Predicted and Measured Retinal Nerve Fiber Layer Thickness From Time-Domain Optical Coherence Tomography Compared With Spectral-Domain Optical Coherence Tomography

Wolfgang A. Schrems, MD; Laura M. Schrems-Hoesl, MD; Delia Bendschneider, MD; Christian Y. Mardin, MD; Robert Laemmer, MD; Friedrich E. Kruse, MD; Folkert K. Horn, PhD

**IMPORTANCE** New methods are needed to compare peripapillary retinal nerve fiber layer thickness (pRNFLT) measurements taken from time-domain optical coherence tomography (TD-OCT) and spectral-domain OCT (SD-OCT).

**OBJECTIVE** To compare the agreement of measured and predicted pRNFLT using different equations based on pRNFLT measurements obtained by TD-OCT and SD-OCT.

**DESIGN, SETTING, AND PARTICIPANTS** Cross-sectional single-center study that took place at the Department of Ophthalmology, University of Erlangen-Nuremberg from November 16, 2005, to June 3, 2015, and included 138 eyes of control participants, 126 eyes of patients with ocular hypertension, 128 eyes of patients with preperimetric glaucoma, and 160 eyes of patients with perimetric glaucoma. All participants had standard clinical examinations to obtain TD-OCT (via Stratus OCT) and SD-OCT (via Spectralis OCT) measurements of pRNFLT. Two groups were matched for diagnostic subgroup, eye side, sex, and age. The TD-OCT measurements of the first group were used to predict the mean SD-OCT and 6-sector vertical-split pRNFLT measurements of the second group and vice versa. The agreement between the predicted pRNFLT calculations of conversion equations and measured pRNFLT of the second group was evaluated by intraclass correlation coefficients and Bland-Altman plots.

**MAIN OUTCOMES AND MEASURES** Mean and sectoral pRNFLT measurements obtained by TD-OCT and SD-OCT as well as the agreement between measured and predicted pRNFLT.

**RESULTS** The agreement for all investigated equations to predict mean pRNFLT measurements with intraclass correlation coefficients ranged from 0.937 to 0.939. Bland-Altman plots demonstrated systemic biases between ~0.7 μm and +1.1 μm for measured and predicted mean pRNFLT measurements. The ratio method demonstrated an intraclass correlation coefficient of 0.969 for the temporal-inferior sector. The best color-code agreement between both OCT devices was achieved by the no conversion method, with κ = 0.731 (95% CI, 0.656-0.806) for the mean pRNFLT.

**CONCLUSIONS AND RELEVANCE** These data suggest that the prediction of mean pRNFLT values by equations derived from TD-OCT and SD-OCT can be conducted with high levels of agreement. In individual cases and singular sectors, high prediction errors may occur. When longitudinal imaging data from both TD-OCT and SD-OCT are available, conversion equations may provide longitudinal comparability.
Optical coherence tomography (OCT) has become a rapidly evolving imaging technique since its introduction in 1991. It has led to significant enhancements of our knowledge of early detection and monitoring of optic nerve disorders, such as glaucoma.

The assessment of retinal nerve fiber layer thickness (RNFLT) obtained by OCT is a key diagnostic feature of structural glaucomatous damage that has been shown by numerous cross-sectional and longitudinal studies. For many years, time-domain optical coherence tomography (TD-OCT) was widely used in the diagnosis and follow-up of patients with glaucoma. The evolution from TD-OCT to spectral-domain OCT (SD-OCT) led to a more than 100-fold faster acquisition process, increased axial image resolution, and enabled the development of eye tracking systems and noise-reduction techniques, leading to a higher repeatability of measurements.

A method to compare periapipillary retinal nerve fiber layer thickness (pRNFLT) measurements obtained from TD-OCT and SD-OCT in patients who were imaged first by one type of OCT and then the other would facilitate the analysis of the progression of glaucomatous optic neuropathy. Furthermore, it would allow comparing pRNFLT obtained by TD-OCT devices reported in earlier clinical trials with those obtained by SD-OCT devices in more recent investigations. Previously, Pierro et al and Seibold et al performed a comprehensive comparison between TD-OCT and SD-OCT pRNFLT measurements, including 3 or more different SD-OCT devices; however, those studies included only healthy eyes.

The purpose of the present study was to investigate whether pRNFLT measurements of SD-OCT using Spectralis OCT could be reliably predicted by means of equations based on TD-OCT measurements using Stratus OCT and vice versa and to compare the agreement and accuracy of measured and predicted pRNFLT.

Methods

Study Design

This cross-sectional controlled single-center study was performed in accordance with the tenets of the Declaration of Helsinki for research involving human participants and was approved by the ethics review board of the medical faculty of the University of Erlangen-Nuremberg. Participants of the study were selected from the Erlangen Glaucoma Registry (1460 participants). We obtained written informed consent from all participants.

If both eyes of a participant were eligible for this study, 1 eye was selected at random. Patients and control participants were examined comprehensively by slitlamp biomicroscopy, gonioscopy, and dilated funduscopy. Goldmann applanation tonometry was performed 5 times in 24 hours to assess intraocular pressure in all patients.

Papillomorphologic evaluation was based on telecentric fundus camera 15° optic disc slides (Carl Zeiss Meditec). Appearance of the optic nerve head was classified as either healthy or glaucomatous based on the absence or presence of glaucomatous optic disc damage characterized by focal rim notchings, diffuse or localized wedge-shaped defects of the RNFL, and an abnormally small neuroretinal rim area, with respect to the size of the optic nerve head and optic disc hemorhages. Two masked glaucoma specialists (C.Y.M. and R.L.) independently graded optic disc slides. In cases of discrepancy, a third clinical glaucoma specialist who was unaware of the diagnosis made the judgment.

Participants with ocular hypertension had intraocular pressure levels more than 21 mm Hg and no signs of structural or functional glaucomatous damage. Patients with preperimetric glaucoma had signs of optic disc damage on optic disc slides without any corresponding visual field loss. Patients with perimetric glaucoma had a glaucomatous-appearing optic disc and pathologically cumulative perimetric defect curves.

All participants included in this study had a best-corrected visual acuity of 20/30 Snellen equivalents or better and clear optic media. Participants were excluded if they had a myopic refractive error exceeding −8 diopters of sphere, a hyperopic refractive error exceeding +6 diopters or 4 diopters of astigmatism, the presence of diabetes mellitus, or any eye disease other than primary open-angle glaucoma.

Spectral-Domain Optical Coherence Tomography

The pRNFLT measurements were obtained by the Spectralis HRA+OCT SD-OCT system (Heidelberg Engineering). Infrared reflection images (λ = 820 nm) and OCT B-scans (λ = 870 nm, 40 000 A-scans per second with 7-μm axial optical resolution) of the dual-beam laser scanning systems were acquired concurrently. The mean of 16 successive circular B-scans (768 A-scans with 12° diameter) centered at the optic disc was automatically calculated to reduce speckle noise. During image acquisition, an incorporated eye tracking system compensated for eye movements. An experienced operator controlled and corrected all segmentations of RNFLT as previously described. Spectralis OCT, version 5.3, was used. The mean pRNFLT and 6 vertical-split sectors of pRNFLT as described by Larrosa et al were evaluated.

Time-Domain Optical Coherence Tomography

In this study, TD-OCT imaging with Stratus OCT, version 4.0.1 (Carl Zeiss Meditec Inc), was performed. The regular pRNFLT...
Comparison of Retinal Nerve Fiber Layer Thickness With TD-OCT vs SD-OCT

Original Investigation Research

Imaging Protocol and Quality Control
An operator who was masked from the scan data obtained all measurements of pRNFLT with both imaging devices in a single session. The TD-OCT and SD-OCT scans were performed in a randomly assigned order on the same day immediately after each other. For TD-OCT only, scans with signal strengths greater than or equal to 5 (maximum, 10) were accepted for further analysis. To decrease the effect of motion artifacts known to occur in TD-OCT, we calculated the mean of 3 consecutive peripapillary scans. For both SD-OCT and TD-OCT, scans with displacement of the scan circle as well as scans with mirror, blink, and out-of-register artifacts were excluded from further analysis. From 1690 TD-OCT scans, 20 (1.2%) were excluded owing to low signal strength and 14 (0.8%) were excluded owing to artifacts or displacement of the scan circle. From 555 SD-OCT scans, 3 (0.5%) were rejected owing to artifacts. A total of 1656 scans for TD-OCT and 552 scans for SD-OCT were included in the final analysis. To compare Stratus OCT measurements with Spectralis OCT measurements, we calculated the mean thickness data of 32 peripapillary sectors (11.25° each). To compare the predicted and actual values of sector RNFLT, we formed 6 new vertical-split sectors for Stratus OCT according to the Spectralis OCT sectors by calculating the mean.

Perimetry
All patients and control participants were measured with standard white-on-white automated perimetry by means of an Octopus 500 computerized automatic static perimeter (Haag-Streit). The percentage of false-negative and false-positive answers had to be lower than 15%. A pathologic visual field test was characterized by clusters of at least 3 adjacent points with P < .05 or 2 adjacent points with P < .01 in the pattern deviation map assessed with Peridata software, version 2.2.3. The first 2 visual field tests from each patient were excluded from further analysis to avoid learning effects.

Main Outcomes and Measures
The cohort was divided into 2 equally composed groups of patients matched for diagnostic subgroup, eye side, sex, and age by a block pseudorandomization process that used the Mersenne-Twister algorithm.12 The OCT data of the first group were used to determine equations (equation group), which were then tested on the second group (test group).

Stratus OCT measurements of the first group were used to predict the pRNFLT of the Spectralis OCT measurements and vice versa. Equations for the mean and 6-sector vertical-split pRNFLT measurement were constructed by the following methods: no conversion, mean difference, multiplication of a mean ratio, and linear regression.

For the no conversion method, we directly used the pRNFLT of the Spectralis OCT measurement to predict the Stratus OCT measurement and vice versa; thus, mean pRNFLT was used interchangeably.

For the mean difference method, we calculated the difference between Spectralis OCT and Stratus OCT for mean and sector data. The difference was subtracted from the Stratus OCT pRNFLT of each participant to predict Spectralis OCT pRNFLT and vice versa.

The mean ratio method involved computing the mean ratio of pRNFLT measurements from Spectralis OCT and Stratus OCT for mean and sector data. The computed value was multiplied by the Stratus OCT pRNFLT of each participant to predict the Spectralis OCT pRNFLT and vice versa.

Linear regression analysis was conducted to fit predictive linear models (\[ y = ax + b \]) to the observed mean and sector pRNFLT measurements, where \( y \) represented the predicted value of OCT, \( a \) represented the slope of the regression line, \( x \) represented the measured value of the other OCT, and \( b \) represented the y-intercept. These fitted models were used to make a prediction of the individual pRNFLT for mean and sector data.

To evaluate the intraclass repeatability of predicted and actual pRNFLT, we calculated the intraclass correlation coefficient (ICC) and 95% CI for mean and sector OCT data. For the ICC calculation, the 2-way single-ratings mixed-effects model was used. Agreement was assessed by Bland-Altman plots13 between the predicted and measured pRNFLT.

The pRNFLT color-code agreement (green, yellow, red, and white) as previously described by Rebolleda et al14 was evaluated by the Cohen \( \kappa \) for mean data after applying the 4 methods mentioned earlier. Mean pRNFLT measurements of all control participants included in this study were used to obtain the age-adjusted first percentile, fifth percentile, and 95th percentile values.

To assess potential demographic and clinical differences between diagnostic subgroups and between test and equation groups with respect to quantitative variables, we used 1-way analysis of variance and paired \( t \) tests. For differences in qualitative variables between subgroups, we performed the Pearson \( \chi^2 \) test. To counteract for the inflation of type I error owing to multiple comparisons, we used the Bonferroni correction.15 Statistical analysis was conducted using SPSS software, version 22.0 (IBM Corp). The significance level was \( P < .05 \).

Results
A total of 138 eyes of control participants, 126 eyes of patients with ocular hypertension, 128 eyes of patients with preperimetric glaucoma, and 160 eyes of patients with perimetric glaucoma were imaged by Stratus OCT and Spectralis OCT. Patients’ characteristics and statistical results are summarized in Tables 1 and 2. The mean defect and the square root of the loss of variance were significantly worse in the perimetric glaucoma group compared with all other diagnostic groups (\( P < .001 \)).

The control participants were younger than all other groups and the perimetric glaucoma group was significantly older than the ocular hypertension and control groups. The
equation and test groups did not differ in age, sex, eye side, diagnostic group, mean defect, and square root of loss of variance. No significant differences between the pRNFLT measurements of both imaging devices were observed for the mean pRNFLT of each diagnostic group and the test and equation groups (Figure 1). There were significant differences between sector pRNFLT measurements in all groups except for the preperimetric glaucoma group (Figure 1). Underlying pRNFLT data in all groups and sectors are summarized in eTable 1 in the Supplement. Equations that were derived from OCT measurements of the equation group are displayed in Table 3.

The percentage of data within 95% of limits of agreement was between 94.6% and 95.3% for the predicted Spectralis OCT and measured Spectralis OCT mean pRNFLT (Figure 2) and 94.9% and 95.3% for the predicted Stratus OCT and measured Stratus OCT mean pRNFLT (Figure 2). Systemic biases were between −0.7 and +1.1 μm and no proportional biases were observed (Figure 2).

For mean pRNFLT, ICCs ranged between 0.937 and 0.939 for all equation methods (eTable 2 in the Supplement). The regression equation method achieved the highest percentage of eyes within a difference smaller than or equal to 5% between the actual and predicted RNFLT, with 51.1% to predict Spectralis OCT mean pRNFLT and 53.6% to predict Stratus OCT mean pRNFLT (eTable 3 in the Supplement). The ratio method showed the highest ICC values for all regional sectors; however, those were not statistically significantly different from the values obtained by unconverted prediction (eTable 4 in the Supplement). The ICCs ranged between 0.770 for the nasal sector and 0.969 for the temporal-inferior sector to predict the Spectralis OCT pRNFLT and between 0.800 and 0.968 to predict the Stratus OCT pRNFLT. For patients with preperimetric glaucoma and perimetric glaucoma, the ICCs for unconverted prediction were lower compared with control participants in 2 nasoinferior sectors (Figure 3).

Color-code agreement between the predicted and actual mean Stratus OCT and Spectralis OCT ranged between $\kappa = 0.678$ (95% CI, 0.599–0.757) and $\kappa = 0.709$ (95% CI, 0.632–0.777), respectively, for the mean difference method and $\kappa = 0.731$ (95% CI, 0.656–0.806) for the no conversion method.

## Discussion

The transition from TD-OCT to SD-OCT imaging to document pRNFLT and monitor the structural progression of glaucoma leads to questions on the agreement and predictability of pRNFLT between the 2 different OCT technologies. In this

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Equation Group</th>
<th>Test Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of eyes</td>
<td>276</td>
<td>276</td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>55.8 (13.6)</td>
<td>55.2 (13.6)</td>
<td>.59</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>138/138</td>
<td>138/138</td>
<td>&gt; .99</td>
</tr>
<tr>
<td>Eye side, right/left</td>
<td>138/138</td>
<td>138/138</td>
<td>&gt; .99</td>
</tr>
<tr>
<td>Diagnostic group, control/ocular hypert/</td>
<td>69/63/64/80</td>
<td>69/63/64/80</td>
<td>&gt; .99</td>
</tr>
<tr>
<td>preperimetric glaucoma/perimetric glaucoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Refraction</td>
<td>−0.7 (2.4)</td>
<td>−0.7 (2.4)</td>
<td>.77</td>
</tr>
<tr>
<td>Defect in the central 30° of the visual</td>
<td>−1.6 (4.3)</td>
<td>−1.5 (4.1)</td>
<td>.86</td>
</tr>
<tr>
<td>mean (SD), μm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Square root of the loss of variance,</td>
<td>3.1 (2.6)</td>
<td>3.1 (2.8)</td>
<td>.81</td>
</tr>
</tbody>
</table>

* Differences between groups were tested for statistical significance with continuous variables for means with the analysis of variance and dichotomous variables with the Pearson χ² test.

Table 1. Demographic and Clinical Characteristics of Included Participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control Participants</th>
<th>Patients With Ocular Hypertension</th>
<th>Patients With Preperimetric Glaucoma</th>
<th>Patients With Perimetric Glaucoma</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of eyes</td>
<td>138</td>
<td>126</td>
<td>128</td>
<td>160</td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>46.2 (15.4)</td>
<td>55.2 (12.9)</td>
<td>59.4 (10.4)</td>
<td>60.6 (10.3)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>68/70</td>
<td>63/63</td>
<td>64/64</td>
<td>84/76</td>
<td>.97</td>
</tr>
<tr>
<td>Eye side, right/left</td>
<td>73/65</td>
<td>73/53</td>
<td>64/64</td>
<td>66/94</td>
<td>.04</td>
</tr>
<tr>
<td>Refraction</td>
<td>−0.7 (2.0)</td>
<td>−0.3 (2.5)</td>
<td>−0.9 (2.4)</td>
<td>−0.9 (2.5)</td>
<td>.10</td>
</tr>
<tr>
<td>Defect in the central 30° of the visual</td>
<td>0.7 (1.3)</td>
<td>0.6 (1.5)</td>
<td>0.1 (1.5)</td>
<td>−6.0 (4.9)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>mean (SD), μm</td>
<td>1.6 (0.7)</td>
<td>1.6 (0.6)</td>
<td>1.8 (0.7)</td>
<td>6.2 (2.9)</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

* Differences between groups were tested for statistical significance with continuous variables for means with the analysis of variance and dichotomous variables with the Pearson χ² test.

* Different mean from the perimetric glaucoma group (pairwise comparisons on the Scheffé test).

* Different mean from the control group (pairwise comparisons on the Scheffé test).

* Statistically significant.
study, we demonstrated that pRNFLT obtained by Spectralis OCT and Stratus OCT devices show high agreement and good predictability for mean pRNFLT measurements.

To date, different studies have addressed comparisons of pRNFLT measurements of SD-OCT and TD-OCT devices.\textsuperscript{9,16-19} Prior studies compared Spectralis OCT and Stratus OCT
Figure 2. Bland-Altman Plots Assess the Agreement Between Predicted and Measured Mean Retinal Nerve Fiber Layer Thickness (RNFLT)

A. No conversion method

B. Mean difference method

C. Ratio method

D. Linear regression method

E. No conversion method

F. Mean difference method

G. Ratio method

H. Linear regression method

The difference between predicted and measured Stratus OCT (A-D) and Spectralis OCT (E-H) RNFLT in control participants, patients with ocular hypertension, patients with preperimetric glaucoma, and patients with perimetric glaucoma.
pRNFLT measurements by answering different scientific questions. Töteberg-Harms et al found the intra- and interobserver repeatability of Spectralis OCT superior to Stratus OCT, especially for glaucomatous eyes. Pinto et al described strong structure-function correlations between the visual fields and both Spectralis OCT and Stratus OCT pRNFLT measurements in the overall and arcuate sectors. Nukada et al showed Spectralis OCT to be superior to Stratus OCT to detect wedge-shaped localized pRNFLT defects as seen on red-free fundus photographs for patients with perimetric and preperimetric glaucoma. Good agreement and high correlation between Spectralis OCT and Stratus OCT was demonstrated previously. In our study, the raw OCT data of both devices were comparable in most of the investigated sectors and subgroups. However, in accordance with previous investigators, we found absolute differences between Stratus OCT and Spectralis OCT pRNFLT measurements. The Spectralis OCT showed significantly higher values in 3 sectors of 3 of the diagnostic subgroups compared with Stratus

*Significantly lower intraclass correlation coefficient (P < .05).
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OCT and significantly lower values in 3 sectors of 2 diagnostic subgroups. These deviations might be owing to differences in segmentation algorithms of both devices or in image-processing procedures, such as the smoothing algorithm of Stratus OCT. Moreover, pRNFLT segmentation errors could be corrected manually for Spectralis OCT but not for Stratus OCT. Therefore, the segmentation errors of Stratus OCT that could not be corrected might have caused differences in pRNFLT measurements. In contrast to Shin et al, we found no differences in the mean pRNFLT. This might be related to the higher number of participants included in our study.

We observed a significant decrease of the ICC in the perimetric and perimetric glaucoma groups compared with the control group in 2 nasal sectors. This might be related to the deteriorating signal to noise ratio for both imaging devices in these sectors and/or dimmer illumination of the nasal RNFL because of the directional reflectance properties of the RNFL, previously reported by Knighton et al.

We could not observe significant differences between the best method and unconverted prediction for group comparisons. Bland-Altman plots showed a comparable percentage of data points within the 95% limits of agreements for all investigated methods and the CIs of the ICCs showed an overlap of the 95% CI. This may be owing to the small mean difference of pRNFLT measured by Spectralis OCT and Stratus OCT.

A test-retest variability of 4.95 µm for mean RNFLT in healthy eyes for Spectralis OCT was reported by Tan et al and 5.2 µm in glaucomatous eyes for Stratus OCT was reported by Budenz.

For all investigated methods, including no conversion, roughly half the eyes in our study showed a difference smaller than 5% between the measured and predicted mean RNFLT for both devices, which, presumably, is in the range of test-retest variability of Spectralis OCT and Stratus OCT. In our study, we included myopic patients with a myopic refractive error of as many as −8 diopters. Because highly myopic eyes have been shown to demonstrate significantly lower pRNFLT than low-moderate myopic eyes, one may speculate that including these patients in our study might have deteriorated the agreement of both OCT devices owing to a smaller signal to noise ratio or other yet unknown factors in these patients.

To predict sector pRNFLT, the ratio method showed the highest accuracy. However, CIs of sector conversion factors showed a considerable overlap, suggesting that a conversion equation may not be necessary for the prediction of sector pRNFLT. The prediction of mean pRNFLT was more robust in comparison with sector pRNFLT. This may be owing to the lower SD of mean pRNFLT compared with sector pRNFLT or owing to differences in the torsional eye position during scanning by Stratus OCT and Spectralis OCT. Particularly, head tilt might produce a significant displacement of the temporal superior nasal inferior temporal plot, with little effect on the global pRNFLT. Because TD-OCT and SD-OCT imaging could not be performed simultaneously, a possible limitation of the direct comparison of our study was the operator-dependent positioning of the scan circle and possible scattering along the scan circle owing to eye motion.

By linking longitudinal pRNFLT measurements obtained by Stratus OCT and Spectralis OCT to achieve longer follow-up data, new insights into the long-term effects and progression of glaucomatous optic neuropathy can be gained, which is of high value owing to the slowly progressive nature of the disease.

We propose that the methods reported in this study could easily be applied to different study populations when longitudinal imaging data from both Stratus OCT and Spectralis OCT are available to determine the best method for conversion and provide longitudinal comparability. As proposed by Kim et al, to reduce variability in 3-dimensional volume data of SD-OCT when compared with TD-OCT, a scan location-matching algorithm could be applied.

Conclusions

Given the lack of confirmatory studies and based on our data, we believe that group comparisons in clinical research could be performed and that the longitudinal comparability of Stratus OCT and Spectralis OCT mean pRNFLT measurements is feasible for OCT data with substantial color-code agreement and excellent correlation for mean temporal-superior and temporal-inferior sectors. Although we identified equations that could ameliorate the agreement of Stratus OCT and Spectralis OCT pRNFLT measurements, 95% CIs of all equations except the regression equation method (eTables 3 and 4 in the Supplement) included 1 for the slope and 0 for the y-intercept, indicating that conversion equations may not be necessary to provide comparability of both imaging devices.

We do not recommend using pRNFLT measurement data of both OCTs interchangeably for treatment decisions of individual patients in clinical practice because this may lead to the misjudgment of pRNFLT owing to possible high prediction errors.

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REFERENCES