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Relationship between Optical Coherence Tomography Angiography Vessel Density and Severity of Visual Field Loss in Glaucoma

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Purpose: To evaluate the association between vessel density measurements using optical coherence tomography angiography (OCT-A) and severity of visual field loss in primary open-angle glaucoma.

Design: Observational, cross-sectional study.

Participants: A total of 153 eyes from 31 healthy participants, 48 glaucoma suspects, and 74 glaucoma patients enrolled in the Diagnostic Innovations in Glaucoma Study.

Methods: All eyes underwent imaging using OCT-A (Angiovue; Optovue, Fremont, CA), spectral-domain OCT (Avanti; Optovue), and standard automated perimetry (SAP). Retinal vasculature information was summarized as vessel density, the percentage of area occupied by flowing blood vessels in the selected region. Two measurements from the retinal nerve fiber layer (RNFL) were used: circumpapillary vessel density (cpVD) (750-μm-wide elliptical annulus around the optic disc) and whole-image vessel density (wiVD) (entire 4.5×4.5-mm scan field).

Main Outcome Measures: Associations between the severity of visual field loss, reported as SAP mean deviation (MD), and OCT-A vessel density.

Results: Compared with glaucoma eyes, normal eyes demonstrated a denser microvascular network within the RNFL. Vessel density was higher in normal eyes followed by glaucoma suspects, mild glaucoma, and moderate to severe glaucoma eyes for wiVD (55.5%, 51.3%, 48.3%, and 41.7%, respectively) and for cpVD (62.8%, 61.0%, 57.5%, 49.6%, respectively) ($P < 0.001$ for both). The association between SAP MD with cpVD and wiVD was stronger ($R^2 = 0.54$ and $R^2 = 0.51$, respectively) than the association between SAP MD with RNFL ($R^2 = 0.36$) and rim area ($R^2 = 0.19$) ($P < 0.05$ for all). Multivariate regression analysis showed that each 1% decrease in wiVD was associated with 0.66 decibel (dB) loss in MD and each 1% decrease in cpVD was associated with 0.64 dB loss in MD. In addition, the association between vessel density and severity of visual field damage was found to be significant even after controlling for the effect of structural loss.

Conclusions: Decreased vessel density was significantly associated with the severity of visual field damage independent of the structural loss. Optical coherence tomography angiography is a promising technology in glaucoma management, potentially enhancing the understanding of the role of vasculature in the pathophysiology of the disease. *Ophthalmology 2016;■:1–11 © 2016 by the American Academy of Ophthalmology*

Glaucoma is a progressive optic neuropathy with unknown cause characterized by the degeneration of retinal ganglion cells and their axons, resulting in a characteristic appearance of the optic disc and visual field loss.[1] There is increasing evidence that optic nerve blood flow impairment and microcirculatory deficiency may have a role in the pathogenesis of glaucoma,[2–4] although the details of this relationship have not been established precisely.[5–7] This is in part due to the instrumentation that has been available and its difficulty in accurately measuring ocular blood flow.[8,9]

In contrast to ocular blood flow, objective, accurate, and quantitative measurements of the optic nerve head (ONH) and macula can be obtained with optical coherence tomography (OCT), which has become the standard for structural evaluation in glaucoma research and clinical practice. However, structural measurements have only moderate correlation with visual field loss.[10–12]

It recently has become possible to obtain noninvasive images to characterize retinal vasculature with OCT angiography (OCT-A),[13,14] which provides reproducible quantitative assessment of the microvasculature in the ONH, peripapillary retina, and macula.[15–20] Recent studies using OCT-A have suggested that this new technology might be useful in the diagnosis, staging, and monitoring of glaucoma.[16,18–20] These measurements also may clarify the role of microcirculation and optic nerve blood flow in the pathogenesis of glaucoma.

This study evaluates the relationship between OCT-A retinal vessel density parameters and functional

Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.ophtha.2016.08.041
ISSN 0161-6420/16

measurements and compares this with standard spectral-domain OCT (SD OCT) structural measurements.

Methods

This was an observational cross-sectional study including 153 eyes from 31 healthy participants, 48 glaucoma suspects, and 74 patients with primary open-angle glaucoma enrolled in the Diagnostic Innovations in Glaucoma Study who underwent OCT-A (Angiovue; Optovue Inc., Fremont, CA)[13–20] and SD OCT ONH imaging (Avanti; Optovue Inc.).

The Diagnostic Innovations in Glaucoma Study eligibility criteria and methodological details have been reported in previous publications.[21] In brief, all participants completed a comprehensive ophthalmologic examination, including best-corrected visual acuity, slit-lamp biomicroscopy, intraocular pressure (IOP) measurement with Goldmann applanation tonometry, gonioscopy, dilated fundus examination, stereoscopic optic disc photography, ultrasound pachymetry, and standard automated perimetry (SAP) in both eyes. Only participants older than 18 years of age with open angles on gonioscopy, and spherical refraction within ±10 diopters were included.

Written informed consent was obtained from all participants. The institutional review board at the University of California San Diego approved all protocols, and the methods described were in agreement with the tenets of the Declaration of Helsinki and the Health Insurance Portability and Accountability Act.

Healthy subjects were required to have an IOP of 21 mmHg or less with no history of elevated IOP, normal-appearing optic discs, intact neuroretinal rims and retinal nerve fiber layer (RNFL), and normal visual field test results defined as a pattern standard deviation (PSD) within the 95% confidence limits and glaucoma Hemifield test result within normal limits. Glaucoma suspects had an IOP ≥22 mmHg or suspicious-appearing optic discs without evidence of repeatable glaucomatous visual field damage.

Glaucoma was defined by the presence of repeatable abnormal SAP results with a glaucoma Hemifield test outside normal limits or PSD outside the 95% normal limits. Patients with glaucoma were additionally classified into 2 groups based on the severity of their visual field damage; mild glaucoma was defined as visual field mean deviation (MD) higher than −6 decibels (dB), and moderate to severe glaucoma was defined as a visual field MD lower than −6 dB.[22] To ensure comparability of age across study groups, only subjects aged ≥45 years were included.

Eyes with a history of intraocular surgery (except for glaucoma surgery or uncomplicated cataract surgery), secondary causes of glaucoma, nonglaucomatous optic neuropathies, vascular or nonvascular retinopathies, and other ocular or systemic diseases known to impair the visual field were excluded from the investigation.

Two blood pressure (BP) measurements obtained in a resting, seated position were taken at least 5 minutes apart using an Omron Automatic (model BP791IT; Omron Healthcare, Inc., Lake Forest, IL) instrument. Mean arterial pressure (MAP) was calculated as MAP = 1/3 systolic BP + 2/3 diastolic BP, and mean ocular perfusion pressure (MOPP) was defined using the following equation: MOPP = 2/3 MAP-IOP.

Standard Automated Perimetry

All participants underwent visual field testing using the 24-2 pattern Swedish interactive threshold algorithm on the Humphrey Field Analyzer (Carl Zeiss Meditec, Dublin, CA) within 6 months of imaging. Only reliable tests (≤33% fixation losses and false-negatives, and ≤15% false-positives) were included. The quality of visual field tests was also reviewed by the Visual Field Assessment Center[23] staff to identify and exclude visual fields with evidence of inattention or inappropriate fixation, artifacts such as eyelid and lens rim artifacts, fatigue effects, and abnormal results caused by diseases other than glaucoma.

Optical Coherence Tomography Angiography

The OCT-A imaging system provides a noninvasive method for visualizing the ONH and retinal vasculature. The image acquisition technique is optimized for the Split-Spectrum Amplitude-Decorrelation Angiography algorithm described in detail by Jia et al.[13] The Split-Spectrum Amplitude-Decorrelation Angiography method captures the dynamic motion of moving scatters, such as red blood cells in a flowing blood vessel, and computes a high-resolution 3-dimensional visualization of perfused vasculature.

The OCT-A characterizes vascular information at each retinal layer as an en face angiogram, a vessel density map (Fig 1), and quantitatively as vessel density (percentage), calculated as the percentage area occupied by flowing blood vessels in the selected region.

For this study, we used vessel density measurements within the peripapillary RNFL in scans with a 4.5×4.5-mm field of view centered on the ONH. Vessel density within the RNFL was measured from the internal limiting membrane to RNFL posterior boundary using standard AngioVue software (version 2015.1.0.90). Measurements were calculated in 2 areas. Whole-image vessel density (wiVD) was obtained over the entire 4.5×4.5-mm scan field, and circumpapillary vessel density (cpVD) was measured in a 750 μm−wide elliptical annulus extending outward from the optic disc boundary, where the inner elliptical contour is obtained by fitting an ellipse to the disc margin on the OCT en face retinal angiogram, and the ring width between inner and outer elliptical contour is defined as the circumpapillary region (Fig 1).

The Imaging Data Evaluation and Analysis Reading Center established a standard protocol for OCT-A image quality review. Trained graders reviewed all images to identify poor-quality scans, defined as blurred images, scans with a signal strength index less than 48, residual motion artifacts visible as irregular vascular pattern or disc boundary on the enface angiogram, local weak signal caused by floaters, and RNFL segmentation errors. Graders also reviewed the location of the optic disc margin for accuracy, and if needed the margin was adjusted manually and confirmed by 2 graders.

Spectral-Domain Optical Coherence Tomography

Avanti SD OCT uses an 840-nm central wavelength, a 22-μm focal spot diameter, and a 70-kHz axial line scan rate that yields an axial resolution of 5 μm in tissue. The ONH map image acquisition protocol was used to obtain RNFL thickness measurements in a 10-pixel-wide band along a 3.45-mm-diameter circle centered on the ONH and rim area measurements.

All participants had both SD OCT and OCT-A imaging performed on the same day. Participants with poor-quality ONH scans defined by an SSI lower than 37 and scans with segmentation failure or artifacts were excluded from the analysis.

A total of 351 eyes of 213 subjects had OCT-A and SD OCT imaging within 6 months of visual field testing and were potentially eligible for inclusion in the analysis. Fifty-four eyes were excluded because of poor-quality OCT-A scans, 16 eyes were excluded because of poor-quality SD OCT images, and 35 eyes were excluded because of unreliable visual field tests. A total of 246 eyes of 153 subjects had good-quality OCT-A, SD OCT, and