Diagnostic Precision of Retinal Nerve Fiber Layer and Macular Thickness Asymmetry Parameters for Identifying Early Primary Open-Angle Glaucoma

MICHAEL SULLIVAN-MEE, CLAUDIA C. RUEGG, DENISE PENSYL, KATHY HALVERSON, AND CLIFFORD QUALLS

• PURPOSE: To evaluate the diagnostic capabilities of intereye and intraeye differences in retinal nerve fiber layer (RNFL) thickness and macular thickness for identifying early primary open-angle glaucoma (POAG).
• DESIGN: Prospective, cross-sectional cohort study.
• METHODS: All subjects were enrolled from an ongoing institutional glaucoma study. We used spectral-domain optical coherence tomography (Spectralis; Heidelberg Engineering) to obtain macular thickness (posterior pole asymmetry scan) and RNFL thickness (circumpapillary scan) in both eyes of 50 early POAG and 50 control subjects. Early POAG subjects had glaucomatous optic neuropathy with mild, reproducible visual field loss in at least 1 eye, and control subjects had normal intraocular pressures, visual fields, and optic nerves. We recorded total, superior, and inferior RNFL and macular thicknesses and then calculated intereye and intraeye differences (asymmetry parameters). Statistical evaluation included receiver operating characteristic and multivariate logistic regression analyses.
• RESULTS: Intereye macular thickness asymmetry had the highest diagnostic sensitivity (88% at 80% specificity; 83% at 95% specificity), followed by total RNFL thickness (88% at 80% specificity; 75% at 95% specificity). Parameters with the largest areas under the receiver operating characteristic curves were: total RNFL thickness (0.937), intereye RNFL asymmetry (0.921), intereye macular thickness asymmetry (0.913), inferior RNFL thickness (0.905), superior RNFL thickness (0.887), intereye inferior macular thickness asymmetry (0.872), and intraeye macular thickness asymmetry (0.860). These 7 values were not significantly different. In multivariate logistic regression analyses, intraeye macular thickness asymmetry, intereye macular thickness asymmetry, intereye RNFL thickness asymmetry, and total RNFL thickness were related independently to early POAG.
• CONCLUSIONS: Structural asymmetry parameters performed well, identifying early POAG as well as RNFL thickness. Further study is indicated to validate these results. (Am J Ophthalmol 2013;156:567–577. Published by Elsevier Inc.)

Accepted for publication Apr 30, 2013.

From the New Mexico Veterans Administration Health Care System, Albuquerque, New Mexico (M.S.-M., C.C.R., D.P., K.H., C.Q.); and the Department of Mathematics and Statistics, University of New Mexico, Albuquerque, New Mexico (C.Q.).
Inquiries to Michael Sullivan-Mee, New Mexico Veterans Administration Health Care System, 1501 San Pedro SE, Albuquerque, NM 87108; e-mail: Michael.Sullivan-Mee@va.gov

ASYMMETRY IS A WELL-KNOWN FEATURE OF PRIMARY open-angle glaucoma (POAG). Intereye differences in intraocular pressure,[1–3] central corneal thickness,[4,5] corneal hysteresis,[6] neuroretinal rim width,[7,8] and degree of visual field loss[2] all have shown associations with POAG. Indeed, an intereye cup-to-disc ratio difference exceeding 0.2 often is used as a diagnostic criterion for POAG.[9,10] Additionally, intraeye asymmetry between superior and inferior measures of visual field sensitivity,[11,12] retinal nerve fiber layer (RNFL) thickness,[13,14] neuroretinal rim width,[15,16] and macular thickness[17,18] also have shown associations with POAG. The glaucoma hemifield test, which compares visual sensitivity between corresponding superior and inferior visual field zones, is a well-known and highly sensitive indicator of early glaucomatous visual field loss.[11,12]

Asymmetry parameters have clinical advantages compared with raw measurement metrics, primarily because these parameters use the fellow eye or fellow hemisphere for comparison, whereas raw measurement metrics are compared with a normative database that is constructed from many different individuals. Consequently, patient-specific factors such as age, race, gender, and diabetes status that may produce measurement differences between individuals do not influence intereye asymmetry metrics because these qualities are intrinsic to both eyes of an individual. Similarly, eye-specific factors such as axial length and optic nerve morphologic features, which tend to be similar between paired eyes but exhibit wide interindividual variation,[19,20] have less impact on asymmetry parameters compared with their effect on raw measurement metrics.

Spectral-domain optical coherence tomography (SD OCT) provides rapid, high-resolution, accurate, reproducible, in vivo measurements for many ocular structures, including RNFL thickness and macular thickness. Although prior studies suggest that both RNFL thickness[21–23] and macular thickness[24–29] are thinner in eyes with glaucoma, diagnostic capability for RNFL thickness

often is found to exceed macular thickness diagnostic capability.[27,28,30,31] Exceptions exist, however, particularly when intraeye macular thickness asymmetry is used instead of measured macular thickness. For instance, when Um and associates divided macular thickness measures into corresponding superior and inferior macular thickness zones and then evaluated symmetry between these zones, they reported that thickness asymmetry between corresponding superior and inferior macular zones was more sensitive than RNFL thickness for detecting early POAG.[29] Inuzuka and associates reported that macular hemifield thickness was reduced in both involved and uninvolved hemiretinas in subjects characterized by field loss in only 1 hemisphere.[32] The authors concluded that retinal structural changes precede the development of visual field loss. Although these latter 2 reports suggest that intraeye macular thickness asymmetry may be beneficial for glaucoma diagnosis, little is known about the relationship between intereye macular thickness asymmetry and glaucoma. We could find only 1 published investigation of intereye macular thickness asymmetry, and that study used normal subjects only.[33] Similarly, we could find only 2 studies that specifically investigated intereye RNFL thickness asymmetry, and both of those studies also included normal subjects only.[34,35]

To facilitate the evaluation of macular thickness asymmetry in glaucoma, software recently was made available commercially by Heidelberg Engineering for use within their SD OCT instrument (Spectralis; Heidelberg Engineering, Carlsbad, California, USA). The scanning protocol is labeled "posterior pole asymmetry analysis," and it acquires macular thickness measurements using 61 high-density raster scans in the macular region.[36] The thickness data then are organized into an 8 × 8 grid (64 separate pixels) that allows direct pixel comparison between corresponding regions of fellow eyes and between corresponding regions of superior and inferior loci of the same eye. Its output includes color-coded maps that highlight regions of relative thinning between eyes and between corresponding hemispheric regions of the same eye (Figure 1). Although these maps provide qualitative information about the spatial aspects of an eye's glaucoma damage, quantitative thresholds for distinguishing normal from abnormal have not yet been provided by the manufacturer, nor have they been published elsewhere.

Considering that no normative data are available for interpreting posterior pole asymmetry analysis, that few published reports have investigated intereye and intraeye RNFL and macular thickness asymmetry in POAG, that asymmetry is a well-known characteristic of POAG, and that asymmetry parameters have diagnostic advantages compared with raw measured metrics, we designed this study to evaluate structural asymmetry relationships further in POAG using SD OCT technology. Moreover, because asymmetry may be more prominent in early stages of POAG[31] and because early POAG generally is more difficult to identify than moderate or later stages of POAG, we developed this study to explore the relative strengths of both intereye and intraeye macular thickness and RNFL asymmetry parameters for identifying early POAG. By calculating threshold values, sensitivities, and areas under receiver operating characteristic curves for both measured and asymmetry parameters, we planned to compare diagnostic utilities for all parameters while establishing clinical values that may aid the differentiation of normal patients from those with early POAG.

METHODS

THE STUDY ADHERED TO THE TENETS OF THE DECLARATION of Helsinki, conformed to Health Insurance Portability and Accountability regulations, and was approved by the University of New Mexico Institutional Review Board, and all subjects completed informed consent before study participation. This study was a cross-sectional cohort study using subjects enrolled in a prospective, longitudinal, observational glaucoma research study at the Albuquerque VA Medical Center. The enrollment criteria were: age 40 years or older; open, normal angles in each eye on gonioscopic examination; no corneal or scleral pathologic conditions that could affect intraocular pressure measurement; refractive error of 5 diopters or less and astigmatism of 3 diopters or less; no prior refractive, corneal, or incisional glaucoma surgery, although routine, uncomplicated cataract surgery was allowed; no secondary glaucoma diagnoses; and no visual field loss resulting from nonglaucomatous pathologic features (including retinal, optic nerve, or visual pathway disorders).

• **STUDY PROTOCOL:** Initial baseline examination included measurement of visual acuity, pupils, refraction, keratometry, axial length, tonometry, and ultrasound pachymetry. Subjects also underwent slit-lamp biomicroscopy, gonioscopy, standard automated perimetry, dilated fundus examination, and SD OCT imaging (Spectralis). Subjects with glaucoma or glaucoma suspicion then were seen at least semiannually, whereas normal subjects generally were seen annually. Semiannual visits included visual acuity measurement, pupil testing, slit-lamp biomicroscopy, tonometry, standard automated perimetry, and RNFL imaging by OCT, whereas annual visits included all the semiannual procedures along with dilated fundus examination and SD OCT posterior pole scans (after asymmetry software was acquired in 2010).

Standard automated perimetry was performed with optimal near-point correction using the Humphrey Visual Field Analyzer II, 24-2 Swedish interactive threshold algorithm standard program (Carl Zeiss Meditec, Inc, Dublin, California, USA). Visual fields were required to meet reliability criteria (false-positive and false-negative rates,