Adjusting Circumpapillary Retinal Nerve Fiber Layer Profile Using Retinal Artery Position Improves the Structure–Function Relationship in Glaucoma

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PURPOSE. To investigate whether correcting the circumpapillary retinal nerve fiber layer (cpRNFL) thickness profile, using retinal artery position and papillomacular bundle tilt, can improve the structure–function relationship in glaucoma patients.

METHODS. Spectral-domain optical coherence tomography (SD-OCT) and visual field measurements were conducted in 142 eyes of 90 subjects with open angle glaucoma. The SD-OCT cpRNFL thickness profile was corrected for retinal artery position and/or papillomacular tilt in all twelve 30° sectors of the optic disc, and the structure–function relationship against corresponding 30° sectorial retinal sensitivity was investigated by using linear mixed model.

RESULTS. Applying a correction to the cpRNFL thickness profile for retinal artery position resulted in a stronger structure–function relationship in all 12 sectors of the optic disc. Furthermore, applying a further adjustment for papillomacular tilt resulted in a further improvement in 9 of 12 sectors.

CONCLUSIONS. Correcting cpRNFL profile, using the retinal artery position significantly strengthened the structure–function relationship. In most optic disc sectors, using the papillomacular bundle tilt improved cpRNFL thickness measurements.

Keywords: glaucoma, optical coherence tomography, retinal nerve fiber layer, retinal artery, structure and function

Optical coherence tomography (OCT) is an imaging technology enabling high-resolution measurements of the retina and is widely used to provide an objective evaluation of glaucomatous structural change.1 Using recent spectral-domain OCT (SD-OCT) machines, it is possible to measure the thicknesses of the circumpapillary retinal nerve fiber layer (cpRNFL), the macular RNFL, and also the macular ganglion cell layer and inner plexiform layer (ganglion cell complex; GCC), all of which are helpful in evaluating glaucomatous structural change.2–10 There is no consensus on which of these measurements is most useful for evaluating glaucomatos change, but specific structures may be preferentially damaged and/or more accurately measured, in a given patient. For example, Cordeiro et al.11 have reported that the diagnostic performance of cpRNFL thickness measurements tends to be better than GCC thickness measurement in patients with a small optic disc, and an inverse effect (GCC thickness measurement outperforms cpRNFL thickness measurement) is observed in patients with a large optic disc. Measured cpRNFL thickness is compared to a normal cpRNFL thickness profile, which is a double-humped curve with maximum thickness at the supratemporal and inferotemporal portions. Thus, the positions of the two normal peaks in cpRNFL thickness have a large influence on the diagnosis of abnormality in the observed measurement. Moreover, there is wide intersubject variation in the mapping of retinal locations to the optic nerve head (ONH),12,13 including in the positions of peak cpRNFL thickness14; this is particularly apparent in myopic eyes.15 We previously have reported that the positions of the retinal arteries are closely related to peak cpRNFL thickness (correlation coefficient = 0.92).15 In agreement with previous articles,16,17 in addition, the cpRNFL profile can be influenced by intersubject variation in the papillomacular bundle tilt.12,18

The purpose of the current study was to investigate whether correcting the SD-OCT cpRNFL thickness profile according to the positions of the retinal arteries and the papillomacular bundle tilt improves the structure–function relationship between cpRNFL thickness and visual field (VF) measurements.

MATERIALS AND METHODS
The study was approved by the Research Ethics Committee of the Graduate School of Medicine and Faculty of Medicine at the University of Tokyo. Written consent was given by the patients for their information to be stored in the hospital database and used for research. This study was performed according to the tenets of the Declaration of Helsinki.

Subjects
All of the following measurements were conducted at the University of Tokyo Hospital between the period of 2010...
through 2012. Subjects underwent complete ophthalmic examinations, including biomicroscopy, gonioscopy, intraocular pressure measurement, funduscopy, refraction and corneal radius of curvature measurements with an automatic refractometer (ARK-900; NIDEK, Tokyo, Japan), best-corrected visual acuity measurements and axial length measurements (IOL Master; Carl Zeiss Meditec, Dublin, CA, USA), as well as imaging with SD-OCT and VF testing (described next).

One hundred forty-two eyes of 90 subjects with open angle glaucoma in a glaucoma clinic at the Tokyo University Hospital were examined retrospectively. Glaucoma was diagnosed when the following findings were present: (1) presence of apparent glaucomatous changes in the ONH, according to a stereo fundus photograph, including either a rim notch with a rim width ≤ 0.1, disc diameter or a vertical cup-to-disc ratio of > 0.7 and an RNFL defect (with its edge at the ONH margin greater than a major retinal vessel) diverging in an arcuate or wedge shape; (2) presence of glaucomatous VF defects, compatible with glaucomatous ONH changes, fulfilling at least one of Anderson-Patella’s criteria, that is, a cluster of ≥ 3 points (3 nonedge points if VF was tested with Humphrey Field Analyzer [HFA; Carl Zeiss Meditec] 30-2 test program) in the pattern deviation plot in a single hemifield (superior/inferior) with P < 0.05—one of which must have been P < 0.01, a glaucoma hemifield test result outside of normal limits, or an abnormal pattern standard deviation with P < 0.05); and (3) absence of other systemic or ocular disorders that could affect the ONH and VF, including intraocular surgeries or refractive surgeries (except for uneventful intraocular lens implantation). Patients aged 20 years or older were included.

Visual field testing was performed, within 3 months from the OCT examination, by using the HFA with the SITA Standard strategy and the Goldmann size III target. Visual fields were measured by using either the 24-2 or 30-2 test program. When VFs were obtained with the 30-2 test program, only the 52 test locations overlapping with the 24-2 test pattern were used in the analysis. Unreliable VFs, defined as fixation losses greater than 20%, or false-positive responses greater than 15% were excluded.20 All of the participants had previous experience in undergoing VF examinations.

**Optical Coherence Tomography Data Acquisition**

Optical coherence tomography data were obtained with the 3D OCT-2000 (Topcon Corp., Tokyo, Japan). All SD-OCT measurements were performed after pupil dilation by using a combination of tropicamide 0.5% with phenylephrine 0.5% (Mydrin-P, Santen, Osaka, Japan). The cpRNFL was measured along a 3.4-mm-diameter circle centered on the disc barycenter; the optic disc center was determined in fundus photographs as the barycenter of the closed spline curve fitted to the automatically determined seven points (with manual correction if required).

The raster scan data and cpRNFL thickness were calculated for 12 cpRNFL sectors each accounting for 30°. A color fundus photograph was simultaneously obtained with the nonmydriatic fundus camera function. The magnification effect was corrected according to the manufacturer-provided formula (a modified Littman’s equation),21,22 which is based on measured refractive error, corneal radius, and axial length. Images influenced by involuntary blinking or saccade or those with quality factor < 60% were excluded.

**Determination of the Positions of Peak cpRNFL Thickness and Retinal Artery**

The measured OCT image was uploaded into Photoshop (Adobe Systems, San Jose, CA, USA), and the positions of peak cpRNFL thickness in the normative data were decided automatically by tracing the cpRNFL profile in ImageJ (version 1.48, http://imagej.nih.gov/ij/; provided in the public domain by the National Institutes of Health, Bethesda, MD, USA). Similarly, in the fundus photograph also obtained by OCT, the positions of major retinal arteries in the superotemporal and inferotemporal areas were automatically identified by identifying the points where the retinal artery and the 3.4-mm-diameter cpRNFL scan circle overlapped, using the ImageJ program (Fig. 1). The angle of the papillomacular bundle tilt was measured by calculating the angle between the macula on the fundus photograph and the center of optic disc as described above, using ImageJ (Fig. 1). Four types of corrections were applied to the 12 30° sectors cpRNFL thicknesses. Correction 1: retinal artery corrected average thickness (RA-aveT); first, the angles of the papillomacular bundle tilt were measured by using either the 24-2 or 30-2 test program. When VFs were obtained with the 30-2 test program, only the 52 test locations overlapping with the 24-2 test pattern were used in the analysis. Unreliable VFs, defined as fixation losses greater than 20%, or false-positive responses greater than 15% were excluded.20 All of the participants had previous experience in undergoing VF examinations.

A different adjustment was made on the opposite side of the retinal artery (i.e., the nasal side of the retina). For example, for identical measurements in the sector between 105° and 135°, the original cpRNFL thickness data would be adjusted to 180 –
Correction 4: papillomacular bundle tilt and retinal artery corrected average thickness (PMT-aveT); corrections 1 and 3 were both applied.

**Statistical Analyses**

The 24-2 HFA VF was divided into 12 sectors corresponding to twelve 30° cpRNFL optic disc sectors derived from the Garway-Heath structure–function map. Then the average retinal sensitivity in each sector was calculated, and the relationship between sectorial average sensitivity and corresponding 30° cpRNFL thickness measurements was analyzed by using (1) the original cpRNFL thickness measurement; (2) RA-aveT; (3) RA-totalT; (4) PMT; and (5) PMTRA-aveT. The relationships were analyzed by using a linear mixed model, whereby patients were treated as a “random effect.” The structure–function relationship for each measurement was compared by using the second-order bias-corrected Akaike Information Criterion (AICc) index. The AIC is an established statistical measure used to evaluate the relationship between variables, and the AICc is a corrected type of the AIC, which provides an accurate estimation even when the sample size is small. Any magnitude of reduction of AICc suggests an improved model, but it is possible to estimate the probability that one particular model is the model that minimizes “information loss.” Suppose that there are n candidate models and the AICc values of those models are AIC1, AIC2, AIC3, ..., AICn. Let AICmin be the minimum of those values. Then exp((AICmin – AICi)/2) can be interpreted as the relative probability that the ith model minimizes the information loss. Thus, the relative probabilities were calculated among models.

All statistical analyses were carried out by using the statistical programming language R (version 3.1.5; The R Foundation for Statistical Computing, Vienna, Austria). The method of Benjamini and Hochberg was used to correct P values for the problem of multiple testing.

**Table 1. Subjects’ Demographics**

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>SD, deg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male/female</td>
<td>63</td>
<td>79</td>
</tr>
<tr>
<td>Eye, right/left</td>
<td>67</td>
<td>75</td>
</tr>
<tr>
<td>52 total deviation, mean ± SD, dB</td>
<td>-4.8 ± 5.1</td>
<td></td>
</tr>
<tr>
<td>Axial length, mean ± SD, mm</td>
<td>25.2 ± 1.4</td>
<td></td>
</tr>
<tr>
<td>Position of retinal artery, superotemporal, mean ± SD, deg</td>
<td>74.2 ± 10.3</td>
<td></td>
</tr>
<tr>
<td>Position of retinal artery, inferotemporal, mean ± SD, deg</td>
<td>296.02 ± 10.83</td>
<td></td>
</tr>
<tr>
<td>Papillomacular bundle tilt, mean ± SD, deg</td>
<td>7.39 ± 4.14</td>
<td></td>
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</tbody>
</table>

SD, standard deviation.
RESULTS

Subject characteristics are given in Table 1. The mean of 52 total deviation values was $-4.8 \pm 5.1$ (−19.8 to 1.73) dB. The positions of peak cpRNFL thickness in the normative database were 69.13° in the superotemporal area and 290.87° in the inferotemporal area. The mean positions of retinal arteries in the cpRNFL scan circle were 74.2° ± 10.3° (50.3° to 108.9°) (mean ± standard deviation [range]) in the superotemporal area and 296.02° ± 10.83° (269.66° to 319.81°) in the inferotemporal area. Average papillomacular bundle tilt was 7.39° ± 4.14° (−3.54° to 19.73°). Retinal artery position in the superotemporal area was significantly correlated to axial length (reftinal artery position in the superotemporal area = 146.64° – 2.87 × axial length; $P < 0.0001$ for axial length, linear mixed model). On the contrary, artery position in the inferotemporal area was not significantly correlated to axial length (retinal artery position in the inferotemporal area = 209.66° − 1.04 × axial length; $P = 0.17$ for axial length, linear mixed model).

Table 2 summarizes 30° cpRNFL thickness measurements in each of the 12 sectors for the original OCT data, RA-aveT, RA-totalT, PMT, and PMTRA-aveT, along with the average retinal sensitivity. There was a significant difference between the original OCT data and RA-aveT in 7 sectors, RA-totalT in 10 sectors, PMT in 10 sectors, and PMTRA-aveT in 9 sectors ($P < 0.05$, linear mixed model; $P$ values corrected for multiple testing with the method of Benjamini and Hochberg).

Table 3 shows the AICc values for the structure-function relationship with the original OCT data, RA-aveT, RA-totalT, PMT, and PMTRA-aveT, at each of twelve 30° cpRNFL sectors. The AICc values with RA-aveT were smaller than the original OCT data in all 12 sectors, indicating a stronger relationship. The AICc values with RA-aveT were smaller than RA-totalT in all 12 sectors. In six sectors the AICc values with RA-aveT were smaller than PMT; however, the AICc values with RA-aveT were larger than PMT in the remaining six sectors. The AICc values with PMT were smaller than the original OCT data in 9 of 12 sectors. Among all the thickness measurements, the smallest AICc values were associated with PMTRA-aveT in nine sectors and RA-aveT in the remaining three sectors. As an example, Figure 3 shows the relationship between original cpRNFL thickness, RA-aveT, RA-totalT, PMT, and PMTRA-aveT, and corresponding VF sensitivity at sector between 255° and 285°.

DISCUSSION

In the current study, various corrections were applied to the cpRNFL thickness profile by using the positions of the retinal artery and the papillomacular bundle tilt. The structure-function relationship between OCT-measured cpRNFL thickness and VF sensitivity was investigated for each corrected measurement in all 12 sectors of the optic disc. As a result, it is suggested that correcting cpRNFL profile, using the retinal artery position, is useful to strengthen the structure-function relationship in all sectors. In most sectors, it was also useful to further correct thickness measurements by using the papillomacular bundle tilt.

We have previously reported that there is wide intersubject variation in the peak positions of the cpRNFL thickness profile, and that these peak positions are closely correlated with retinal artery angles.15 This correlation is much weaker with the retinal vein angle,15 in agreement with other reports.16,17 In eyes with glaucomatous structural change, the original peak positions of cpRNFL thickness cannot be specified. This information is very important when assessing the cpRNFL profile and glaucomatous structural damage because the position of the retinal artery is largely influenced by the...
elongation of the eye; however, the degree of elongation cannot be solely explained by a longer axial length because there is a large individual variation in axial length at birth. More specifically, different degrees of elongation must occur in eyes during growth when the axial length in adult eyes is identical but different at birth. This degree of elongation may affect the cpRNFL thickness profile, as represented by the peak positions, and also the artery angle. Thus, the normal cpRNFL profile may not be directly applicable to a glaucomatous eye, owing to a shift in the cpRNFL profile. We have previously shown that retinal artery positions in glaucomatous eyes may be important markers of the position of peak cpRNFL thickness before glaucomatous structural change. The current results support this hypothesis and suggest that correcting the SD-OCT cpRNFL thickness profile, using retinal artery position, results in a stronger structure-function relationship at all positions of the ONH. This correction is straightforward to compute, as the retinal artery angle can be identified very easily on the OCT fundus photograph and does not require axial length to be measured.

Papillomacular tilt variation is also important to consider when assessing the cpRNFL profile, and numerous reports suggest there is a wide intersubject variation in the papillomacular tilt angle. In the current study, applying a correction for papillomacular tilt did not result in any measurable improvement in the structure–function relationship at all positions of the ONH. This correction is straightforward to compute, as the retinal artery angle can be identified very easily on the OCT fundus photograph and does not require axial length to be measured.

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### Table 3. AICc Values for the Structure–Function Relationship Between Retinal Sensitivity and Sectorial cpRNFL Thickness With and Without Correction for Retinal Artery Positions and Papillomacular Tilt

<table>
<thead>
<tr>
<th>Sector</th>
<th>Original</th>
<th>RA-aveT</th>
<th>RA-totalT</th>
<th>PMT</th>
<th>PMTRA-aveT</th>
<th>Rank</th>
<th>Probability</th>
<th>15° to 45°</th>
<th>Rank</th>
<th>Probability</th>
<th>45° to 75°</th>
<th>Rank</th>
<th>Probability</th>
<th>75° to 105°</th>
<th>Rank</th>
<th>Probability</th>
<th>105° to 135°</th>
<th>Rank</th>
<th>Probability</th>
<th>135° to 165°</th>
<th>Rank</th>
<th>Probability</th>
<th>165° to 195°</th>
<th>Rank</th>
<th>Probability</th>
<th>195° to 225°</th>
<th>Rank</th>
<th>Probability</th>
<th>225° to 255°</th>
<th>Rank</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>345° to 15°</td>
<td>1257.8</td>
<td>1242.6</td>
<td>1276.4</td>
<td>1249.2</td>
<td>1258.1</td>
<td>4</td>
<td>5.3 × 10⁻⁵</td>
<td>1342.9</td>
<td>3</td>
<td>1.5 × 10⁻¹¹</td>
<td>1360.6</td>
<td>5</td>
<td>7.8 × 10⁻¹⁰</td>
<td>1316.8</td>
<td>4</td>
<td>2.3 × 10⁻⁹</td>
<td>1342.3</td>
<td>3</td>
<td>7.1 × 10⁻⁶</td>
<td>1299.9</td>
<td>2</td>
<td>0.10</td>
<td>1328.2</td>
<td>3</td>
<td>2.1 × 10⁻¹²</td>
<td>1359.8</td>
<td>4</td>
<td>1.2 × 10⁻⁹</td>
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<tr>
<td>15° to 45°</td>
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<td></td>
<td>3</td>
<td>1.5 × 10⁻²</td>
<td>1347.2</td>
<td>5</td>
<td>1.7 × 10⁻¹²</td>
<td>1359.8</td>
<td>4</td>
<td>1.2 × 10⁻⁹</td>
<td>1302.1</td>
<td>2</td>
<td>0.011</td>
<td>1328.6</td>
<td>2</td>
<td>0.0069</td>
<td>1329.3</td>
<td>5</td>
<td>1.8 × 10⁻⁹</td>
<td>1358.1</td>
<td>4</td>
<td>0.018</td>
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<tr>
<td>45° to 75°</td>
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<td></td>
<td></td>
<td>3</td>
<td>1.5 × 10⁻³</td>
<td>1342.3</td>
<td>3</td>
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<td>1299.9</td>
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Relative probability is defined as the possibility this model minimizes the information loss, compared with the model with smallest AICc.
cpRNFL Profile and Retinal Artery Position

...rim is used in the previous study. It is possible that the influence of papillomacular tilt is exaggerated when cpRNFL is measured at a 3.4-mm diameter projected from the optic disc, as compared to on the optic disc.

In the current study, adjusting cpRNFL thickness measurements using the papillomacular tilt angle (PMT) resulted in a stronger structure–function relationship in 9 of 12 sectors. Furthermore, AICc values from the linear model using PMTRA-aveT were smaller than AICc values from the linear model using RA-aveT in 9 of 12 sectors, indicating a stronger structure–function relationship.

One limitation of the current study was the lack of any measurements in healthy eyes. A further study should be carried out to compare the diagnostic performance of cpRNFL with and without correction for papillomacular tilt and retinal artery position, in particular because of the small amount of change between the cpRNFL thickness in the original value and with any corrections. However, OCT measurements, including the cpRNFL thickness profile, are not used solely for the diagnosis of glaucoma, but also for evaluating glaucomatous progression. For the latter, investigation of the structure–function relationship is still the key and we were therefore less concerned with diagnostic performance in this study. Further, glaucomatous eyes without any perimetric damage were not included in the current study. The usefulness in this population should be investigated in a future study. It is important to note that many other optical factors can also affect the cpRNFL thickness profile, such as scan circle diameter, anterior segment power, and scan angle of the ONH. A further study should be carried out to shed light on these issues, collecting data from eyes with a wider range of variation in measurements, such as refractive error and axial length.

Finally, in the current study it was assumed that changes in cpRNFL thickness due to the elongation of the eyeball occur in a linear fashion around the optic disc; however, this may actually occur in a nonlinear manner; for example, the influence may be more prominent in the temporal retina. A further study is needed to observe how the cpRNFL profile is correlated with any elongation of the eyeball, in particular how this may change during growth periods. In addition, the Japanese form of open angle glaucoma may be slightly different this may change during growth periods. In addition, the Japanese form of open angle glaucoma may be slightly different. Further study is needed to observe how the cpRNFL profile is correlated with any elongation of the eyeball, in particular because of the small amount of change between the cpRNFL thickness in the original value and with any corrections. However, OCT measurements, including the cpRNFL thickness profile, are not used solely for the diagnosis of glaucoma, but also for evaluating glaucomatous progression. For the latter, investigation of the structure–function relationship is still the key and we were therefore less concerned with diagnostic performance in this study. Further, glaucomatous eyes without any perimetric damage were not included in the current study. The usefulness in this population should be investigated in a future study. It is important to note that many other optical factors can also affect the cpRNFL thickness profile, such as scan circle diameter, anterior segment power, and scan angle of the ONH. A further study should be carried out to shed light on these issues, collecting data from eyes with a wider range of variation in measurements, such as refractive error and axial length.

In conclusion, correcting the SD-OCT cpRNFL profile by using retinal artery position was useful to strengthen the structure–function relationship and significantly in glaucoma patients. It may also be useful to further correct cpRNFL measurements by using the papillomacular bundle tilt. A further study should be carried out to compare the diagnostic performance of cpRNFL with and without correction for papillomacular tilt and retinal artery position, using both normative and glaucomatous eyes.

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References


