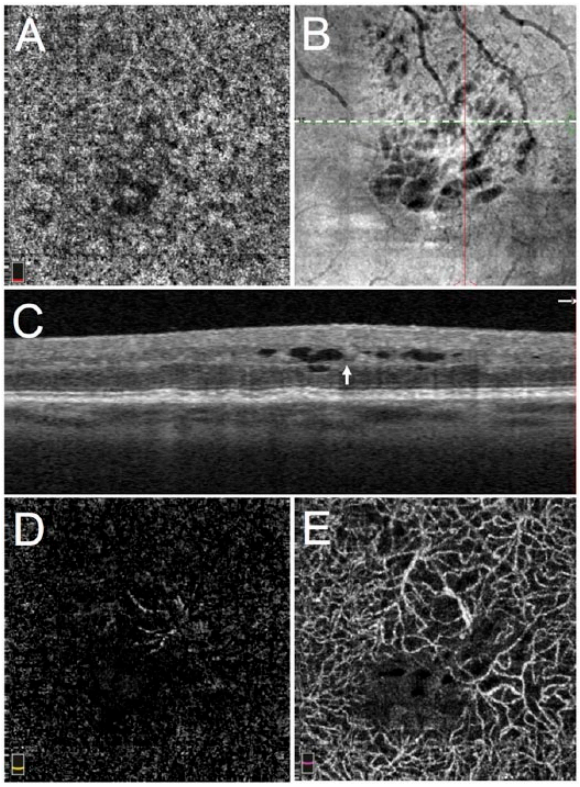

Figure 4. Type III choroidal neovascularization (CNV) in exudative age-related macular degeneration (retinal angiomatous proliferation) in the left eye of a 68-year-old man, treatment-naive. (A) 3 × 3 mm spectral domain optical coherence tomographic (SD-OCT) angiogram of the choriocapillaris showing patchy loss of flow signal due to overlying intraretinal fluid; (B) en face structural optical coherence tomography (OCT) of the same area showing patchy hyporeflectivity corresponding to intraretinal cystic fluid, as well as hyperreflectivity corresponding to retinal blood vessels; (C) OCT B scan through area of intraretinal fluid and type III CNV (arrow) (corresponding to the white dotted line in B). Width of OCT B scan is equivalent to width of angiograms in (A), (D), and (E). (D) OCT angiogram of the outer retina shows part of the CNV centrally. (E) OCT angiogram of the deep capillary plexus showing dilated CNV vessel with surrounding loss of flow signal due to intraretinal fluid.

about 20% of the AMD eyes, there was absence or diminution of choroidal blood flow adjacent to the CNV.

Souied and colleagues[28,29] have described OCTA features of type II and type III neovascularization in AMD. They described 2 morphologic patterns of type II CNV on SD-OCTA (RTVue XR Avanti Angiovue): a "medusa-shaped" lesion and a "glomerulus-shaped" lesion. Most lesions were connected to a larger feeder vessel extending from the choroid. Eyes with type III CNV were characterized by a tuft-shaped high-flow vascular network arising from the deep capillary plexus in the outer retinal layer with adjoining telangiectatic vessels.

Waheed and colleagues[30] compared visualization of CNV using SD-OCTA (RTVue XR Avanti AngioVue) versus SS-OCTA (1050-nm prototype developed at Massachusetts Institute of Technology). Because SS-OCTA uses a longer 1050-nm wavelength, it penetrates deeper into the choroid than 850-nm wavelength SD-OCTA. They imaged eyes with type I, type II, or combined type CNV in exudative AMD using both SD-OCTA and SS-OCTA. In almost all of the images, SS-OCTA detected a larger area of the CNV compared with SD-OCTA. The mean CNV area visualized for 3 mm × 3 mm images was 0.95 mm^2 for SS-OCT and 0.34 mm^2 for SD-OCT. This may be due to the fact that SD-OCTA was unable to visualize occult parts of the neovascular complex. Given its longer wavelength, ultrahigh-speed SS-OCTA may be able to overcome signal attenuation associated with SD-OCTA such as from the RPE, media opacities, and any overlying hemorrhage.

Sarraf and colleagues[31] have used OCTA to quantify the response of type II CNV lesions to anti-VEGF treatments in a patient with exudative AMD. They performed sequential SSADA OCTA of a type II neovascular membrane prior to and at various times following initiation of monthly ranibizumab injections. They showed that the lesion area decreased by 40% at 4 weeks after the first injection and that the vascular density decreased by 50%. At 4 weeks after the second injection, the lesion size had further decreased by 30% and the vessel density had decreased by 25%. They noted that the caliber of the main feeder vessel did not change and hypothesized that the larger feeder vessel may be more resistant to anti-VEGF therapy possibly due to the presence of overlying pericytes that do not surround the smaller vessel branches of the membrane.

Sarraf and colleagues[32] have also studied type III CNV lesions with OCTA (RTVue XR Avanti AngioVue). In a study of 29 eyes with type III wet AMD, of which more than half had previously been treated with anti-VEGF, a distinct neovascular membrane could be seen in 10 eyes (34%) on OCTA. In all of these eyes, the lesions were active on OCT with evidence of intraretinal or subretinal fluid. Type III CNV lesions appeared as small tufts of high-flow vessels in the outer retinal layer. In all eyes, a feeder vessel was seen connecting the CNV with the deep retinal capillary plexus. About 80% of lesions were associated with pigment epithelial detachment. In one patient who had follow-up imaging after receiving an intravitreal aflibercept injection, the CNV lesion was no longer seen on subsequent OCTA.

Souied and colleagues[33] used OCTA (RTVue XR Avanti AngioVue) to characterize the structural and vascular features of subretinal fibrosis. Subretinal fibrosis and atrophy develop following exudative AMD and is associated with a poor visual outcome. They analyzed 49 eyes in patients with evidence of subretinal fibrosis based on FA and SD-OCT. They identified several phenotypic morphologies of vascular networks found within subretinal fibrotic scars, which they have termed "pruned vascular tree," "vascular loop," and "tangled network." These vascular networks could not be seen on FA and appeared only as a compact and homogeneous hyperreflective lesion on SD-OCT.

Conclusions

Optical coherence tomographic angiography is a new, rapid, noninvasive imaging modality that can provide detailed visualization of the retinal and choroidal vasculature with 3D depth resolution. Although the technology is still in its infancy, there is growing interest in using OCTA to image neovascularization for a multitude of diseases, including AMD. Optical coherence tomographic angiography can provide detailed visualization of the structure, size, location, and blood flow of neovascular membranes. It may be useful in identifying nonexudative "subclinical CNV" lesions prior to detection with conventional imaging such as OCT and FA. Earlier detection could enable better monitoring of patients at high risk of conversion to neovascular AMD that may lead to earlier treatment, although the implications of earlier detection and treatment on visual prognosis remain to be seen. Although the benefits to OCTA are clear, there remain many limitations to this new imaging modality. Because it measures contrast based on movement, any background motion of the eye will cause noise artifact and degrade image quality. Media opacities and hemorrhage can cause shadow artifacts, and normal vasculature can lead to projection artifacts. Moreover, some neovascular membranes with low flow may not be visualized due to limits in the resolution of the machine. With time, more advanced algorithms and scanners will be able to more precisely subtract artifact and acquire images with ultrahigh resolution. Further studies are needed to correlate OCTA with clinical findings in both exudative and nonexudative AMD and to compare with other imaging modalities. Future investigations with OCTA to examine the natural history, progression, and response to treatment in AMD may ultimately lead to a better understanding of the pathogenesis of this disease and improved patient outcomes.

Author Contributions

Conceived and designed the review: DS. Analyzed the data: JM, PN, RD, DS. Wrote the first draft of the manuscript: JM, RD. Contributed to the writing of the manuscript: PN, RD. Made critical revisions and approved the final manuscript: MG, AF, DS All the authors reviewed and approved the final manuscript.

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