AMERICAN ACADEMY™
OF OPHTHALMOLOGY

Projection-Resolved Optical Coherence Tomography Angiography of Macular Retinal Circulation in Glaucoma

Hana L. Takusagawa, MD, Liang Liu, MD,* Kelly N. Ma, MD, MPH, Yali Jia, PhD, Simon S. Gao, PhD, Miao Zhang, PhD, Beth Edmunds, MD, PhD, Mansi Parikh, MD, Shandiz Tehrani, MD, PhD, John C. Morrison, MD, David Huang, MD, PhD*

Purpose: To detect macular perfusion defects in glaucoma using projection-resolved optical coherence tomography (OCT) angiography.

Design: Prospective observation study.

Participants: A total of 30 perimetric glaucoma and 30 age-matched normal participants were included.

Methods: One eye of each participant was imaged using 6 × 6−mm macular OCT angiography (OCTA) scan pattern by 70-kHz 840-nm spectral-domain OCT. Flow signal was calculated by the split-spectrum amplitude-decorrelation angiography algorithm. A projection-resolved OCTA (PR-OCTA) algorithm was used to remove flow projection artifacts. Four en face OCTA slabs were analyzed: the superficial vascular complex (SVC), intermediate capillary plexus (ICP), deep capillary plexus (DCP), and all-plexus retina (SVC + ICP + DCP). The vessel density (VD), defined as the percentage area occupied by flow pixels, was calculated from en face OCTA. A novel algorithm was used to adjust the vessel density to compensate for local variations in OCT signal strength.

Main Outcome Measures: Macular retinal VD, ganglion cell complex (GCC) thickness, and visual field (VF) sensitivity.

Results: Focal capillary dropout could be visualized in the SVC, but not the ICP and DVP, in glaucomatous eyes. In the glaucoma group, the SVC and all-plexus retinal VD (mean ± standard deviation: 47.2%±7.1% and 73.5%±6.6%) were lower than in the normal group (60.5%±4.0% and 83.2%±4.2%, both $P < 0.001$, *t* test). The ICP and DCP VD were not significantly lower in the glaucoma group. Among the overall macular VD parameters, the SVC VD had the best diagnostic accuracy as measured by the area under the receiver operating characteristic curve (AROC). The accuracy was even better when the worse hemisphere (inferior or superior) was used, achieving an AROC of 0.983 and a sensitivity of 96.7% at a specificity of 95%. Among the glaucoma participants, the hemispheric SVC VD values were highly correlated with the corresponding GCC thickness and VF sensitivity ($P < 0.003$). The reflectance compensation step in VD calculation significantly improved repeatability, normal population variation, and correlation with VF and GCC thickness.

Conclusions: On the basis of PR-OCTA, glaucoma preferentially affects perfusion in the SVC in the macula more than the deeper plexuses. Reflectance-compensated SVC VD measurement by PR-OCTA detected glaucoma with high accuracy and could be useful in the clinical evaluation of glaucoma. *Ophthalmology 2017;■:1−11* © *2017 by the American Academy of Ophthalmology*

Supplemental material available at www.aaojournal.org.

Glaucoma is the second leading cause of blindness worldwide, affecting more than 60 million people and predicted to affect 79.6 million by 2020.[1−3] Early diagnosis and close monitoring of glaucoma are important given glaucoma's insidious onset with irreversible nerve damage associated with vision loss. Although studies of glaucoma traditionally have focused on the optic nerve and peripapillary retina, there are multiple reasons to evaluate the macula in glaucoma diagnosis and monitoring.

Histologic studies have shown that glaucoma results in loss of retinal ganglion cells (RGCs) and more than 30% of the ganglion cells in the eye reside in the macula.[4,5] Many recent optical coherence tomography (OCT) studies have shown that macular thinning is associated with glaucoma and that the thinning preferentially affects the ganglion cell complex (GCC), the innermost layers of the retina, which include the retinal nerve fiber layer (NFL), ganglion cell layer (GCL), and inner plexiform layer (IPL).[6−8] Diagnostic accuracy for glaucoma can be improved when macular OCT measurements focus particularly on the GCC.[6,9,10] Given that a preponderance of RGCs reside in the macula, studies have suggested that early glaucomatous damage involves the macula.[11] Recent studies have shown that early visual field (VF) loss often occurs in the central 10 degrees of vision, an area represented by the macula.[12] Focal loss of the GCC on OCT appears to be an excellent predictor

http://dx.doi.org/10.1016/j.ophtha.2017.06.002
ISSN 0161-6420/17

of progression from preperimetric to perimetric glaucoma.[13] However, glaucomatous damage in macular retinal circulation has not been demonstrated.

Optical coherence tomography angiography (OCTA) with the split-spectrum amplitude-decorrelation angiography algorithm has provided a quick and reproducible way to qualitatively and quantitatively show areas of decreased or altered perfusion in the eye.[14–19] By using OCTA, Jia et al[14] demonstrated significantly decreased perfusion at the optic nerve head in glaucoma and Liu et al[15] similarly showed decreased perfusion in the peripapillary retina. More recently, we developed a "projection-resolved" algorithm that effectively suppresses projection artifacts on both en face and cross-sectional angiograms and enhances depth resolution of vascular networks.[20,21] By using projection-resolved OCTA (PR-OCTA), we are now able to visualize the distinct vascular patterns in the 4 retinal plexuses. This study aims to compare the macular circulation in normal participants and glaucomatous participants in different retinal plexuses and to detect and characterize macular circulation defects in glaucoma using PR-OCTA.

Methods

Study Population

This prospective observation study was performed from September 16, 2014, to February 20, 2016, at the Casey Eye Institute, Oregon Health & Science University (OHSU). The research protocols were approved by the Institutional Review Board at OHSU, carried out in accordance with the tenets of the Declaration of Helsinki. Written informed consent was obtained from each participant.

All participants were part of the Functional and Structural Optical Coherence Tomography for Glaucoma study. The inclusion criteria for the perimetric glaucoma group were (1) an optic disc rim defect (thinning or notching) or NFL defect visible on slit-lamp biomicroscopy; and (2) a consistent glaucomatous pattern, on both qualifying Humphrey Swedish Interactive Thresholding Algorithm 24-2 VFs, meeting at least 1 of the following criteria: pattern standard deviation outside normal limits ($P < 0.05$) or glaucoma hemifield test outside normal limits.

For the normal group, the inclusion criteria were (1) no evidence of retinal pathology or glaucoma; (2) a normal Humphrey 24-2 VF; (3) intraocular pressure (IOP) <21 mmHg; (4) central corneal pachymetry >500 μm; (5) no chronic ocular or systemic corticosteroid use; (6) an open angle on gonioscopy; (7) a normal-appearing optic nerve head and NFL; and (8) symmetric optic nerve head between left and right eyes.

The exclusion criteria for both groups were (1) best-corrected visual acuity <20/40; (2) age <30 or >80 years; (3) refractive error of >+3.00 diopters or <−7.00 diopters; (4) previous intraocular surgery except for an uncomplicated cataract extraction with posterior chamber intraocular lens implantation; (5) any diseases that may cause VF loss or optic disc abnormalities; or (6) inability to perform reliably on automated VF testing. One eye from each participant was scanned and analyzed.

Visual Field Testing

The VF tests were performed with the Humphrey Field Analyzer II (Carl Zeiss, Inc, Oberkochen, Germany) set for the 24-2 threshold test, size III white stimulus, using the Swedish Interactive Thresholding Algorithm.

Optical Coherence Tomography

A 70-kHz, 840-nm wavelength spectral-domain OCT system (Avanti RTVue-XR, Optovue Inc, Fremont, CA) was used. The AngioVue version 2014.1.0.2 software was used to acquire OCTA scans.

Image Acquisition and Processing

The macular region was scanned using a 6 × 6−mm volumetric angiography scan centered on fixation. Each volume was composed of 304 line-scan locations at which 2 consecutive B-scans were obtained. Each B-scan contains 304 A-scans. The AngioVue software uses the split-spectrum amplitude-decorrelation angiography algorithm, which compares the consecutive B-scans at the same location to detect flow using motion contrast.[22] Each scan set comprises 2 volumetric scans: 1 vertical-priority raster and 1 horizontal-priority raster. The AngioVue software uses an orthogonal registration algorithm to register the 2 raster volumes to produce a merged 3-dimensional OCTA.[23] Two sets of scans were performed within 1 visit.

The merged volumetric angiograms were then exported for custom processing using the Center for Ophthalmic Optics & Lasers-Angiography Reading Toolkit software, which removes flow projection artifacts and calculates reflectance-compensated vessel density (VD). These custom programs were developed at the Casey Eye Institute using the MATLAB (Mathworks Inc, Natick, MA) programming language. The OCTA scans contain both volumetric flow (decorrelation) data and structural (reflectance) data. The PR-OCTA algorithm retains flow signal from real blood vessels while suppressing projected flow signal in deeper layers, which appears as downward tails on cross-sectional angiograms and duplicated vascular patterns on en face angiograms.[20,24] Projection-resolved OCTA could visualize up to 4 retinal plexuses: the radial peripapillary capillary plexus (RPCP), the superficial vascular plexus (SVP), the intermediate capillary plexus (ICP), and the deep capillary plexus (DCP).[21,25–28] In the temporal portion of the macula, the RPCP (residing in the NFL) is very thin and cannot be distinguished from the SVP; therefore, we combine the RPCP and the SVP into the superficial vascular complex (SVC). Four en face OCTA slabs were analyzed for VD measurement: SVC, ICP, DCP, and all-plexus retina (SVC + ICP + DCP) (Fig 1). Segmentation of the retinal layers was done by automated MATLAB programs that operate on the structural OCT data. An en face angiogram of each slab was obtained by maximum flow (decorrelation value) projection. The VD, defined as the percentage area occupied by the large vessels and microvasculature, was evaluated in the entire 6 × 6−mm scan area excluding of the foveal avascular zone (FAZ), which was defined as a 0.6-mm diameter circle centered at the FAZ. The GCC thickness was averaged over the same region. Superior and inferior hemispheric averages were obtained by dividing the scan area across the horizontal meridian.

Because we found VD to be strongly correlated with signal strength index in previous studies, we developed a reflectance-adjustment method that corrected the artifactually lower flow signal in regions of reduced reflectance (e.g., due to media opacity or pupil vignetting).[29] The method is based on statistical analysis of the relationship between the flow noise in the FAZ with reflectance in retinal tissue, in which the reflectance was manipulated by simulated media opacity (optical filters). In the extrafoveal retina, the average reflectance in the inner nuclear, outer plexiform, and outer nuclear layers to adjust the threshold flow signal value used to classify vessel versus static tissue on en face OCTA. Reflectance compensation is another aspect of the OCTA technique that can be used with PR-OCTA or non−PR-OCTA.