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Commentary on Lavia et al: progress of optical coherence tomography angiography for visualizing human retinal vasculature

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Commentary

Optical coherence tomography angiography (OCTA) provides three-dimensional, depth-resolved images of retinal and choroidal vasculature *in vivo* by detecting motion contrast from blood cells moving in vessel lumens.¹ The technology has emerged speedily in just a few years since its commercial introduction, allowing new insights into retinal vascular diseases that were incompletely understood from dye-based angiography.^{1 2} An article by Lavia et al³ takes further steps towards making OCTA a quantitative tool in the clinic by documenting a large normative database with new software to remove projection artifact.

There are several capillary beds and a continuous parafoveal capillary ring in the macula of humans⁴ and non-human primates.⁵ Apart from the peripapillary area, these capillary beds are known as superficial (in the nerve fiber layer and inner aspect of the ganglion cell layer), intermediate (on inner and outer aspects of the inner nuclear layer), and deep (between the inner nuclear layer and outer plexiform layer) plexus. The deep capillary plexus is planar, whereas the others are 3-dimensional due to connecting vascular loops and vertical segments. A capillary-free zone immediately adjoins arteries, in the superficial plexus only.⁶ The direction of blood flow in these capillary beds is actively debated.^{7, 8} A common metric to many OCTA studies is vessel density (VD), that is, the percentage of retinal area that is occupied by vessels, in a projection image of either the entire retinal thickness or in one anatomic layer isolated by automatic or manual segmentation. A second common metric is

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the area or equivalent diameter of the foveal avascular zone (FAZ) within the bounds of the parafoveal capillary ring. The FAZ exhibits high inter-individual variability in diameter and area that is inversely related to the volume and shape of the foveal pit, attributed to glial-vascular relationships that become established during late fetal development.^{9, 10}

In their new article,³ Lavia et al developed a normative database for macular OCTA using an RTVue XR Avanti (Optovue, Fremont CA) and new software for projection artifact removal, as well as motion artifact removal and sharpness enhancement. In 148 eyes of 84 patients aged 22.2 to 75.8 and with maculas carefully screened to be normal, the authors measured VD in capillary beds and area of the FAZ. Images were selected with a stringent standard of 70 for signal strength index (SSI). Individual capillary beds were isolated by generously inclusive boundaries (9 μ m from anatomical layers indicated by reflective bands on structural OCT). The authors found that VD was higher in the superficial and intermediate capillary plexuses (47.8% and 45.4%, respectively) than in the deep capillary plexus (31.6%). Further, they found that with age, VD decreased in all 3 plexuses (r^2 of 0.37–0.46), especially in the deep plexus, and FAZ area increased. Observed VD increased as SSI increased, i.e., more vessels were seen in better images. VD was reported in two macular subregions, i.e., within 300 μ m of the perifoveal capillary ring and in the perifovea, as well as superior and inferior hemi-fields, and four quadrants. Lavia et al suggest that deep capillary plexus is vulnerable to disease processes; lower anatomic density and greater diminution with age contributes.

Strengths of this study include a large cohort with healthy maculas, wide age range, current software including Projection Artifact Removal and improved segmentation (including around the foveal singularity¹¹), and comprehensive reporting of tabulated data for ease of reference. Relative to recent other studies establishing normative databases acquired with the same OCTA device,^{12–16} Lavia et al have newer software, data from three plexuses (also reported by others¹⁶) vs two or combined, two macular subregions (also reported by others¹⁴) vs one, and high SSI criterion (70, vs 40–50^{8, 13–15}). Others studies reported larger sample size^{14, 16} or wider age range.¹⁶ Where measured in a series of normal aged eyes, macular VD has been shown to decrease^{12, 13, 16} and the FAZ to expand^{12, 16} with age (but see¹³), an overall synergism that is encouraging. Limitations of Lavia et al³ dataset include lack of independent validation (see below), continued dependence of detectability on image quality, slightly different segmentation from other studies, lack of correction for refractive error in these eyes lacking severe myopia, lack of generalizability to pathologic cases with deranged laminar architecture, and omission of oldest ages, of relevance to age-related macular degeneration.

Variability of VD across the literature suggests that some artifact still persists in OCTA and may impede the wider adoption of this technology. VD measured in two comparably-designed studies (Lavia et al³ and Garrity et al⁸) highlights this challenge: VD in the superficial plexus was 47.8% in one study³ vs 15.48% in the other⁸, and the deep plexus was 31.6%³ vs 16.33%.⁸ Other groups reported values of 52.6% and 57.9%¹³ and 51.5 and 57.4%¹⁷ for superficial and deep plexuses, respectively. These differences are likely methodological in origin, i.e., segmentation boundaries used for generating *en face*

angiograms, thresholding strategies used for discriminating flow versus non-flow areas, or analysis software used for calculating VD.

Retinal vascular imaging techniques are most valuable when they are validated, that is, compared to a gold-standard measurement of vessel structure and abundance in histology. Although lack of a gold-standard for OCTA has been mentioned,¹⁴ recent laboratory studies of human vascular biology suggest that this roadblock can be overcome. The Dao-Yi Yu group in Perth, Western Australia, has published on visualizing and quantifying retinal vasculature in human donor eyes.^{18–21} These studies notably use micro-cannulation and perfusion of the central retinal artery to label endothelium with specific fluorescent markers, and capture images at precise retinal depths using confocal microscopy. As in *in vivo* OCTA, these authors also find that VD in the deep capillary plexus is lower than in the superficial and intermediate plexuses, both within (17% vs 29–33%) and near (16% vs 27%) the macula.^{18–20} However, these values are lower by half than those found *in vivo* by Lavia et al,³ and they are comparable to those found by Garrity et al⁸ for the deep plexus (and not superficial). The Yu group also found that relative to tissue measurements made at the microscope, OCTA underestimates VD and overestimates capillary diameter.^{21–23} Interestingly, laboratory validation studies included donor eyes subjected to *ex vivo* OCTA imaging during intravascular perfusion with blood, prior to histology. It was not possible to apply these techniques to maculas due to post-mortem retinal detachment;²¹ eyes obtained very rapidly after death might offer better outcomes.

Thus, OCTA visualization of retinal vessels is continuing to improve, with the recent article by Lavia et al representing a very solid forward step. While convergence on trends such as age-related FAZ expansion and reduced VD is promising, a worthwhile goal is to achieve anatomic accuracy in OCTA imaging of retinal vasculature. The retina is one part of the central nervous system where remarkably precise visualization can be achieved, thanks to ocular optics, and with it, subcellular detail about pathophysiology. Successes in single photoreceptor imaging for gene therapy trials²⁴ and inner retinal diagnostics for glaucoma²⁵ evolved from clear visualization and accurate enumeration of retinal photoreceptors and ganglion cells, respectively, in human tissues.^{26, 27} We can expect similar future success for OCTA, as new laboratory data are forthcoming simultaneously with device technology development.

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