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Editorial

Potential clinical applications of optical coherence tomography angiography in glaucoma

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Elevated intraocular pressure has been identified as a major risk factor for primary open-angle glaucoma (POAG), and current treatments focus on reducing the intraocular pressure to prevent disease progression. However, some glaucomatous patients continue to progress despite intraocular pressure lowering, and in these patients, other risk factors like decreased ocular perfusion pressure and vascular dysfunction may be causative factors.[1,2]

The recent advent of optical coherence tomography angiography (OCTA) has allowed for fast and noninvasive assessment of microvasculature in the peripapillary retina and macula.[3] Different strategies have been used for assessing microvasculature in different OCTA machines. The AngioVue was one of the first optical imaging instruments that provided quantitative and reproducible vessel measurements using split-spectrum amplitude decorrelation angiography (SSADA). Recently, Cirrus optical coherence tomography (OCT), Spectralis OCTA, and Topcon have been introduced and use OCT-based microangiography (OMAG), full-spectrum probabilistic, and OCT Angiography Ratio Analysis (OCTARA) algorithm for generating angiographic images, respectively. OCTA investigations in POAG have shown reduced microcirculation in the peripapillary retina[4−6] and the superficial macula.[6−8] They showed a moderate relationship between microvasculature and function in glaucomatous patients.[5] *An important and unanswered question is how can OCTA findings affect clinical practice?*

Is it helpful in early detection of glaucoma? One of our first OCTA studies showed that vascular density in a group of glaucoma patients with a single hemifield was reduced in perimetrically intact hemiretina of these eyes.[9] In another study,[6] we measured the vascular densities in the macula and the peripapillary area in eyes with unilateral glaucoma and demonstrated that OCTA measurements detect changes in retinal microvasculature before visual field damage in unaffected eyes. Moreover, OCTA may detect glaucomatous damage in early stages of the disease. However, other studies reported no significant differences between inner macular thickness and inner macular vessel density, and longitudinal studies are needed to determine whether OCTA measures can improve the detection of glaucoma.[10] Nevertheless, we can conclude from these studies that there are some cases that microvascular attenuation occurs before changes in retinal nerve fiber layer (RNFL) thickness or function.

Can OCTA help us in the later course of the disease? Detection of glaucomatous change in advanced glaucoma is challenging because of the increased variability of visual fields and the existence of "floor effect" observed in RNFL thickness measurements obtained using optical imaging instruments.[11] We have reported a stronger relationship between vasculature and function, compared to thickness and function, in eyes with advanced glaucoma. Additionally, in a longitudinal study on predominantly moderate to advanced glaucoma eyes over a mean of 13 months, Shoji and colleagues[12] showed that serial OCTA measurements can detect glaucomatous change in macula vessel density in eyes without evidence of loss in structure. OCTA promises to be a tool that can provide a more informative outcome measure in advanced glaucoma, compared to ganglion cell complex (GCC) and RNFL thickness, and could extend the dynamic range of the OCT measurements.

So is there any additive information from vessel density measurements beyond thickness? Yarmohammadi et al.[5] showed that the microvascular attenuation was significantly correlated with visual field damage in POAG eyes even after controlling for thickness. We know that optic nerve head and RNFL changes often occur before detectable visual field changes.[1,2] *What useful information can we obtain from OCTA*

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beyond thickness? Is it useful for prediction of glaucoma progression? Most investigations of OCTA vessel density to date have been cross-sectional. Moghimi et al.[13] in a longitudinal study showed that lower baseline macular and peripapillary vessel densities were associated with a faster rate of RNFL progression in mild to moderate glaucoma over a mean of 27 months. Importantly, they showed that this association was independent of the structural baseline RNFL thickness, suggesting that OCTA may offer additional information to the evaluation of the risk of glaucoma progression and prediction of rates of disease worsening. Microvascular dropout has also been demonstrated as a biomarker for visual field deterioration, especially in eyes with disc hemorrhage. [14] These findings suggest that assessment of peripapillary and macular vessel density may add significant information to the evaluation of the risk of glaucoma progression and prediction of rates of disease worsening. *So what is the explanation for these findings?* One reason might be that reduced optic disc and retina perfusion leads to faster retinal ganglion cell (RGC) death. *What if reduced perfusion on OCTA were a biomarker for sick dysfunctional RGCs with lower metabolic demands?* Characterizing the vasculature by detection of flowing red blood cells to meet the metabolic needs of cells could be a surrogate for neural tissue oxygenation and metabolism and may reflect functional status of the RGCs before structural changes occur.

Is the role of OCTA the same in different subtypes of glaucoma? A significantly lower peripapillary vessel density in pseudoexfoliation glaucoma (PXG) compared to POAG has been shown, suggesting greater impaired perfusion defects in PXG.[15] Rao et al.[16] showed that microvascular dropout is also detectable in primary angle closure glaucoma (PACG). However, the sensitivity of the peripapillary vessel density to detect glaucoma appeared to be better in POAG compared with PACG, and they proposed that the ocular perfusion abnormality in PACG had lower prevalence compared with POAG.

Last but not least are the factors that may affect microvascular perfusion. There are several concerns that should be addressed in future studies. *What ocular, systemic, and physiologic parameters affect vessel density measurements? Do systemic medications affect retinal perfusion? How about topical medications? Is there any diurnal variation? Is there any change in vessel density when we are lying down?* Although topical beta blockers have been shown to reduce OCTA measurements,[17] our understanding of other potential variables' effects on vessel density is limited.

OCTA is a novel, noninvasive imaging technology that is providing insight into the role of microvascular changes during glaucomatous process. Previously, many captured OCTA images have artifacts. However, new higher resolution images with wider fields have removed large vessels from vascular measurements and have been approved by Food and Drug Administration (FDA) for the usage in clinical practice, and will be promising in improving early diagnosis, detecting progression, and possibly detecting dysfunctional RGCs for future neuroprotective therapies.

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