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Peripapillary and Macular Vessel Density in Patients with Primary Open-Angle Glaucoma and Unilateral Visual Field Loss

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Purpose: To characterize OCT angiography (OCT-A) vessel density of patients with primary open-angle glaucoma (POAG) with unilateral visual field (VF) loss.

Design: Cross-sectional study.

Participants: A total of 33 patients with POAG with a VF defect in 1 eye (mean VF mean deviation [MD], −3.9±3.1 decibels [dB]) and normal VF in the other eye (mean VF MD, −0.2±0.9 dB) and 33 healthy eyes.

Methods: All subjects underwent OCT-A imaging, spectral-domain (SD)-OCT imaging, and VF testing. OCT-A retinal vascular measurements were summarized as whole image vessel density (wiVD), circumpapillary vessel density (cpVD), and parafoveal vessel density (pfVD). Inter-eye differences in vascular measures, as well as SD OCT retinal nerve fiber layer (RNFL), macular ganglion cell complex (mGCC) thickness, and rim area measurements in glaucoma and healthy eyes were compared. Areas under the receiver operating characteristic curves (AUROCs) were used to evaluate diagnostic accuracy for differentiating between unaffected eyes of patients with POAG and healthy eyes.

Main Outcome Measures: Difference in OCT-A vessel density and SD OCT structural parameters between unaffected eyes of patients with POAG with the fellow affected eyes and healthy controls.

Results: Mean wiVD in unaffected eyes of patients with POAG (52.0%) was higher than in their fellow affected eyes (48.8%) but lower than in healthy eyes (55.9%; $P < 0.001$). Mean circumpapillary RNFL (cpRNFL) thickness, mGCC thickness, and rim area measurement in unaffected eyes of patients with POAG (87.5 μm, 87.7 μm, and 1.0 mm^2) were also higher than those measurements in their fellow eyes (76.5 μm, 79.5 μm, and 0.8 mm^2; $P < 0.001$) and lower than in healthy eyes (98.0 μm, 94.5 μm, and 1.4 mm^2; $P < 0.001$). The AUROCs for differentiating unaffected eyes of patients with POAG from healthy eyes were highest for wiVD (0.84), followed by mGCC (0.78), cpRNFL (0.77), and pfVD (0.69).

Conclusions: OCT-A measures detect changes in retinal microvasculature before VF damage is detectable in patients with POAG, and these changes may reflect damage to tissues relevant to the pathophysiology of glaucoma. Longitudinal studies are needed to determine whether OCT-A measures can improve the detection or prediction of the onset and progression of glaucoma. *Ophthalmology 2017;■:1−10 © 2017 by the American Academy of Ophthalmology*

Despite being a bilateral disease, glaucomatous neuropathy often presents asymmetrically with asymmetric visual field (VF) loss.[1,2] Several studies have documented the presence of subclinical glaucomatous changes in various structural regions, such as neuroretinal rim, retinal nerve fiber layer (RNFL), macular ganglion cell complex (mGCC), lamina cribrosa, and prelaminar tissue, in fellow eyes of patients with glaucoma and unilateral VF loss.[3−12] Structural abnormalities of the optic nerve head (ONH) and RNFL are known to often precede the development of VF damage detected by standard automated perimetry (SAP).[13,14] Moreover, perimetrically unaffected eyes of patients with glaucoma have been shown to be at higher risk for developing VF abnormalities.[15−18] There has been limited evidence on the retrobulbar hemodynamics[19,20] and vascular structure of the choroid[21−23] in glaucoma eyes with unilateral VF damage.

Although the pathogenesis of primary open-angle glaucoma (POAG) remains unclear,[24] a potential pathogenic role for ocular blood flow and the microvascular networks of the retina has long been recognized.[25−27] The recent development of OCT-angiography (OCT-A) allows visualization of retinal microvasculature with a high level of precision. Furthermore, OCT-A provides reproducible quantitative measurement of the vascular networks in various retinal regions.[28] Earlier studies using OCT-A in glaucoma have demonstrated that vessel density measurements in the optic disc, peripapillary retina, macula, and choroidal structures are associated with the severity of glaucomatous VF damage.[29−34] Most recently, it has been shown that OCT-A

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is capable of detecting microvascular attenuation of the peripapillary and macular regions even in perimetrically intact hemiretinae of eyes with single-hemifield VF defects.[35]

The aim of the present study was to compare the microvasculature of healthy eyes with affected and unaffected eyes of patients with POAG and unilateral VF damage.

Methods

Patients with POAG and healthy subjects from the Diagnostic Innovations in Glaucoma Study (DIGS) (clinicaltrials.gov identifier, NCT00221897) were included. All study methods adhered to the tenets of the Declaration of Helsinki and the Health Insurance Portability and Accountability Act and were approved by the institutional review boards at the University of California, San Diego. Informed consent was obtained from all participants.

Study Participants

This was a cross-sectional observational study including 33 patients with POAG with unilateral VF loss and 33 healthy controls enrolled from the DIGS subjects who completed optic disc and macular OCT-A imaging (Avanti AngioVue; Optovue, Inc, Fremont, CA), and ONH and macular imaging using spectral-domain OCT (SD OCT; Avanti; Optovue, Inc). Details of the DIGS protocol and eligibility criteria have been described.[36]

All participants underwent ophthalmological examination, including assessment of best-corrected visual acuity, slit-lamp biomicroscopy, intraocular pressure (IOP) measurement with Goldmann applanation tonometry, gonioscopy, central corneal thickness (CCT) measured with ultrasound pachymetry (DGH Technology, Inc, Exton, PA), dilated fundus examination, simultaneous stereophotography of the optic disc, VF testing by SAP (Humphrey Field Analyzer; 24-2 Swedish interactive threshold algorithm; Carl Zeiss Meditec, Jena, Germany), SD OCT, and OCT-A imaging. Perimetry and all imaging tests were conducted within a 6-month period.

Systemic measurements included systolic and diastolic blood pressure (BP) measured at the height of the heart with an Omron Automatic BP instrument (model BP791IT; Omron Healthcare, Inc, Lake Forest, IL). Mean arterial pressure was derived as 1/3 systolic BP + 2/3 diastolic BP. Mean ocular perfusion pressure (MOPP) was calculated as the difference between 2/3 of mean arterial pressure and IOP.

Inclusion criteria common to all subjects were (1) aged $\geq$18 years, (2) open angle on gonioscopy, and (3) best-corrected visual acuity of 20/40 or better. Exclusion criteria were (1) history of intraocular surgery (except uncomplicated cataract or glaucoma surgery), coexisting retinal pathology, nonglaucomatous optic neuropathy, uveitis, or ocular trauma; (2) diagnosis of Parkinson's disease, Alzheimer's disease, dementia, or history of stroke; (3) diabetic or hypertensive retinopathy; (4) unreliable VFs; and (5) poor-quality OCT-A or SD OCT scans. Participants with systemic hypertension or diabetes mellitus were included unless they met exclusion criterion number 3.

Glaucomatous VF damage was defined as a Glaucoma Hemifield Test outside normal limits and a pattern standard deviation (PSD) outside 95% normal limits confirmed on at least 2 consecutive, reliable (fixation losses and false-negatives $\leq$33% and $\leq$15% false-positives) tests with consistent glaucomatous damage (focal or diffusely narrowed neuroretinal rim, focal or diffuse RNFL loss on optic disc stereophotographs graded by masked experts). Diagnosis of POAG with unilateral VF loss was defined as having 1 eye diagnosed with repeatable glaucomatous VF damage, with the contralateral eye showing no VF defects. Contralateral eyes of patients with glaucoma were required to have consistently normal and reliable VF results from at least >2 SAP tests. In addition, they required having no test points with a probability level less than 2% or no clusters of $\geq$3 adjacent points with a probability of less than 5% on the pattern deviation probability plots. Appearance of the optic disc was not considered in the determination of eligibility for patients within the POAG group.

Healthy eyes were required to have IOP <21 mmHg with no history of elevated IOPs, normal-appearing optic disc, intact neuroretinal rim and RNFL, and a minimum of 2 reliable normal VF tests. One eye from each healthy subject was selected randomly for inclusion in the analysis.

Spectral-Domain OCT Imaging

All subjects underwent ONH and macular imaging using the Avanti SD OCT system with a 70-kHz axial line rate, 840-nm central wavelength, 22-μm focal spot diameter, and 5-μm axial resolution in tissue. Circumpapillary RNFL (cpRNFL) thicknesses measurements were obtained using the ONH map protocol, and the mGCC thickness was obtained using the mGCC scanning protocol. The ONH map protocol calculates cpRNFL thicknesses in a 10-pixel−wide band along a 3.45-mm diameter circle centered on the ONH. The mGCC scanning protocol is a 7×7 mm^2 raster scan composed of 1 horizontal B scan with 933 A-scans and 15 vertical B scans with 933 A-scans per B-scan. The mGCC thickness was measured from the internal limiting membrane to the inner plexiform layer boundary. Only good-quality ONH and macular scans, defined by scans with a signal strength index of more than 37 and without segmentation failure or artifacts such as missing or blank areas were included in the analysis.

OCT-Angiography Image Acquisition and Processing

OCT-A imaging was performed using the AngioVue on the same day as SD OCT imaging and by the same operator. The AngioVue provides noninvasive characterization of the retinal vasculature by using the motion contrast technique and an efficient OCT angiography algorithm, the split-spectrum amplitude-decorrelation angiography (SSADA). Details have been described.[28] Briefly, the SSADA algorithm detects motion of the red blood cells by measuring variations in the reflectance amplitude between the consecutive B-scans at the same location. The software (version 2016.1.0.35) generates high-resolution 3-dimensional visualization of the perfused retinal vasculature at the capillary level. Vascular information is characterized as a vessel density map (Figs 1 and 2) and quantitatively as vessel density (%). Vessel density is automatically calculated as the proportion of measured area occupied by flowing blood vessels, which were defined by pixels with decorrelation values above the SSADA threshold level.

In this report, vessel density in the peripapillary RNFL was analyzed in 4.5×4.5-mm OCT-A scans centered on the ONH, and parafoveal vessel density (pfVD) was analyzed in 3×3-mm OCT-A scans centered on the fovea. Vessel density within the RNFL was measured from the internal limiting membrane to the RNFL posterior boundary. Whole image vessel density (wiVD) was measured over the entire scan field, and circumpapillary vessel density (cpVD) was calculated within a 750-μm−wide elliptical annulus extending from the optic disc boundary. Macular vessel density was measured within the inner retinal layers extending from the internal limiting membrane to inner plexiform layer, which is consistent for superficial vascular plexus. Parafoveal vessel density was calculated in a 1.5-mm−wide parafoveal,

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