



Quantitative optical coherence tomography angiography of the peripapillary circulation in glaucoma

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Comment on: Yarmohammadi A, Zangwill LM, Diniz-Filho A, *et al.* Relationship between Optical Coherence Tomography Angiography Vessel Density and Severity of Visual Field Loss in Glaucoma. *Ophthalmology* 2016;123:2498-2508.

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The cause of glaucoma, a disease defined by degeneration of retinal ganglion cells associated with cupping of the optic nerve head (ONH) and progressive vision loss, continues to be debated despite numerous advances in ophthalmic imaging and diagnostics. Although elevated intraocular pressure is often implicated, many studies, using a variety of imaging techniques including plain fundus photography, fluorescein angiography, laser Doppler flowmetry, and color Doppler ultrasound (1-4), have suggested that insufficiencies of ONH circulation may play a role in glaucoma pathogenesis. While all of these imaging modalities have been informative, each has a set of limitations, including low spatial resolution, invasiveness, restriction to superficial vessels, lack of repeatability, and modality specific artifacts. Optical coherence tomography angiography (OCTA), an imaging technology that can produce high resolution, three-dimensional images of fundus microcirculation, is well suited to overcome many of these limitations (5).

In 2012, Jia *et al.* first described the use of OCTA in quantifying ONH perfusion (6). In this proof of concept study, OCT imaging using the split-spectrum amplitude-decorrelation angiography (SSADA) algorithm was used to measure local microcirculation in the peripapillary regions, and demonstrated a reduction in ONH perfusion in a small cohort of early glaucoma patients. The amplitude-based method of SSADA is sensitive to flow in all directions, making quantification independent of the angle of incidence between OCT beam and direction of blood flow. Furthermore, amplitude decorrelation, as compared to amplitude variance, is less affected by signal strength and

allows for greater reliable comparisons between subjects. These factors make SSADA a useful tool for quantifying retinal microcirculation and studying glaucoma related vascular changes.

A recent study by Yarmohammadi *et al.* investigated the relationship between vessel density, as measured with OCTA, and severity of visual field loss in glaucoma (7). The authors measured peripapillary vessel density in eyes of healthy subjects, glaucoma suspects, mild (visual field mean deviation >-6 dB) and moderate to severe (visual field mean deviation <-6 dB) primary open-angle glaucoma (POAG) patients. They reported a stepwise qualitative and quantitative loss in microcirculation in each more severely affected patient group, and a relatively strong association between peripapillary vessel density and glaucomatous visual field damage ($R^2=0.54$). Interestingly, vascular-functional correlations were stronger than structural (RNFL thickness and optic nerve rim area)-functional correlations, and when multivariate analysis adjusted for these measurements of structural damage, vessel density remained independently associated with visual field loss.

Yarmohammadi *et al.* limited their vessel density calculations to the superficial vascular plexus contained between the internal limiting membrane and posterior boundary of the RNFL, whereas other studies have measured vessel density in the full thickness retinal slab (8,9). Both of these methods successfully avoid the well described problem of projection artifact, where moving blood cells within overlying vessels cast shadows onto deeper structures, which is misinterpreted as blood flow by the OCTA algorithm (10). While studying the deeper

layers of perfusion in isolation is of interest, particularly as some have suggested that the posterior ciliary artery microcirculation supplies the initial site of glaucoma ONH pathology (11), obtaining meaningful OCTA data is limited by projection artifact. In another recent publication from the same group, focal dropout of the peripapillary choroidal microvasculature was demonstrated in glaucomatous eyes, and was spatially associated with lamina cribrosa defects (12). The authors should be commended for strictly defining vascular drop out as a complete loss of decorrelation signal, rather than accepting a less stringent threshold of a partial, quantitative decrease in deep-layer microvascular density, as this increases our confidence that identified areas have true flow loss. However, they correctly acknowledge that projection artifact from superficial vessels could result in false-positive detection of blood flow and incorrect classification in the study. Isolation of deep layer circulation within the optic disc, as compared to the peripapillary region, is even more problematic due to the complex anatomy of highly reflective structures. Projection-resolved OCTA, or other correction methods, may be capable of providing a solution to these problems in future studies (13). An additional consideration when interpreting OCTA data is the effect of local OCT reflectance signal strength, which can be weakened by a number of factors including vitreous opacities and pupil edge vignetting resulting in decreased decorrelation signal. Adjustment for reflectance variation has been shown to increase vessel density measurement reliability in OCTA and should be incorporated into future studies (14).

In addition to POAG, other types of glaucoma have recently been studied with OCTA. Scripsema *et al.* demonstrated a correlation between peripapillary vessel density and severity of glaucomatous vision loss in both POAG and normal tension glaucoma (9). Furthermore, the authors introduce the concept of generating color-coded capillary density maps with OCTA data, which, much like the familiar topographic maps used by clinicians to track RNFL thickness, may prove useful in quickly and objectively evaluating RPC density loss in glaucoma patients. Primary angle-closure glaucoma (PACG), which remains the predominate form of glaucoma in East Asia, has also been investigated. In one study, the diagnostic ability of peripapillary vessel density parameters of OCTA was found to be very similar for both PACG and POAG, and comparable to RNFL thickness measurements (15). In another group of PACG eyes, OCTA vessel density findings showed that perfusion of and near the optic nerve were

more sensitive to intraocular pressure than elsewhere in the retina (15). These studies highlight the potential OCTA has in comparing and contrasting the underlying mechanisms of different glaucoma subtypes.

In a disease such as glaucoma, where the underlying cause remains unknown, physicians rely on clinical associations to predict disease progression and inform treatment decisions. At the moment, associations of IOP and structural changes, as determined by physical exam and structural imaging, with glaucomatous vision loss are the principal tools in the treating physician's toolbox. With the observational findings of Yarmohammadi *et al.* and others, the association between glaucoma and impaired ONH perfusion is strongly supported. Longitudinal studies will help determine the temporal relationship between perfusion changes and disease progression, and to define the clinical role of OCTA in measuring the rate and severity of vessel density loss in glaucoma patients.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related

to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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