Perspective

OCT Angiography-based Evaluation of the Choriocapillaris in Neovascular Age-related Macular Degeneration

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Abstract

Neovascular age-related macular degeneration (AMD) can lead to rapid, irreversible vision loss in untreated eyes. While the pathogenesis of neovascular AMD remains incompletely understood, the choriocapillaris has been hypothesized as the initial site of injury. Due to limitations of dye-based angiography, *in vivo* imaging of the choriocapillaris has been a longstanding challenge. However, the clinical introduction of optical coherence tomography angiography (OCTA) has enabled researchers and clinicians to noninvasively image the choriocapillaris vasculature, allowing the evaluation of the choriocapillaris in eyes with a variety of pathologies. In this perspective, we review important OCTA-based findings regarding choriocapillaris impairment in neovascular AMD and discuss limitations and future directions of OCTA technologies in the context of this disease.

Keywords: Choriocapillaris; Neovascular AMD; OCTA; Wet AMD

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INTRODUCTION

Age-related macular degeneration (AMD) is a leading cause of visual impairment and is projected to affect 288 million individuals by 2040.[1] Over time, AMD can progress from earlier stages of dry AMD, characterized by drusen and pigmentary changes, to late-stage AMD, defined by neovascularization and/or complete retinal pigment epithelium (RPE) and outer retinal atrophy (cRORA).[2, 3] Neovascular AMD—also known as wet AMD—is characterized by choroidal neovascularization (CNV), which can present as abnormal blood vessel formation in

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the sub-RPE space (Type I), subretinal space (Type II), and/or neurosensory retina (Type III), or even a combination of these subtypes.[4, 5] Neovascularization can additionally be classified as exudative, with leakage from blood vessels, or non-exudative, without leakage.[6]

While the pathophysiology of neovascular AMD is insufficiently understood, evidence of choriocapillaris dysfunction has been found in affected eyes, and it has been hypothesized that the choriocapillaris is the initial site of injury.[7–10] The choriocapillaris is the dense, monolayer capillary network of the choroid below Bruch's membrane and the RPE which is responsible for nutrient supply and waste removal to and from the RPE and outer retina.[11] Due to its important role in supporting the RPE, researchers have suggested that choriocapillaris flow impairment leads to increased ischemia and vascular endothelial growth factor (VEGF) expression by the RPE, which, in turn, promotes neovascularization.[5, 7] Imaging and evaluating the choriocapillaris in eyes with neovascular AMD is therefore of great research and clinical interest.

Longitudinal changes in the choriocapillaris have been, until recently, difficult to assess because traditional dye-based angiography is not well suited for choriocapillaris imaging. For example, fluorescein angiography (FA) obscures fine choriocapillaris vasculature due to leakage from neovascularization; and, while indocyanine green angiography (ICGA) does not suffer from leakage, lack of depth resolution results in the choriocapillaris being obscured by larger choroidal vasculature. Moreover, dye-based methods are invasive, can cause discomfort, and, more rarely, allergic reactions.[12] However, the recent clinical introduction of optical coherence tomography angiography (OCTA),[13–15] a functional extension of OCT, has provided clinicians and researchers with a noninvasive, depth-resolved tool that is well suited for choriocapillaris imaging. Since its introduction, OCTA has been extensively used to qualitatively and quantitatively analyze the choriocapillaris in eyes with neovascular AMD. In this perspective, we overview some of these OCTA-based findings, note current technological limitations, and discuss promising future directions.

OCTA Imaging of the Choriocapillaris in Neovascular AMD

Although FA has been historically considered the gold-standard imaging technique for identifying neovascular AMD, OCTA is able to detect CNV with similar sensitivity and specificity and is now more commonly used to detect neovascular AMD and assess the choriocapillaris vasculature of patients with neovascular AMD.[16, 17] OCTA studies have consistently reported choriocapillaris impairment in the area below and surrounding CNV lesions secondary to neovascular AMD. Additionally, choriocapillaris flow impairment have also been reported to be larger throughout the macula in patients with neovascular AMD compared to age-matched controls.[18, 19] More recently, researchers have used OCTA to quantitatively analyze the spatial distribution of choriocapillaris impairment surrounding CNV lesions. For example, studies have shown that in eyes with CNV secondary to AMD, choriocapillaris flow impairment is most severe in the region immediately surrounding the lesion.[19–22] These findings agree with histological studies, which have reported similar spatial trends in choriocapillaris impairment,[23, 24] and seem consistent with the hypothesis that choriocapillaris impairment precedes CNV development.

OCTA studies have also examined differences in choriocapillaris impairment amongst eyes with varying types of CNV secondary to AMD. In one study, greater choriocapillaris flow deficits were reported in the peripheral macula in eyes with Type 3 CNV than in eyes with Type 1 and/or Type 2 CNV.[25] Increased choriocapillaris flow impairment in fellow eyes of patients with unilateral Type 3 CNV compared to fellow eyes of patients with unilateral Type 1 or Type 2 CNV has also been observed.[26] Additionally, statistically significant increases in choriocapillaris flow impairment have been shown in patients with exudative, neovascular CNV compared to their fellow eye with non-exudative, CNV.[27] Because all types of CNV has been shown to be present in areas with choriocapillaris impairment and CNV has also been shown to be associated with reduced growth of GA, CNV development may be an adaptive mechanism to overcome decreased choriocapillaris flow and ischemia.[21, 27–29] These findings suggest that changes in the choriocapillaris vasculature may play an important role in the development and progression of neovascular AMD.

Currently, the standard treatment for neovascular AMD consists of intravitreal injections of VEGF inhibitors. Before the availability of anti-VEGF treatments, patients with neovascular AMD experienced rapid and severe vision loss due to leakage of blood and fluid from abnormal vessels. Anti-VEGF treatment has been shown to be effective in resolution of fluid and hemorrhage and improvement of visual acuity.[30–32] Although many patients benefit from this treatment, others continue to experience progressive vision loss or show improvement for only a short period of time. Factors such as baseline visual acuity and age have been shown to predict anti-VEGF treatment response in neovascular AMD.[33, 34] However, the pathophysiology leading to insufficient response to anti-VEGF treatment is unknown. Increased complexity and size of CNV lesion has been found to be associated with increased number of anti-VEGF injections required for adequate response.[35] Using OCTA, more complex and larger CNVs have also been shown to be associated with choriocapillaris flow deficits.[36] Thus, it is possible that increased choriocapillaris flow deficits may predict poor response to anti-VEGF treatment. Additionally, in one study, reduced choriocapillaris vessel density was found in patients with neovascular AMD receiving continuous and long-term anti-VEGF treatment.[37] This could be due to initially decreased choriocapillaris blood flow in these patients leading to the increased necessity for continuing treatment. This finding was further corroborated in a study showing decreased baseline choriocapillaris vessel density in neovascular AMD patients with decreased response to anti-VEGF treatment.[38] Further evaluation of the choriocapillaris using OCTA may help determine additional qualitative and quantitative metrics for prediction of anti-VEGF response.

Limitations of OCTA Imaging of the Choriocapillaris in Neovascular AMD

Although OCTA imaging has proved to be a valuable tool for *in vivo* choriocapillaris imaging, it has limitations that clinicians and researchers should consider. Perhaps most important in the context of choriocapillaris evaluation is the difference in performance between the two types of currently available commercial OCTA devices: spectral-domain OCTA (SD-OCTA) and swept-source OCTA (SS-OCTA). The shorter, ~840 nm wavelength light used in commercially available spectral domain OCTA (SD-OCTA) instruments is more strongly attenuated by the RPE compared to the longer, ~1050 nm wavelength light used in commercially available swept source OCTA (SS-OCTA) instruments. These attenuation differences are exacerbated by certain pathological features present in eyes with neovascular AMD, including drusen and exudation.[39–41] Therefore, when available, we recommend SS-OCTA for choriocapillaris imaging in neovascular AMD, and urge caution when interpreting SD-OCTA choriocapillaris data.

Artifacts in OCTA choriocapillaris imaging can also arise through processing and analysis steps. For example, neovascular AMD often results in substantial distortion of normal retinal anatomy, which can cause errors in automated retina layer segmentation, lead to incorrect choriocapillaris slab boundaries, and, therefore, to erroneous choriocapillaris en face images. OCTA images are obtained from structural OCT data and OCTA cannot be reliably performed in regions with lower OCT signal Additionally, some OCTA algorithms are not normalized by the OCT signal level, which results in a strong interdependence between the OCTA signal level and OCT signal intensity. Thus, without correction, areas of low OCT signal can appear to have low OCTA signal, irrespective of blood flow.[42] Conversely, normalized OCTA algorithms require removal or masking of low OCT signal regions which have invalid OCTA data. This can result in the opposite effect, blood flow can be present, but not visualized in OCTA.[43] Therefore, it is important to understand processing and analysis steps when interpreting choriocapillaris OCTA data. For more details, we refer readers to recently published reviews on OCTA and choriocapillaris imaging.[14, 44]

Future Directions of OCTA Imaging of the Choriocapillaris in Neovascular AMD

The enthusiasm for OCTA imaging in the clinical, commercial, and research communities has resulted in continuing innovation and improvement in OCTA technology, which will have a positive impact on OCTA imaging of the choriocapillaris in the future. One direction of investigation, which

has been pursued by our group and others, is OCTA imaging using variable interscan times. Specifically, as noted in the early development of OCTA, the ability of OCTA to detect blood flow is closely related to the interscan time—the time between repeated B-scans.[45–49] By varying the interscan time, different blood flow speeds can be detected and resolved, and relative blood flow speeds can be inferred.[48, 49] We expect that OCTA utilizing multiple interscan times will be better able to detect subtle choriocapillaris blood flow impairments. For example, using the variable interscan time analysis (VISTA) procedure, our group has demonstrated that some choriocapillaris flow deficits surrounding CNV lesions are apparent at shorter (1.5 ms)—but not longer (3.0 ms)—interscan times, suggesting different levels of blood flow impairment as opposed to full choriocapillaris vasculature loss.[22]

We are also enthusiastic about instrument and processing advances that will improve the resolvability of the choriocapillaris vasculature. Currently, commercial OCTA instruments cannot resolve structural details of the tightly packed choriocapillaris vasculature, particularly in the fovea where it is most dense, due to a combination of limited transverse OCT resolution, A-scan density, and speckle noise. However, research groups have demonstrated well-resolved foveal choriocapillaris vasculature using adaptive optics[50] as well as MHz A-scan rate systems.[50–53] Volumetric averaging has also shown the ability to improve the resolvability of choriocapillaris vasculature.[54, 55] We believe that these approaches may enable researchers to study morphological features of the choriocapillaris vasculature in addition to areas of flow impairment.

SUMMARY

OCTA imaging enables noninvasive imaging of the choriocapillaris, including in eyes with neovascular AMD. OCTA studies have shown choriocapillaris alterations around and beneath CNV lesions, with impairment most pronounced in regions closest to the lesion. Despite its advantages, the complexity of OCTA processing and analysis introduces potential artifacts, particularly for choriocapillaris imaging, where the OCT beam is attenuated by the RPE, precise segmentation is required. Nevertheless, due to the importance of choriocapillaris evaluation in neovascular AMD and other retinal pathologies, innovations from clinicians, researchers, and companies are poised to make substantial advances in choriocapillaris imaging for the next generation OCTA instruments.

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Conflicts of Interest

NKW: Allegro (C), Regeneron (C), Apellis (C), Optovue (R), Heidelberg (R), Nidek (R, C), Topcon (C), Zeiss (R), Stealth (C), Genentech (C), Astellas (C), Gyroscope (Employee), Ocudyne (shareholder), Boehringer Ingelheim (C); JGF: Optovue (I, P), Topcon (F), VISTA-OCTA (P); VP: none; EM: VISTA-OCTA (P), Gyroscope (C).

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