Adjustment of the Retinal Angle in SD-OCT of Glaucomatous Eyes Provides Better Intervisit Reproducibility of Peripapillary RNFL Thickness

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PURPOSE. To report an automated method for adjustment of the retinal angle in spectral-domain optical coherence tomography (SD-OCT) and compare its intervisit reproducibility of the peripapillary retinal nerve fiber layer (RNFL) thicknesses of glaucomatous eyes to that obtained by the Cirrus algorithm.

METHODS. Fifty-six glaucoma and glaucoma suspect subjects were repeatedly imaged, and optic nerve head (ONH)-centered OCT image volumes ($200 \times 200 \times 1024$ voxels, $6 \times 6 \times 2$ mm³, Cirrus HD-OCT machine) were acquired within a 4-month period from one eye of the 56 patients. Retinal angle correction in B-scans was accomplished by adjusting the angle using the voxel aspect ratio of the SD-OCT followed by straightening of rotated A-scans. The RNFL layer was automatically segmented using the Iowa Reference Algorithm. Reproducibility of the peripapillary RNFL thicknesses was determined by intraclass correlation coefficient (ICC), coefficient of variation (CV), repeatability coefficient (RC), and 95% tolerance limit (TL) for the Iowa Reference Algorithm without and with the retinal angle correction and for the Cirrus algorithm (Cirrus version 5.1.0.96).

RESULTS. The angle corrected Iowa Reference Algorithm (ICC: 0.990, 95% confidence interval [CI]: 0.983–0.994) for peripapillary RNFL thicknesses showed significantly better reproducibility than the nonangle corrected algorithm (ICC: 0.964, 95% CI: 0.940–0.979) and the Cirrus algorithm (ICC: 0.960, 95% CI: 0.933–0.976) based on the 95% CIs for the ICCs.

CONCLUSIONS. Angle correction leads to more consistent peripapillary RNFL thicknesses. This may lead to improved management of patients with glaucoma.

Keywords: spectral-domain coherence tomography (SD-OCT), retinal angle adjustment, peripapillary retinal nerve fiber layer (RNFL) thickness

Glaucoma causes degeneration of the retinal ganglion cells, including their axons at the optic nerve head (ONH) and in the nerve fiber bundles.¹ Spectral-domain optical coherence tomography (SD-OCT), providing cross-sectional images of the retina with high axial resolution, has been widely used to analyze thinning of the neuroretinal rim and the retinal nerve fiber layer (RNFL).² Current commercial OCT scanners generate retinal volumetric images with variable tilt due to the positioning of the scanning beam in the pupil and resultant angle of incidence on the retina.³ Another cause of the oblique OCT image volumes is staphyloma, or abnormal curvature of the posterior pole in myopic eyes.

We hypothesize that when intraretinal layer thickness in the OCT volume is measured, the retinal angle, which is equivalent to the angle between the incident light and a line normal to the retina pointed toward the focal center of the retina, should be taken into account for more reliable measurement. Figure 1 shows measurements without and with consideration of the retinal angle (θ) for the peripap-

illary RNFL thickness. The RNFL thickness (t_2) when considering θ is thinner than the RNFL thickness (t_1) when not considering θ . Hariri et al.³ reported the effect of the retinal angle on measurement of the macular thickness and volume in the OCT images and manually measured them using image-analysis software. Automated adjustment to compensate for the nonperpendicular angles of incidence to the retina, to the best of our knowledge, has not been studied previously.

The purpose of the present study was to propose an automated method for adjustment of the retinal angles in ONH-centered OCT volumes of glaucomatous eyes, to determine whether adding this adjustment to the Iowa Reference Algorithm (available in the public domain at <http://www.biomed-imaging.uiowa.edu/downloads/>) yields improved intervisit reproducibility of the peripapillary RNFL thicknesses, and to compare it with the reproducibility obtained with a commercially available Cirrus algorithm.

FIGURE 1. Central B-scan of the ONH-centered OCT volume (OD) representing two measurements for the peripapillary RNFL thickness. The t_2 measurement considers the retinal angle (θ) determined by the dotted line depicting the retinal shape, whereas the t_1 measurement, along the direction of the A-scan, does not.

METHODS

Human Subjects and Data Acquisition

This study received approval from the institutional review board of the University of Iowa and adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants recruited consecutively from the outpatient glaucoma service at the University of Iowa.

Although spectral-domain optical coherence tomography image volumes (Cirrus HD-OCT; Carl Zeiss Meditec, Inc., Dublin, CA), stereo fundus photographs (3Dx; Nidek Inc., Fremont, CA), and intraocular pressure (IOP) values were obtained from both eyes of all subjects, only one eye randomly chosen from each patient was used for analysis in the present study. The ONH-centered SD-OCT image volumes were acquired using the optic disc cube 200×200 protocol. Each volume is composed of $200 \times 200 \times 1024$ voxels, corresponding to physical dimensions of $6 \times 6 \times 2$ mm³.

The study subjects have been described previously.⁴ Briefly, glaucoma and suspected glaucoma subjects were included in the study, but patients with angle-closure and combined mechanism glaucoma were excluded. Glaucoma was diagnosed by combining structural (optic disc cupping, focal thinning of the neuroretinal rim, and the RNFL) and functional changes (visual field defects), with or without elevated IOP. Suspected glaucoma was defined as ocular hypertension with elevated IOP above 21 mm Hg without evidence of glaucomatous optic neuropathy or suspicious optic discs with vertical cup-to-disc ratio > 0.7 or asymmetry between fellow eyes > 0.2 with normal visual fields.⁵

Adjustment of the Retinal Angle in the ONH-Centered OCT Volume

Our approach to adjust the retinal angle in the B-scan was performed after adjustment for the voxel aspect ratio (which is $30.15 \times 30.15 \times 1.96$ μm³). The method initially automatically detects two surfaces (surface 1: internal limiting membrane [ILM], surface 2: outer boundary of the retinal pigment epithelium [RPE]) from ONH-centered OCT volumes (Fig. 2A) using our previously reported graph-theoretic approach.^{6,7} Additionally, the optic disc was automatically detected by our previously reported voxel-column classification method using

FIGURE 2. (A) Original B-scan in the data coordinate space. (B) Spline fitted to the outer boundary of the RPE excluding the ONH region. (C) Retinal orientation derived from the spline. (D) B-scan in the physical coordinate space adjusted for voxel aspect ratio of the SD-OCT. (E) B-scan rotated clockwise by θ_{1_mean} obtained by averaging the θ_1 values calculated in the previous, current, and next B-scans. (F) Aligned B-scan.

features of retinal structures and regional OCT voxel intensities.^{6,8} After segmentation of the surfaces and the optic disc, a spline was fitted to surface 2 while excluding the segmented ONH region for each B-scan (Fig. 2B). The center of the optic disc was defined as the centroid of the segmented optic disc. Two points on the spline having the x -directional distance (d) from the x -position (x_c) of the optic disc center were determined, to create a line representing the retina (Fig. 2C). Various d values were considered to find a d value providing the best reproducibility of peripapillary RNFL thickness. The angle (θ_1) of line L_1 was calculated by making use of the following equation, using the x -, z -directional voxel sizes (30.15 μm, 1.96 μm) and the angle (θ_2) of line L_2 in the B-scan in the physical coordinate space adjusted for voxel aspect ratio of the SD-OCT (Fig. 2D).

$$\tan \theta_1 = a_1/b_1, \quad \tan \theta_2 = a_2/b_2, \quad a_2 = a_1 \times \text{VoxelSize}_Z, \\ b_2 = b_1 \times \text{VoxelSize}_Z$$

$$\rightarrow \theta_1 = \tan^{-1} \left(\frac{\text{VoxelSize}_Z}{\text{VoxelSize}_X} \times \tan \theta_2 \right)$$

Parameter b_2 is the z -directional distance from the top of the adjusted B-scan to center C_2 on line L_2 and was calculated by multiplying b_1 in the data coordinate space by the z -directional voxel size. Parameter a_2 in the adjusted B-scan is the x -directional distance and was calculated using the b_2 and the angle (θ_2) between the vertical line and the line perpendicular to line L_2 . Parameter a_1 was calculated by dividing a_2 by the x -directional voxel size. For continuous transition of the angle (θ_1) across B-scans, the angle (θ_{1_mean}) in the current B-scan was obtained by averaging the angles (θ_1 s) calculated in the previous, current, and next B-scans. The B-scan rotated around center C_1 by θ_{1_mean} (Fig. 2E) was straightened by rearranging rotated A-scans (Fig. 2F). The adjusted OCT volume was obtained by applying the same approach to all B-scans forming the volume.

Measurement of the Peripapillary RNFL Thickness

Two surfaces defining RNFL were automatically segmented from the ONH-centered OCT image volumes using the Iowa Reference Algorithms (available in the public domain from

TABLE. Intervisit Reproducibility of the Peripapillary RNFL Thicknesses Obtained From the Standard Iowa Reference Algorithm, Our New Angle-Corrected Iowa Reference Algorithm, and the Cirrus Algorithm

Method	OCT	<i>n</i>	Mean, μm (95% CI)	SD, μm	ICC (95% CI)	CV, %	RC, μm	95% TL, μm
Iowa Reference Algorithm	Visit 1	56	74.09 (69.17–79.01)	18.80	0.964 (0.940–0.979)	3.02	9.63	5.06
	Visit 2	56	74.09 (69.48–78.70)	17.59				
Angle-corrected Iowa Reference Algorithm	Visit 1	56	71.47 (66.74–76.20)	18.07	0.990 (0.983–0.994)	1.61	5.06	2.62
	Visit 2	56	71.78 (66.97–76.58)	18.34				
Cirrus algorithm	Visit 1	56	77.11 (73.25–80.96)	14.73	0.960 (0.933–0.976)	2.77	7.94	4.79
	Visit 2	56	77.52 (73.90–81.14)	13.82				

<http://www.biomed-imaging.uiowa.edu/downloads>). Our custom graph-theoretic approach uses edge-based cost functions, which consist of inverted gradient magnitudes of the dark-to-bright transition for the upper surface and the bright-to-dark transition for the lower surface from top to bottom of the OCT volume.^{6,7} The Iowa Reference Algorithm implementations for automated RNFL and optic disc segmentations were applied to the original OCT volumes and to the angle-adjusted OCT volumes. Mean peripapillary RNFL thickness was calculated by averaging the segmented RNFL thickness on the 3.46-mm-diameter circle coinciding with the center of the segmented optic disc.

Statistical Analysis

A paired *t*-test was performed to compare mean peripapillary RNFL thicknesses of all OCT image volumes (visits 1, 2) measured by two different algorithms. Reproducibility of the mean peripapillary RNFL thicknesses of two visits was determined by intraclass correlation coefficient (ICC), coefficient of variation (CV), repeatability coefficient (RC), and 95% tolerance limit (TL) for our layer segmentation method without/with the retinal angle correction and for the Cirrus algorithm. The ICC is a statistic representing agreements between two measurements of the same eyes and was calculated on the basis of a two-way random model for ANOVA using statistical software (R version 2.15.2, R Development Core Team; provided in the public domain at <http://www.r-project.org/>; R Foundation for Statistical Computing, Vienna, Austria).⁹ The CV was defined as a normalized measure of dispersion of two measurements and was calculated by dividing the SD of two measurements (intervisit SD) by the mean of the two measurements. The RC was defined as the value providing an interval, within which 95% of the differences of two measurements lie, and was obtained by multiplying the SD of the difference of the two measurements by 1.96.^{10,11} The 95% TL was defined as the value providing an interval, for which there is 95% confidence that it will contain 95% of all differences of two measurements, and was calculated as $1.645 \times \sqrt{2} \times \text{intervisit SD}$.^{12,13}

RESULTS

Fifty-eight consecutive patients including 20 males and 38 females were enrolled in the study. They were composed of 54 patients of Caucasian, three of African American, and one of Hispanic origins, and their mean age was 62.9 ± 14.8 (mean $\pm$ SD) years. Thirty-one patients were diagnosed as having glaucoma, and the other 27 patients had suspected glaucoma. Their Humphrey visual field analyzer mean deviation was -1.89 ± 3.08 dB, and the mean pattern SD was 3.36 ± 3.02 dB.

Repeat ONH-centered OCT image volumes were obtained within a 4-month period (75.4 ± 19.8 days, ranging from 7 to

116 days) from both eyes of the 58 glaucoma patients and suspects. The OCT volumes acquired from only one eye randomly chosen for each subject were included in the study. Two Caucasian subjects with OCT volume pairs having obvious motion artifacts through the optic disc, clipped A-scans through the 3.46-mm peripapillary circle, or low signal strength (<6), were excluded from analysis. For the study, a total of 112 OCT volumes (29×2 OD OCT volumes, 27×2 OS OCT volumes obtained from 56 patients) were used.

For our adjustment method of the retinal angles in the ONH-centered OCT image volumes, a *d* value was used to create a line representing the retina. In preliminary work, to find the *d* value (in mm), 0.05, 0.1, 0.2, 0.3, 0.5, and 1.0 were tested, and although the differences were small, 0.1 mm (3.3 pixels) showed the highest ICC value. In the experimental data, the lines determined by the 0.1 mm were temporally tilted by $4.5 \pm 4.4^\circ$, ranging from -10.1° to 14.5° in the B-scan adjusted for voxel aspect ratio of the SD-OCT.

The peripapillary RNFL thicknesses measured by the Iowa Reference Algorithm after angle correction OCT volumes (mean: $71.62 \mu\text{m}$, 95% confidence interval [CI]: 68.27 – $74.98 \mu\text{m}$) were significantly thinner than those obtained by the Iowa Reference Algorithm without adjustment volumes (mean: $74.09 \mu\text{m}$, 95% CI: 70.73 – $77.45 \mu\text{m}$) ($P < 0.001$, 95% CI of the difference: 1.87 – $3.07 \mu\text{m}$) and those obtained by the Cirrus algorithm (mean: $77.31 \mu\text{m}$, 95% CI: 74.68 – $79.95 \mu\text{m}$) ($P < 0.001$, 95% CI of the difference: 4.55 – $6.83 \mu\text{m}$). Intervisit reproducibility of the peripapillary RNFL thicknesses obtained from the repeat OCT image volumes is shown in the Table for the Iowa Reference Algorithm, the angle-corrected Iowa Reference Algorithm, and the Cirrus algorithm (Cirrus version 5.1.0.96; Carl Zeiss Meditec, Inc.). Angle-corrected RNFL thicknesses (ICC: 0.990, 95% CI: 0.983–0.994) showed significantly better reproducibility than non-angle-corrected RNFL thicknesses (ICC: 0.964, 95% CI: 0.940–0.979) and Cirrus RNFL thicknesses (ICC: 0.960, 95% CI: 0.933–0.976) based on the 95% CIs for the ICCs. In addition, the angle-corrected RNFL thicknesses (CV: 1.61 μm , RC: 5.06 μm , 95% TL: 2.62 μm) represented less variation of two measurements than the non-angle-corrected RNFL thicknesses (CV: 3.02 μm , RC: 9.63 μm , 95% TL: 5.06 μm) and the Cirrus RNFL thicknesses (CV: 2.77 μm , RC: 7.94 μm , 95% TL: 4.79 μm) based on the CVs, RCs, and 95% TLs.

Based on the Bland-Altman plots shown in Figure 3, the differences of the intervisit peripapillary RNFL thicknesses obtained from the adjusted OCT volumes were smaller than those measured from the unadjusted OCT volumes and those obtained by the Cirrus algorithm (see the mean $\pm$ RC values). In addition, for all three algorithms, no relationship was observed between the measured thickness differences and the corresponding average thickness values.

FIGURE 3. Bland-Altman plots for the intervisit peripapillary RNFL thicknesses obtained from original OCT volumes (mean: 0.00 μm , mean + RC: 9.63 μm , mean – RC: –9.63 μm), adjusted OCT volumes (mean: –0.30 μm , mean + RC: 4.75 μm , mean – RC: –5.36 μm), and by the Cirrus algorithm (mean: –0.41 μm , mean + RC: 7.53 μm , mean – RC: –8.35 μm).

DISCUSSION

Intervisit reproducibility of the peripapillary RNFL thicknesses obtained from spectral-domain optical coherence tomography is important for monitoring glaucoma progression. For consistent measurements, we have introduced an automated method for adjustment of the retinal angles in the OCT image volumes caused by the position of the scanning beam in the pupil.

Generally, the peripapillary RNFL thicknesses segmented after correction of the retinal angles showed better intervisit reproducibility compared with those obtained without the angle adjustment. The RNFL thicknesses measured by the Iowa Reference Algorithm perpendicularly to the retina after adjustment were more consistent than those measured vertically without adjustment and those obtained by the Cirrus algorithm.

The peripapillary RNFL thicknesses segmented after adjustment were thinner than those segmented without adjustment since the RNFL thickness perpendicularly measured to the retina is thinner than that obliquely measured (Fig. 1). They were also thinner than the RNFL thicknesses segmented by the Cirrus algorithm since the Cirrus algorithm tends to detect the edge below retinal blood vessels as the outer surface of the RNFL, whereas the Iowa Reference Algorithm has a tendency to segment the surface passing through the blood vessels. Additionally, differences in the optic disc center locations by the selected approaches could cause an effect on the peripapillary RNFL thickness measurements.¹⁴

Some prior studies noticed the fact that the retinal angle in the OCT image volume has an effect on the RNFL thickness measurement, and they tried to consider the retinal angle. Hwang et al.¹⁵ investigated the effects of myopic optic disc tilt and rotation on peripapillary RNFL thickness measured by SD-OCT. The eyes in the tilted group had thicker temporal RNFL thickness and more temporally positioned superior/inferior peak locations than those in the nontilted group. Hariri et al.³ evaluated the effect of angle of incidence on macular thickness and volume measurements obtained by SD-OCT. They used image-analysis software (ImageJ software, version 1.42q; available in the public domain at <http://rsbweb.nih.gov/ij/index.html>; developed by Wayne Rasband, National Institutes of Health [NIH], Bethesda, MD) to manually measure the oblique macular thickness in each B-scan image. Hong et al.¹⁶ proposed a measurement method considering three-dimensional (3D) scan angles for peripapillary RNFL thickness from ONH-centered OCT volumes. However, they did not mention

how to suppress the y -directional eye motion artifacts caused by slow scanning speed, which is necessary for measurement of the 3D RNFL thickness. Compared with their method, we calculated the peripapillary RNFL thickness in 2D by measuring the z -directional distance from the B-scan, where the retinal angle was adjusted based on the line representing the retina. If the motion artifact problem can be solved, our method would be easily extended to 3D.

Several studies have described reproducibility of peripapillary RNFL thickness using SD-OCT in glaucoma subjects. Mwanza and colleagues¹⁷ showed ICC of 0.972, CV of 2.7%, and 95% TL of 3.89 μm . Leung and associates¹⁸ showed ICC of 0.963 and CV of 1.79% using Cirrus. The reproducibility parameters obtained from the Cirrus algorithm in this study are slightly worse than those reported in the previous studies. More low-quality OCT scans may be included in our data set. Others have used different SD-OCT devices to study intravisit reproducibility of RNFL thickness. Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany) showed ICC of 0.996, CV of 1.74%,¹⁹ 1.2–1.4% CV,²⁰ and 0.99–0.98 ICC, 1.3–2.7% CV.²¹ OCT/SLO device showed ICC of 0.993 and CV of 2.0%.²²

There are several limitations to the proposed adjustment method. The first one is that our method is not applicable if each B-scan image does not include the outer boundary of the RPE to create a line depicting the retinal shape. The second one is that the Iowa Reference Algorithm used to detect the outer boundary of the RPE must provide reliable RPE segmentation. The third one is that our method is a 2D angle-adjustment approach, although the retina in the OCT volume is tilted in 3D since the Cirrus cube scan volumes (which we used in this study) are not axially registered in contrast to other manufacturers' scanners that use active eye tracking and simultaneous dual-beam imaging. To extend our method to 3D, y -directional motion artifacts would need to be suppressed, which we are currently studying. The fourth limitation is that the reproducibility improvement of peripapillary RNFL thicknesses obtained by our method over the Cirrus algorithm is small. The differences in RC and 95% TL are 2.88 μm and 2.17 μm , respectively, which may not be clinically relevant.

In conclusion, adding angle correction to the Iowa Reference Algorithm for measuring peripapillary RNFL thicknesses increased measurement reproducibility in patients with early glaucoma. The angle-corrected Iowa Reference Algorithm also exhibits better reproducibility than the Cirrus algorithm on the same patients. The Iowa Reference Algorithm is available in the public domain for research use at <http://rsbweb.nih.gov/ij/>

www.biomed-imaging.uiowa.edu/downloads/. More reproducible thickness measurement of the peripapillary RNFL has the potential to improve the treatment and management of patients with glaucoma.

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