Correlation between Local Glaucmatous Visual Field Defects and Loss of Nerve Fiber Layer Thickness Measured with Polarimetry and Spectral Domain OCT

Folkert K. Horn, Christian Y. Mardin, Robert Laemmer, Delia Baleanu, Anselm M. Juenemann, Friedrich E. Kruse, and Ralf P. Tornow

PURPOSE. To study the correlation between local perimetric field defects and glaucoma-induced thickness reduction of the nerve layer measured in the peripapillary area with scanning laser polarimetry (SLP) and spectral domain optical coherence tomography (SOCT) and to compare the results with those of a theoretical model.

METHODS. The thickness of the retinal nerve fiber layer was determined in 32 sectors (11.25° each) by using SLP with variable cornea compensation (GDxVCC; Laser Diagnostics, San Diego, CA) and the newly introduced high-resolution SOCT (Spectralis; Heidelberg Engineering, Heidelberg, Germany). Eighty-eight healthy subjects served as control subjects, to determine the thickness deviation in patients with glaucoma. The relationship between glaucomatous nerve fiber reduction and visual field losses was calculated in six nerve fiber bundle–related areas. Sixty-four patients at different stages of open-angle glaucoma and 26 patients with ocular hypertension underwent perimetry (Oc-tapus G1; Haag-Streit, Koniz, Switzerland) and measurements with the two morphometric techniques.

RESULTS. Sector-shaped analyses between local perimetric losses and reduction of the retinal nerve fiber layer thickness showed a significant association for corresponding areas except for the central visual field in SLP. Correlation coefficients were highest in the area of the nasal inferior visual field (SOCT, 0.81; SLP, 0.57). A linear model describes the association between structural and functional damage.

CONCLUSIONS. Localized perimetric defects can be explained by reduced nerve fiber layer thickness. The data indicate that the present SOCT is useful for determining the functional-structural relationship in peripapillary areas and that association between perimetric defects and corresponding nerve fiber losses is stronger for SOCT than for the present SLP. (Clinical-Trials.gov number, NCT10049423.) (Invest Ophthalmol Vis Sci. 2009;50:1971–1977) DOI:10.1167/iovs.08-2405

Knowledge of the relationship between structural and functional damage in glaucoma may be helpful in understanding the pathogenesis of the disease and in observing the progress of the disease over a period. This relationship has been measured with sensory tests and various imaging techniques.1–4 Significant correlations have been described between perimetric tests and optic disc parameters, such as the area of the neuroretinal rim or the nerve fiber layer thickness. Despite the local information of computerized white-on-white perimetry, the perimetric mean defect of the whole visual field has been used as a quantitative measure of functional ability.5–7 However, local correspondence may be important to judge progression, and therefore several studies have compared local visual field defects and corresponding local change in retinal structure. Photographic methods as well as modern scanning laser devices have been used to measure retinal structures and to investigate the association between focal structural damages and possible losses in the corresponding visual field area (Gar-way-Heath DF, et al. IOVS 2005;46:ARVO E-Abstract 980).1,2,8 A matter of particular interest is the topographic association between glaucomatous scotomas and losses in the course of the nerve fiber layer bundles.9,10 Retinal nerve fiber layer (RNFL) thickness can be measured with optical coherence tomography (OCT) and scanning laser polarimetry (SLP). Recently, spectral domain optical coherence tomography (SOCT) has been introduced in glaucoma diagnosis as a more accurate measurement technique for the study of retinal layers.

Diagnostic values in glaucoma detection of SLP and OCT technique have been documented, but only a few studies have been conducted to investigate the association between local RNFL and corresponding perimetric losses by using both methods in the same individuals. In the present study, RNFL thickness was measured in three subject groups with SLP and a newly introduced SOCT. In earlier statistical evaluations, significant correlations between local RNFL reduction and local sensitivity loss were found by using linear and nonlinear regression analysis. Recently, a linear model based on a few simple assumptions was proposed to describe this relationship, and it was shown that local perimetric losses and data from the time domain OCT fit the model.9,10 So far, results of SLP and SOCT have not been shown to fit this model.

The purpose of this study was to quantify local field loss of conventional computerized white-on-white perimetry and local RNFL reduction measured with SOCT and SLP in the same individuals and to compare the results with the recently published linear model for the relation between field loss and RNFL reduction.

METHODS

PROCEDURES

All patients who participated in this study were thoroughly examined by slit lamp inspection, application tonometry, fundoscopy, gonioscopy, perimetry, and papillometry. In addition, a 24-hour intraocular...
pressure profile (six determinations) was obtained for all patients. Papillometric evaluations of patients were based on 15° color photographs (telecentric fundus camera; Carl Zeiss Meditec, Dublin, CA) and subsequent planimetry (Summasketch III; Summagraphics, Seymour, CT) of the area of the optic disc and the neuroretinal rim area.11 To reduce the possible influence12,13 of the optic disc size, we did not include eyes with disc areas larger than 4 mm² in the study. Criteria for glaucoma diagnosis were an open anterior chamber angle and glaucomatous appearance of the optic nerve head, including an unusually small neuroretinal rim area in relation to the optic disc size and cup-to-disc ratios that were larger vertically than horizontally.14 These analyses were independently performed ophthalmoscopically and planimetrically by three glaucoma specialists (CYM, RL, AMJ). All individuals included in the study had clear optic media and visual acuity of 0.7 or better. On the day of examination, intraocular pressure was equal to or less than 21 mm Hg in all individuals. Exclusion criteria were all eye diseases other than glaucoma, the presence of diabetes mellitus, and a myopic refractive error exceeding −6 D. All patients were members of the Erlangen Glaucoma Registry, with yearly visits to our glaucoma service. The patients were referred by ophthalmologists for further diagnosis and follow-up of glaucoma. The inclusion/exclusion criteria and the type of examinations are defined in a protocol that was approved by the local ethics committee. The study protocol adhered to the tenets of the Declaration of Helsinki for research involving human subjects. Informed consent was obtained from all participants.

Subjects

Glaucoma Group. All 64 patients in this group had glaucomatous optic disc damage. The heterogeneous cohort of patients with glaucoma (34 women, 30 men; age, 62.5 ± 9.2 years) included 31 patients with primary open-angle glaucoma characterized by elevated intraocular pressure measurements higher than 21 mm Hg; 11 patients with secondary open-angle glaucoma with elevated intraocular pressure measurements due to pigmentary glaucoma (5 patients); pseudoexfoliation (5 patients); or traumatic anterior chamber angle recession (1 patient); and 22 patients with normal-pressure glaucoma. For the diagnosis of normal-pressure glaucoma, all intraocular pressure measurements had to be less than 21 mm Hg without medication. In these latter patients, ophthalmoscopy, medical history, and neuroradiologic, neurologic, and medical examinations did not reveal any other reason than glaucoma for the optic nerve damage. As we were interested in the correlation between nerve fiber loss and possible functional defects, we included patients with early and those with advanced glaucoma: 14 patients had diffuse, 34 had local, and 16 had no visual field losses in conventional white-on-white perimetry. The mean (±SD) of perimetric mean defects (MD) in the glaucoma cohort was 6.9 ± 6.0 dB, and corrected loss variance (CLV) in this group was 40.1 ± 43.4 dB² (standard indices of the Octopus G1 program; Haag-Streit). The local visual field losses were: 2.8 ± 4.3 dB (central), 6.5 ± 8.4 dB (nasal inferior), and 5.9 ± 7.3 dB (nasal superior). In this patient group, one eye of each patient was selected—always the eye with more advanced perimetric loss.

Ocular Hypertension Group. Patients in this group (26 patients: 14 men, 12 women; age, 57.8 ± 9.8 years) had intraocular pressures above 21 mm Hg in repeated measurements. All of them had normal results in white-on-white perimetry and normal optic discs. The perimetric MD was −0.9 ± 1.0 dB, and corrected loss variance was 2.1 ± 1.5 dB². One randomly selected eye of each patient was used in the study.

Control Group. The study included 88 normal eyes of 88 healthy subjects (32 women, 56 men; age, 58.1 ± 9.9 years). RNFL data of these subjects were necessary to determine sector-specific normal data for SLP and SOCT measurements. Findings in slit lamp inspection, white-on-white perimetry and/or FDT perimetry, tonometry, and funduscopy were normal. Optic discs were inspected and classified as normal by at least two experienced ophthalmologists. One randomly selected eye of each patient was used in the study.

FIGURE 1. Location of test points using Octopus perimetry (Haag-Streit, König, Switzerland) and superposition of an upside down nerve fiber photograph. The 59 test positions were arranged according to the course of the nerve fibers. Dotted lines: borders between visual field areas, delineated to study the correlation between localized perimetric losses and RNFL reduction.

Perimetry

All patients underwent visual field tests with standard white-on-white perimetry with a computerized static projection perimeter (Octopus 500; Haag-Streit). All patients had experience in sensory tests and had at least one earlier determination with the present perimeter. Those tests with more than 12% false-positive or negative responses were excluded. The present measurement algorithm (Octopus program G1, three phases) includes 59 test positions arranged according to the course of the nerve fibers (Fig. 1). Two commercial software programs (PeriData perimetry interpretation software, ver. 7.3.2; PeriData, Hürth, Germany, and statistical software SPSS; SPSS, Chicago, IL) were used to calculate local MDs based on a map of perimetric nerve fiber bundles similar to the one presented in a study by Garway-Heath et al.10 on the basis of test points of the perimeter (Humphrey; Carl Zeiss Meditec). Thus, in the present study, we used mean values of six visual field areas (Fig. 2). To calculate the mean visual field loss in these six areas, we calculated the antilog values at all single test positions and averaged them.13 For presentation and statistical analysis, these averaged values were converted back to the decibel scale.

Spectral Domain Optical Coherence Tomography

All normal subjects and patients were scanned using a commercially available SOCT system (Spectralis HRA+OCT, Heidelberg Engineering). This instrument uses a wavelength of 820 nm in the near-infrared spectrum in the SLO mode. The light source of the SOCT is a super luminescent diode with a wavelength of 870 nm. Infrared images and OCT scans (40,000 A-scans/second) of the dual laser scanning systems are acquired simultaneously. Twenty to 25 consecutive circular B-scans (3.4 mm diameter, 768 A-scans) centered at the optic disc were automatically averaged to reduce speckle noise. An online tracking system compensated for eye movements. The presently available manufacturer’s software version allows measurements of the total retinal thickness, but not of the RNFL thickness separately. To measure the RNFL thickness, B-scan images were exported as TIF files (8 bit/pixel). The upper and lower borders of the RNFL were manually segmented.
by an experienced assistant using a purpose-written macro for ImageJ (ver. 1.32; developed by Wayne Rasband, National Institutes of Health, Bethesda, MD; available at http://rsb.info.nih.gov/ij/index.html). The assistant was not informed about the disease classification. RNFL thickness was calculated as the distance between these two borders with a calibration factor of 3.87 μm/pixel (provided by Heidelberg Engineering). Compared with time-domain B-scan images, the spectral domain B-scans image showed less noise, higher resolution, and higher contrast for the RNFL, so that the borders could be clearly identified and marked. The retinal vessels within the RNFL were considered to be part of the RNFL. B-scans with unclear borders, as well as mean images with insufficient alignment and focus were excluded. A parameter describing the image quality is not available in the present Spectralis software version (Heidelberg Engineering). To show the distribution of RNFL thickness around the optic disc, we averaged the thickness data of the circular scan to 32 sectors (11.25° each) and, to correlate the data with results from visual field areas (Fig. 1), we grouped the 32 peripapillary sectors in which the RNFL thickness was determined (numbers shown in white on black). Six nerve fiber bundle–related zones were formed similar to those introduced in a prior study\(^1\) (numbers shown black on white). Black ring: the calculation area used in SLP measurements. Dotted line: the position of the scan circle of the SOCT. Numbering and nomenclature for visual field areas (corresponding optic disc zones are given in brackets, with 0° corresponding to clock hour 9): 1, central (315–34°); 2, nasal-inferior (34–79°); 3, inferior (79–124°); 4, temporal (124–225°); 5, superior (225–270°); 6, nasal-superior (270–315°).

**Figure 2.** Correspondence of visual field areas and optic disc segmentation. Throughout this study we used the following nomenclature: *areas* of visual field defects were based on local perimetric test positions whereas peripapillary *zones* were based on thickness measurements in *sectors*. *Left*: visual field areas in this study. *Right*: 32 peripapillary sectors in which the RNFL thickness was determined (numbers shown in white on black). Six nerve fiber bundle–related zones were formed similar to those introduced in a prior study\(^1\) (numbers shown black on white). Black ring: the calculation area used in SLP measurements. Dotted line: the position of the scan circle of the SOCT. Numbering and nomenclature for visual field areas (corresponding optic disc zones are given in brackets, with 0° corresponding to clock hour 9): 1, central (315–34°); 2, nasal-inferior (34–79°); 3, inferior (79–124°); 4, temporal (124–225°); 5, superior (225–270°); 6, nasal-superior (270–315°).

**Statistical Methods**

The RNFL thicknesses measured in the control subjects were used to determine local thickness deviation in all 32 sectors. Description of the results includes means and standard deviations. RNFL reduction was calculated in absolute (micrometers) and in relative (percentage) values for the graphic comparison of data derived from SLP and SOCT. The graphic presentations of thickness data show the mean and 95% confidence interval (CI). Comparisons between groups were made completely in the perimetric test field. To compare correlation coefficients, we calculated confidence intervals by bootstrap estimation, using the free data analysis environment R (ver. 2.6.2, www.r-project.org). Other analyses were performed in commercial software (SPSSWIN (ver. 15; SPSS Inc.). The level of significance was \(a = 0.05\) in all statistical tests. A Bonferroni correction for multiple testing was used by multiplying the observed \(P\) with the number of comparisons within each analysis.\(^2\)

To show the association between local perimetric losses and relative RNFL thickness, we calculated a theoretical curve according to a...
linear model given by Hood et al.\textsuperscript{9} Briefly, this model assumes that the measured RNFL thickness $T_M$ consists of two components: $T_M = T_A + T_R$, where $T_A$ is the thickness of the RGC axons, and $T_R$ is the residual or base thickness including glia cells and blood vessels.

As the visual field sensitivity decreases, the thickness $T_A$ decreases also, whereas the residual thickness $T_R$ does not change. The axons' thickness $T_A$ is linearly related to the relative linear sensitivity $S$:

\[ S = \frac{T_A}{T_A^0} \]

where $T_A^0$ is the axonal thickness of a normal subject, and $S$ is defined as $10^{-D/10}$.

The expression converts the measured defect value $D$ (in decibels) to the relative linear sensitivity $S$. A normal subject is characterized by $D = 0$, $S = 1$, and $T_A = T_A^0$. The resulting expression for the relation between the measured RNFL thickness $T_M$ and the relative sensitivity $S$ is $T_M = T_A^0 \times S + T_R$, and the relation between the measured RNFL thickness $T_M$ and $D$ is $T_M = T_A^0 \times 10^{-D/10} + T_R$.

In this article (Fig. 3), the measured values $T_M$ and $D$ are presented in a log-linear plot. For better comparability of SLP and OCT results, which show different thicknesses, the thickness in Figure 3 is given in relative values: $T_{rel} = \frac{T_M}{T_{avg}}$, where $T_{avg}$ is the average RNFL thickness in our control subjects ($T_{rel}$ in percents, $D$ in decibels). The solid line in Figure 3 represents the linear relation between $T_{rel}$ and $S$, according to the linear model. The residual thickness was calculated for each zone as the median of the RNFL data when local visual field losses were greater than 10 dB.

**RESULTS**

To study the relationship between nerve fiber damage and perimetric defects in nerve fiber bundle-related areas, we calculated the deviations from measurements in normal subject. Figure 4 shows the distribution of the RNFL thickness around the optic disc in 32 sectors in the different study groups. Mean sectoral thicknesses, as measured with SOCT, ranged from 60 to 144 $\mu$m in the control eyes and from 49 to 87 $\mu$m in the glaucomatous eyes (Fig. 4A). When the SLP technique was used for determination of the RNFL thickness, the range was from 29 to 86 $\mu$m in the control eyes and from 28 to 64 $\mu$m in the glaucomatous eyes. Figure 4B gives an
ated zones in all study groups are given in Table 1.

However, this finding is not significant if an adjustment according to observed for several sectors in the SLP measurements. How-
nonlinearities (i.e., “the number”) were not considered. In addition, new results may be biased in these areas and the main focus should be on nasal areas (numbers 1, 2, and 6 in Fig. 1).

In our correlations between optic disc zones and corresponding field areas, the structure-function relationship is more obvious with SOCT than with SLP, as can be seen in Table 2 and Figure 3. In agreement with earlier reports, the SOCT data correlated significantly with visual field defects in all arcuate superior and inferior visual field areas, but not in the central visual field. This lack of correlation is in concordance with the observation that SLP-derived RNFL thickness loss is generally low in this area, despite considerable perimetric losses. This result indicates that the diagnostic value of the present polarimeter depends on the localization of the patients’ functional defects. However, this does not mean that the diagnostic value of SLP is generally lower than that of the SOCT technique; one should keep in mind that only a small part of the total information from the SLP (namely, the thickness under the measurement ring) are included in this study, whereas other contributions to the devices’ nerve fiber index (i.e., “the number”) were not considered. In addition, new methods used in SLP such as the ECC (enhanced corneal compensation) acquisition technique and a more advanced quality assessment (TSS [typical scan score] quality score) may lead to higher diagnostic accuracy. It has been reported that 15% to 44% of examined subjects have an atypical birefringence pattern that can influence the SLP measurements. Therefore, the present differences between SOCT and SLP may be smaller if all subjects with atypical birefringence pattern are excluded. Choi et al. and Mai et al. showed that the structure-function relationship is well improved by using the ECC technique. The ECC technique and the TSS quality score were not available in our GDx software, and atypical retardation patterns were only assessed qualitatively. Further-

**DISCUSSION**

To investigate the relationship with bundle-related visual field defects, we used the deviation of the RNFL thickness from normal subjects, as absolute values differ between the SLP and OCT techniques. In the past, the correlation between localized perimetric losses and measurements of the optic nerve was studied in corresponding sectors using parameters of the neuroretinal rim and the thickness of the nerve fiber layer. When comparing results of these studies, it should be considered that analyses with HRT and planimetry are based on optic disc data, whereas the results of SLP and SOCT, as used in the present study, are measured in the peripapillary region, not on the border of the optic disc. When comparing results of peripapillary zones, one has to keep in mind that test grids of the present perimetric test routines cover only a part of the temporal visual field (maximum vertical eccentricity of the Octopus G1: 26°). Therefore correlation results may be biased in these areas and the main focus should be on nasal areas (numbers 1, 2, and 6 in Fig. 1).

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**FIGURE 4.** (A) Mean values (±95% CI) of retinal thickness as determined with the SLP and SOCT in 32 peripapillary sectors in normal subjects, patients with ocular hypertension or glaucoma (t, temporal; s, superior; i, inferior; n, nasal). Absolute RNFL thickness data are higher in SOCT than in SLP measurements. (B) Deviation from normal RNFL thickness for all subjects. In patients with glaucoma, losses of nerve fiber thickness were more pronounced in the inferior and superior sectors than in the nasal or temporal ones.
TABLE 2. Correlations between Peripapillary Optic Disc Zones and Defects in Visual Field Areas Determined in Glaucomatous Eyes

<table>
<thead>
<tr>
<th>Optic Disc Zone vs. Visual Field Area</th>
<th>1 Central</th>
<th>2 Nasal-Inferior</th>
<th>3 Inferior</th>
<th>4 Temporal</th>
<th>5 Superior</th>
<th>6 Nasal-Superior</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOCT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>-0.75, &lt;0.001</td>
<td>-0.81, &lt;0.001</td>
<td>-0.68, &lt;0.001</td>
<td>-0.47, &lt;0.001</td>
<td>-0.57, &lt;0.001</td>
<td>-0.77, &lt;0.001</td>
</tr>
<tr>
<td>Ocular hypertension</td>
<td>-0.61 to -0.85</td>
<td>-0.68 to -0.88</td>
<td>-0.46 to -0.79</td>
<td>-0.22 to -0.68</td>
<td>-0.37 to -0.72</td>
<td>-0.64 to -0.85</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>-0.49 to -0.001</td>
<td>-0.49, &lt;0.001</td>
<td>-0.26 to -0.67</td>
<td>-0.28 to -0.63</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SLP</td>
<td>-0.27 to -0.18</td>
<td>-0.35 to -0.72</td>
<td>-0.36 to -0.76</td>
<td>-0.07 to -0.54</td>
<td>-0.26 to -0.67</td>
<td></td>
</tr>
</tbody>
</table>

Data are Spearman correlation coefficients with 95% CI for the six optic disc zones versus visual field area.
Functional–Structural Relationship with SLP and SOCT 1977

VCC, a lack of correspondence was seen in the area of the papillomacular bundle where SOCT indicated a loss of more than 50% of the normal RNFL thickness in the advanced glaucomas (Fig. 3, visual field area 1). Ongoing long-term studies in patients with progressive glaucoma should reveal whether the present relationships can be confirmed intraindividually.

References


