AMERICAN ACADEMY™
OF OPHTHALMOLOGY

Peripapillary and Macular Vessel Density in Patients with Glaucoma and Single-Hemifield Visual Field Defect

Adeleh Yarmohammadi, MD,[1] Linda M. Zangwill, PhD,[1] Alberto Diniz-Filho, MD, PhD,[1] Luke J. Saunders, PhD,[1] Min Hee Suh, MD,[1,2] Zhichao Wu, BAppSc(Optom), PhD,[1] Patricia Isabel C. Manalastas, MD,[1] Tadamichi Akagi, MD, PhD,[1,3] Felipe A. Medeiros, MD, PhD,[1] Robert N. Weinreb, MD[1]

Purpose: To compare hemifield differences in the vessel density of the peripapillary and macula in open-angle glaucoma eyes with visual field (VF) defect confined to one hemifield using optical coherence tomography angiography (OCT-A).

Design: Cross-sectional study.

Participants: A total of 58 eyes of 58 patients with glaucoma with VF loss confined to a single hemifield and 28 healthy eyes.

Methods: Retinal vasculature information was summarized as circumpapillary vessel density (cpVD) and perifoveal vessel density (pfVD). Circumpapillary retinal nerve fiber layer (cpRNFL) and macular ganglion cell complex (mGCC) thickness were calculated using spectral domain optical coherence tomography (SD OCT). Paired and unpaired *t* tests were used to evaluate differences between the perimetrically affected and intact hemiretinae and healthy hemiretinae. Linear regression analyses were performed to evaluate the associations between VF measures with vascular and structural measurements.

Main Outcome Measures: Total and hemispheric cpVD, pfVD, cpRNFL, mGCC, and mean sensitivity (MS).

Results: Mean cpVD and pfVD in the intact hemiretinae of glaucoma eyes (59.0% and 51.1%, respectively) were higher than in the affected hemiretinae (54.7% and 48.3%, respectively; $P < 0.001$) but lower than in healthy eyes (62.4% and 53.8%, respectively; $P < 0.001$). Similar results were noted with cpRNFL and mGCC thickness measurements ($P < 0.05$ for both). The strongest associations between MS in the affected hemifields were found for cpVD ($r = 0.707$), followed by pfVD ($r = 0.615$), cpRNFL ($r = 0.496$), and mGCC ($r = 0.482$) in the corresponding hemiretinae ($P < 0.001$ for all). Moreover, the correlations in the intact hemifields between MS with cpVD and pfVD were higher ($r = 0.450$ and 0.403) than the correlations between MS and cpRNFL and mGCC thickness measurements ($r = 0.340$ and 0.290; P values <0.05 for all).

Conclusions: Reduced peripapillary and macular vessel density was detectable in the perimetrically intact hemiretinae of glaucoma eyes with a single-hemifield defect. Vessel density attenuation in both affected and intact hemiretinae was associated with the extent of VF damage in the corresponding hemifields. Optical coherence tomography angiography potentially shows promise for identifying glaucomatous damage before focal VF defects are detectable. *Ophthalmology 2017;■:1–11* © *2017 by the American Academy of Ophthalmology*

Glaucoma is a multifactorial optic neuropathy of unknown cause.[1] There is mounting evidence that vascular factors play a role in the pathogenesis of the disease.[2,3] However, the study of ocular vasculature in glaucoma has been a challenge because of several limitations in the imaging modalities[4–7]; therefore, the contribution of ocular vasculature in the pathogenesis of glaucoma has remained unclear. Several studies have shown that structural injury often precedes detectable visual field (VF) loss as measured by standard automated perimetry (SAP).[8–11] In eyes with VF damage confined to a single hemifield, there is evidence that both the retinal nerve fiber layer (RNFL) and the macular ganglion cell complex (mGCC) thickness are reduced even in the retinal hemispheres corresponding to the perimetrically intact hemifields.[12–14] However, there is limited information on whether the microvasculature is reduced in eyes with localized glaucomatous functional loss and on its possible contribution to the natural course of the disease.[15]

Optical coherence tomography angiography (OCT-A)[16] is a noninvasive imaging technique that provides reproducible quantitative assessment of the vasculature in the optic nerve, peripapillary retina, and macula.[17–20] Recent reports using OCT-A in glaucoma eyes documented attenuation of vasculature in the optic nerve head (ONH)[17,19] and peripapillary area.[18,19,21] However, there is limited evidence on the extent of microvascular damage in eyes with more localized glaucomatous defects,[22,23] and, to our knowledge, there are no reports characterizing vasculature in the macula of eyes with glaucoma.

http://dx.doi.org/10.1016/j.ophtha.2017.01.004
ISSN 0161-6420/17

The objective of this study was to quantitatively assess the retinal vessel density of the peripapillary and macula in the perimetrically intact hemiretinae of glaucoma eyes with single-hemifield focal VF defects using OCT-A. A further aim was to evaluate the associations between vessel density measures in both affected and intact hemiretinae with the extent of VF damage in their corresponding hemifields.

Methods

Study Participants

A total of 58 patients with glaucoma and 28 healthy controls meeting the eligibility criteria were recruited from the longitudinal Diagnostic Innovations in Glaucoma Study (DIGS) conducted at the Hamilton Glaucoma Center, University of California, San Diego (UCSD). The DIGS protocol and eligibility criteria have been described.[24] Informed consent was obtained from all participants. The UCSD Institutional Review Board approved all protocols and methods described adhered to the tenets of the Declaration of Helsinki and the Health Insurance Portability and Accountability Act.

As part of the DIGS protocol, all study participants underwent a complete ophthalmologic examination, including assessment of best-corrected visual acuity, slit-lamp biomicroscopy, intraocular pressure (IOP) measurement with Goldmann applanation tonometry, gonioscopy, ultrasound pachymetry, dilated fundus examination, and simultaneous stereophotography of the optic disc. Systemic measurements included 2 blood pressure (BP) measurements obtained using an Omron Automatic (model BP791IT, Omron Healthcare, Inc, IL) BP instrument. Mean arterial pressure was calculated as 1/3 systolic BP + 2/3 diastolic BP. Mean ocular perfusion pressure (MOPP) was defined as the difference between 2/3 of mean arterial pressure and IOP.

Participants also completed OCT-A (AngioVue; Optovue, Inc, Fremont, CA) and spectral-domain optical coherence tomography (SD OCT) (Avanti; Optovue, Inc) ONH imaging along with SAP. Inclusion criteria common to DIGS participants were age >18 years, open angles on gonioscopy, and best-corrected visual acuity of 20/40 or better. Participants included in this study were required to have good-quality OCT-A and SD OCT imaging, and also have ≥2 reliable SAP tests. Further inclusion criteria for patients with glaucoma were (1) repeatable glaucomatous VF damage defined as a Glaucoma Hemifield Test result outside normal limits and a pattern standard deviation (PSD) outside 95% normal limits and (2) glaucomatous VF abnormalities exclusively in 1 hemifield as defined by a cluster of ≥3 adjacent points in the pattern deviation (PD) plot with a probability of less than 5% including at least 1 point having a probability less than 1% in at least 2 repeatable and consecutive SAP tests. A perimetrically intact hemifield required having no test points with a probability level <2% or no clusters of ≥3 adjacent points with a probability of <5% on the PD plot. Eyes that were included in the present study had VF abnormalities, such as focal scotomas, nasal steps, arcuate scotomas, altitudinal defects, or any other abnormalities that met our inclusion criteria. If both eyes met the inclusion criteria, 1 eye was randomly selected for analysis. Healthy controls were required to have (1) an IOP <21 mmHg with no history of elevated IOP; (2) normal-appearing optic disc, intact neuroretinal rim, and RNFL on clinical examination; and (3) a minimum of 2 reliable normal VFs, defined as a PSD within 95% confidence limits and a Glaucoma Hemifield Test result within normal limits.

Exclusion criteria common to both study groups were history of intraocular surgery (except for uncomplicated cataract surgery or glaucoma surgery), coexisting retinal pathologies, non-glaucomatous optic neuropathy, uveitis, or ocular trauma. Participants with systemic hypertension and diabetes mellitus were included unless they were diagnosed with diabetic or hypertensive retinopathy. Participants with unreliable VF results and poor-quality OCT-A or SD OCT scans were excluded from this study.

Standard Automated Perimetry

Standard automated perimetry VF tests were performed using Swedish Interactive Threshold Algorithm standard 24-2 threshold test (Humphrey Field Analyzer 750 II-I; Carl Zeiss Meditec, Inc, Dublin, CA). All participants who were included were familiar with SAP testing from earlier exposure to at least 2 VF examinations.

The quality of VF tests was reviewed by the Visual Field Assessment Center staff at UCSD. Only participants with reliable tests (≤33% fixation losses and false-negative errors, and ≤15% false-positive errors) were included in this study. Visual fields that were found to have the following artifacts also were excluded: evidence of rim and eyelid artifacts, inattention or fatigue effects, or VF damage caused by a disease other than glaucoma.

For hemifield-specific analyses in the glaucoma eyes, the average total deviation (TD), PD, and mean sensitivity (MS) were calculated in each hemifield on the basis of the individual test points excluding the blind spot. Sensitivity in decibels at each test location was converted to the linear scale of 1/Lambert (1/L) and then averaged to obtain MS values in a linear scale in each hemifield. In the healthy eyes, the "intact" hemifield was randomly selected, and VF indices were calculated in a similar fashion.

Optical Coherence Tomography Angiography Image Acquisition and Processing

All subjects underwent OCT-A imaging with a commercially available OCT-A system, the AnvioVue (Optovue, Inc) that is incorporated in the Avanti SD OCT system. The AngioVue imaging system provides a noninvasive method of characterizing the vascular structures of the retina at the capillary level. Details of this technology have been described.[25] Briefly, it uses the split-spectrum amplitude-decorrelation angiography algorithm to capture the dynamic motion of moving particles, such as red blood cells, and provides a high-resolution 3-dimensional angiogram of perfused retinal vasculature (Fig 1). The AngioVue characterizes vascular information at various user-defined retinal layers[26] qualitatively as a vessel density map and color-coded vessel area density. Quantitatively, it provides vessel density (%) measurements calculated as the percentage of measured area occupied by flowing blood vessels being defined as pixels having split-spectrum amplitude-decorrelation angiography algorithm−based decorrelation values above the threshold level.

For this study, peripapillary vessel density was derived from the images acquired with a 4.5×4.5 mm^2 field of view centered on the optic disc. Macular vessel density measurements were calculated from 3×3 mm^2 scans centered on the fovea. For both measurement regions, segmentation was performed using the OCT intensity B-scans. Peripapillary vessel density measurements were calculated within the RNFL in a slab from the internal limiting membrane (ILM) to the RNFL posterior boundary. Macular superficial vessel density measurements were calculated in a slab from the ILM to the posterior boundary of the inner plexiform layer (IPL).

Total and hemispheric measurements of the vasculature were obtained in 2 regions: (1) Total circumpapillary vessel density (cpVD) was calculated in a region defined as a 750 μm−wide elliptical annulus extending from the optic disc boundary based on 360° global area and eight 45° sectors as shown in Figures 1 and 2.