Relationship between Visual Field Sensitivity and Retinal Nerve Fiber Layer Thickness as Measured by Scanning Laser Polarimetry

Patricio G. Schlottmann,1 Stefano De Cilla,1 David S. Greenfield,2 Joseph Caprioli,3 and David F. Garway-Heath1

PURPOSE. To evaluate the strength and pattern of the relationship between visual field (VF) sensitivity and retinal nerve fiber layer (RNFL) thickness measurements by scanning laser polarimetry (SLP).

METHODS. Fifty-four eyes of 54 normal subjects (age, 42 ± 15 years; VF mean deviation [MD], −0.69 ± 1.01 dB) and 51 eyes of 51 glaucoma patients (age, 66 ± 14 years; VF MD, −0.92 ± 5.43 dB) were imaged with an SLP using fixed corneal compensation (FCC) and variable corneal compensation (VCC). VF sensitivity was recorded in the dB and the 1/L scales. Linear and logarithmic relationships were sought globally and in six VF sectors. Relationships of VF and RNFL thickness with age were sought in normal subjects.

RESULTS. Both VF sensitivity and RNFL thickness declined with age (as determined by the regression slope): −0.13% (P = 0.0005) and −0.64% (P = 0.0001) per year for dB and 1/L VF sensitivity, respectively, and −0.25% (P = 0.003) per year for VCC RNFL thickness. FCC RNFL thickness was not statistically significantly related to age. The relationship of VF sensitivity to VCC global (R² = 0.49) and sectoral (R² = 0.00–0.47) RNFL thickness was greater than for FCC global (R² = 0.12) and sectoral (R² = 0.00–0.21) RNFL thickness. Relationships were curvilinear with the dB scale, with logarithmic regression of dB VF sensitivity against RNFL thickness being significantly better than linear regression. Logarithmic regression of 1/L VF sensitivity against RNFL thickness was no better than linear regression. Logarithmic regression of 1/L VF sensitivity against RNFL thickness was no better than linear regression. Logarithmic regression of 1/L VF sensitivity against RNFL thickness was no better than linear regression. Logarithmic regression of 1/L VF sensitivity against RNFL thickness was no better than linear regression. Logarithmic regression of 1/L VF sensitivity against RNFL thickness was no better than linear regression.

CONCLUSIONS. The strength of the structure/function relationships compare well with previous reports in the literature. The relationships were curvilinear with the dB scale and linear with the 1/L scale, and were much stronger with VCC than with FCC RNFL thickness measurements. (Invest Ophthalmol Vis Sci. 2004;45:1823–1829) DOI:10.1167/iovs.03-0692

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Glaucoma, the leading cause of irreversible blindness worldwide,1 is an optic neuropathy characterized by a progressive pattern of injury to the optic nerve and retinal nerve fiber layer (RNFL). To evaluate the extent of this damage and to estimate the rates of disease progression, it is important to establish the nature of the correlation between function (ganglion cell activity) and structure (ganglion cell distribution).

Several studies suggest that visual field (VF) loss is preceded by neuroretinal rim or RNFL loss and that progression of disc change may be detected before that of VF change.2–5 This is often ascribed to a “functional reserve” whereby ganglion cells can be damaged early in the disease without affecting sensitivity. The relationship between electrophysiological, psychophysical, and anatomic measurements in glaucoma was described as a continuous linear structure-function relationship.6 This study supports the hypothesis that there is no ganglion cell functional reserve, the impression of which is a result of the logarithmic decibel (dB) scaling of the VF.

Visual field testing is commonly used to diagnose, assess progression, and estimate the severity of glaucoma. Measurements made with white-on-white perimetry are usually recorded in the logarithmic (dB) scale. The curvilinear relationship between dB light sensitivity and ganglion cell number may be explained at least in part by the logarithmic scale.7 This logarithmic scale minimizes sensitivity changes at high dB levels and maximizes changes at low dB levels. A curvilinear relationship has also been described between dB VF sensitivity and neuroretinal rim measurements.8–11

Standard automated perimetry is still the gold standard to assess VF sensitivity, but there is no such standard to measure relevant structures in glaucoma. Current clinical techniques of RNFL examination, such as slit lamp fundus examination under red-free light and analysis of black-and-white photographs, are limited to providing mainly qualitative or semiquantitative assessments that requires some degree of observer experience.12,13 New methods including confocal scanning laser ophthalmoscopy, optical coherence tomography, and scanning laser polarimetry have been developed to provide real-time, quantitative information describing the optic disc and RNFL.14 The GDx is a scanning laser polarimeter developed by Laser Diagnostic Technologies (San Diego, CA) that uses scanning laser technology coupled with an integrated polarization modulator/detector to provide a retardation map of the peripapillary retina based on the birefringent properties of the RNFL.14 The polarization state of light is modulated by retardation in one axis (slow axis) by its passage through the nerve fibers of the RNFL. This retardation is in proportion to the thickness of the RNFL.15 Other birefringent structures of the eye are the cornea16 and the Henle fiber layer in the macula.17 The lens and the vitreous have little net birefringence. As the cornea contributes significant retardation, it needs to be compensated.18

In an earlier version of the GDx, an integrated component that compensated for the corneal retardation contribution was used. This was a fixed corneal compensator (FCC) that as-
sumed all individuals had a slow axis of corneal birefringence of 15° nasally downward and a magnitude of 60 nm. Greenfield et al. 19 described the corneal slow axis variability between individuals, and the important effect of corneal polarization axis and magnitude on the discriminating power of scanning laser polarimetry in mild to moderate glaucoma has been demonstrated. 17,20,21 When the importance of individual anterior segment compensation was appreciated, a prototype GDx with a variable corneal compensator (VCC) was introduced to achieve individualized corneal compensation. 17 In the VCC, the radial birefringence of Henle’s fiber layer in the macula was used as an “intraocular polarimeter” for measurement of corneal birefringence. Based on these measurements, the VCC was adjusted for each eye. Recent work has concluded that the discriminating power between normal and glaucomatous eyes is increased when the VCC is used 17–25 and that the VCC also improves the relationship between RNFL thickness measured with scanning laser polarimetry and VF. 24,25

The purpose of this study was to evaluate the strength and pattern of the relationship between VF sensitivity and RNFL thickness using FCC and prototype VCC scanning laser polarimetry.

**METHODS**

Fifty-four normal eyes of 54 normal control subjects, and 51 eyes of 51 patients with glaucoma were recruited prospectively from three sites (the Glaucoma Division of the Jules Stein Eye Institute, Los Angeles, CA; the Glaucoma Research Unit, Moorfields Eye Hospital, London, UK; and the Bascom Palmer Eye Institute, Palm Beach Gardens, FL). This study was approved by the Institutional Ethics Committees of each recruiting center, and adhered to the Declaration of Helsinki, with informed written consent obtained from all participants.

**Normal Subjects**

Normal subjects were recruited from staff members, friends or spouses of patients, or volunteers. Inclusion criteria were normal VF (as defined below), optic discs without structural abnormalities, such as coloboma or optic nerve head drusen, intraocular pressure <21 mm Hg, no previous history of ocular disease, and no family history of glaucoma. One eye was randomly selected for study if both were eligible. All subjects had visual acuity of 20/40 or better, with ametropia <7 diopters, and were at least 18 years of age.

**Patients with Glaucoma**

Glaucoma subjects were patients from the above institutions. Diagnosis was based on the VF examination (as defined below). Inclusion criteria were reproducible glaucomatous VF defects, optic discs without structural abnormalities, such as coloboma or optic nerve head drusen, and no other disorders that might cause VF loss. One eye was randomly selected for study if both were eligible. All subjects had visual acuity of 20/40 or better, with ametropia <7 diopters, and were at least 18 years of age.

**Exclusion Criteria for Both Groups**

Subjects excluded from the study had a history of diabetes, leukemia, AIDS, uncontrolled systemic hypertension, arteriosclerosis, dementia or multiple sclerosis, or concomitant use of hydroxychloroquine or chloroquine. Patients with previous corneal surgery, including photorefractive surgery, retinal surgery, or implantation of a primary or secondary intraocular lens, were also excluded.

**Visual Field Testing**

All VF testing was performed with the Humphrey Field Analyzer model 640 or 750 (Carl Zeiss-Meditec, Dublin, CA) and the 24-2 full threshold or 24-2 SITA standard program. Only VFs with the following reliability indices were included: fixation losses <15%, false positive responses <25%, and false negative responses <25%. A glaucomatous VF was defined as a reproducible defect of two or more contiguous points with P < 0.01 loss or greater, or three or more contiguous points with P < 0.05 loss or greater, or a 10-dB difference across the nasal horizontal midline at two or more adjacent points in the total deviation plot. 26 A normal VF was taken to be one in which there were no sensitivity losses matching the criteria for glaucoma.

VF sensitivity was recorded for each point using the dB [10 · log(1/Lambert)] and the 1/Lambert scales. No adjustment was made for type of thresholding algorithm.

The VF was divided into sectors based on the relationship between the central VF and optic disc, derived from a previously published optic disc-visual field map (Fig. 1). 27

**Image Acquisition**

Technical details of the Nerve Fiber Analyzer have been described above. For this study, the GDx was modified by an alteration of the corneal compensation unit with a hardware fixture consisting of two optical retarders incorporated into the scanning head designed to rotate relative to each other, to provide compensation for birefringence of any magnitude and axis. 17–25

The subjects were imaged with the GDx Nerve Fiber Analyzer, software version 1.0.16 (Laser Diagnostic Technologies) modified to permit the calculation of retardation arising in the cornea from the macular birefringence pattern. The operator ensured that each subject was appropriately aligned without head tilt. All subjects had five sets of 15° images obtained; three sets of one to three images were centered on the fovea, and two sets of three images were centered on the optic disc.
FIGURE 2. Plot of the mean global visual field sensitivity in dB units against mean global retinal nerve fiber layer thickness in micrometers, determined with variable corneal compensation. *Filled diamonds* represent eyes tested with the full-threshold visual field strategy and *open circles* represent eyes tested with the SITA visual field strategy. The *ellipses* identify possible outliers.

### Table 1. Study Population Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Normals (Mean ± Standard Deviation (range))</th>
<th>Glaucoma Mean (range)</th>
<th>P Value</th>
</tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td>42 ± 15 (19 to 76)</td>
<td>66 ± 16 (30 to 87)</td>
<td>&lt; 0.0001*</td>
</tr>
<tr>
<td>IOP (mm Hg)</td>
<td>14 ± 3 (10 to 19)</td>
<td>14 ± 4 (5 to 35)</td>
<td>NS*</td>
</tr>
<tr>
<td>Field mean deviation (dB)</td>
<td>-0.7 ± 1.0 (1.0 to -2.6)</td>
<td>-6.9 ± 5.6 (0.3 to -20.3)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Refraction (D)</td>
<td>-0.9 ± (-6.9 to 5.3)</td>
<td>-0.8 ± 2.6 (-6.4 to 2.9)</td>
<td>NS*</td>
</tr>
<tr>
<td>Eye side (% right)</td>
<td>66</td>
<td>58</td>
<td>0.4†</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>30</td>
<td>44</td>
<td>NS†</td>
</tr>
</tbody>
</table>

IOP, intraocular pressure; MD, mean defect; dB, decibels; D, diopters; NS, not significant.

* T test.
† Chi squared.

For the first two sets, images were acquired of the macula and peripapillary areas with the corneal compensator in the fixed position (magnitude 60 μm, axis 15° nasally downward) as in the previous hardware version of the GDx. Three repeat images of the macula were then obtained with the corneal compensator set to zero (no compensation). The macular scans were then used to calculate the magnitude and orientation of the required anterior segment compensation from an annulus 1 mm in diameter positioned concentric to the fovea; the means were taken of the three scans. The compensator was then set to neutralize the birefringence from the anterior segment of the individual eye. Neutralization was confirmed by repeat images of the macula demonstrating that the anterior segment birefringence had been neutralized—defined as a uniformly dark macular birefringence pattern—often with a central ‘donut’ shape, representing the Henle fiber distribution. The final set of measurements was then taken of the peripapillary area with the compensator in its neutralizing position.

A subjective assessment of image quality of macula images was made on the basis of the brightness and evenness of fundus illumination, motion artifact, and centration on the fovea. The operator discarded poor-quality images. Software-generated image quality assessment was used to evaluate images centered on the optic disc, which were also checked by subjective assessment.

Optic disc-centered images were aligned manually to generate a mean image. The RNFL thickness was measured along an annular ellipse 10 pixels wide, concentric with, and 1.75 times, the diameter of the ellipse drawn over the scleral ring. All measurements were generated with the GDx software.

### Data Analysis and Statistics

Association between RNFL thickness, VF sensitivity, and age were sought by linear regression analysis using the ‘least squares’ method. VF sensitivity was treated as the dependent variable and RNFL thickness as the independent variable in all regressions assessing the VF/RNFL relationship. As dB values are a logarithmic transform of differential light sensitivity (DLS), logarithmic regression was chosen for comparison with linear regression to assess relationships between variables. Equations for the linear regression analysis took the form $y = a + bx$. Equations for logarithmic regression took the form $y = a + b \log 10(x)$. A paired $t$-test was performed to evaluate the null hypothesis that the absolute prediction errors (absolute values of the residuals) have the same mean for both models (logarithmic and linear regression). Significance was assumed at $P < 0.05$.

The linearity of the relationship between VF sensitivity and RNFL thickness was assessed by plotting the residuals of the linear regression against RNFL thickness. A significant fit ($P < 0.05$) of a quadratic regression of the residuals against RNFL thickness was taken to indicate a nonlinearity in the VF sensitivity/RNFL thickness relationship.

The relationship between RNFL thickness, for both FCC and VCC settings, and VF sensitivity were calculated for the whole field and field sectors using linear and logarithmic regression analysis for both dB and 1/L scales.

### Results

The study population characteristics are summarized in Table 1. There was a range in severity of VF loss in the glaucoma group. Mean deviations ranged between 0.26 dB and −20.35 dB with a mean of −6.92 dB.

In the normal group, RNFL thickness declined with age. The mean slope (95% prediction intervals for the slope) using FCC settings was −0.19% (+0.25% to −0.62%) per year ($P = 0.39$),
and that using the VCC was $-0.25\%$ ($-0.08\%$ to $-0.43\%$) per year ($P = 0.003$). VF sensitivity declined with age at the rate of $-0.64\%$ ($-0.35\%$ to $-0.95\%$) per year ($P = 0.0001$) using the 1/L scale, and $-0.13\%$ ($-0.08\%$ to $-0.20\%$) per year ($P = 0.0005$) when using the dB scale. Because both RNFL thickness and VF sensitivity declined with age, and at similar rates, the RNFL thickness and VF sensitivities were not adjusted for age in the regression analyses.

**Variable Corneal Compensator Setting**

The regression of global dB VF sensitivity against global RNFL thickness was significantly nonlinear (quadratic regression on residuals, $P = 0.007$). Two sets of possible outliers were evident in the scatterplot (Fig. 2). When either, or both, these sets were excluded, the regression remained significantly nonlinear (all $P < 0.02$). Two VF strategies were used (full threshold and SITA) in this study (Fig. 2), and the distribution of tests between normal and glaucoma groups was not equal (7/54 normal subjects and 25/51 glaucoma patients underwent full threshold VF testing). To test the potential effect on the relationship of marginally lower VF thresholds obtained from full threshold testing, tests of linearity were performed on the subset of subjects tested with the SITA algorithm (Table 2). Analyses of the whole field (global), and inferonasal and inferotemporal sectors were significantly nonlinear in full data set and the SITA subset. Nonlinearity in the nasal sector was significant in the full data set and of borderline significance. Nonlinearity in the nasal sector was significant ($P = 0.001$) using the 1/L scale and linear regression method. There was no relationship between VF sensitivity and RNFL thickness in the temporal sector with any unit or regression analysis.

**Fixed Corneal Compensation**

$R^2$ values for VF sensitivity regressions against RNFL thickness were markedly smaller with the FCC (Table 6) than with the VCC settings.

**DISCUSSION**

Assessing the amount of glaucomatous damage is the first step toward the correct management of glaucoma. This is usually estimated by observation of structures affected by glaucoma (RNFL and optic nerve head) and by testing visual function (VF test). Periodic assessment is the way to establish the rate of progression. It is of fundamental importance to know the way in which damage to specific structures affects visual function.

In this study, an objective quantitative measurement of RNFL thickness, as measured by the GDx, was correlated with a quantitative measurement of VF that depends on subjective responses of a patient. The relationship between RNFL thickness, as measured by the scanning laser polarimeter, and VF sensitivity compares well with structure/function correlation studies reported in the literature. The global and sec-
Differential light sensitivity (DLS) is measured in VF testing in a logarithmic (dB) scale because this facilitates the appreciation of the wide range in retinal sensitivity found in normal and diseased eyes, and the psychometric function (frequency of seeing curve) conventionally is modeled in logarithmic units. However, a previous study assessed the relationship of seeing curve (conventionally in logarithmic dB scale) and a linear model of dB functional relationship in the normal and glaucoma subjects, and showed that the relationship between DLS and both PERG amplitude and neuroretinal rim area was curvilinear in the dB scale, and linear in the 1/L DLS scale. These results are consistent with the present study and indicate that, if the true underlying relationship between structure and function is curvilinear with the dB scale, and a linear model of dB functional progression is assumed, then one will underestimate the rate of change at near normal values, giving the impression of a functional reserve. It also results in the overestimation of the rate of change at more advanced stages of VF loss. The findings of this study support the hypothesis that there is no ganglion cell functional reserve but a continuous structure to function relationship, and that the impression of a functional reserve results, at least in part, from the logarithmic (dB) scaling of the VF.

Selection bias has the potential to affect the apparent structure/function relationship. In this study, glaucoma was defined on the basis of VF loss, without requirements for structural damage. However, patients were recruited from glaucoma clinics, and an assessment of structural damage usually forms a part of the diagnostic procedure. This is likely to strengthen the discovered structure/function relationship, though is unlikely to affect its pattern. Because the selection criteria were based on VF damage, it is likely that patients with VF loss, but healthier optic nerves, are included. The opposite group, patients with glaucomatous optic discs but no VF loss, were excluded. It is possible that this group of patients would exhibit functional reserve and this possibility requires further study. The effect of this selection bias would work in the opposite direction to the findings of this study, that structural damage appears more advanced than dB VF loss in the early stages of glaucoma.

The analysis in this study assumed the same structure/function relationship in the normal and glaucoma subjects, and visual inspection of the plots (Fig. 3) suggests that all subjects are part of the same distribution. However, further work is required to confirm or refute this assumption.

Visual field tests are a way of estimating loss of function associated with ganglion cell drop-out, and do not provide a direct measure of ganglion cell function. In previous studies, where relationships between VF and rim area were sought to describe the structure/function relationship, the function of ganglion cells was related to an anatomic structure (the neuroretinal rim), which comprises axons of ganglion cells and other structures such as blood vessels and glial cells. In this

![Figure 3. Plot of the mean global visual field sensitivity in 1/L units against mean global retinal nerve fiber layer thickness in micrometers, determined with variable corneal compensation. Filled diamonds represent eyes tested with the full threshold visual field strategy and open circles represent eyes tested with the SITA visual field strategy.](http://iovs.arvojournals.org/pdfaccess.ashx?url=/data/journals/iovs/932926/)

### Table 5. Slopes and 95% Prediction Intervals of Slope for Relationship between VF Sensitivity and RNFL Thickness

<table>
<thead>
<tr>
<th>Slope</th>
<th>95% Prediction Intervals of Slope</th>
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<tbody>
<tr>
<td>Global</td>
<td>36.7</td>
</tr>
<tr>
<td></td>
<td>29.4–44.0</td>
</tr>
<tr>
<td>Temporal</td>
<td>5.3</td>
</tr>
<tr>
<td></td>
<td>–7.0–17.6</td>
</tr>
<tr>
<td>Superotemporal</td>
<td>14.7</td>
</tr>
<tr>
<td></td>
<td>9.4–19.9</td>
</tr>
<tr>
<td>Supranasal</td>
<td>12.4</td>
</tr>
<tr>
<td></td>
<td>9.9–15.0</td>
</tr>
<tr>
<td>Nasal</td>
<td>19.0</td>
</tr>
<tr>
<td></td>
<td>13.2–24.8</td>
</tr>
<tr>
<td>Inferonasal</td>
<td>9.9</td>
</tr>
<tr>
<td></td>
<td>7.3–12.5</td>
</tr>
<tr>
<td>Inferotemporal</td>
<td>13.4</td>
</tr>
<tr>
<td></td>
<td>10.1–16.8</td>
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</table>

* Derived with VCC setting and 1/L scale, using linear regression analysis.
study, ganglion cell function correlated with RNFL thickness (related more directly to ganglion cell axon numbers). Because scanning laser polarimetry measures birefringence of the tissue in the peripapillary area, and it is believed that birefringence arises principally from microtubules within the ganglion cell axons,15 this technology may be more appropriate for structure/function correlation and result in higher correlations. No structure/function relationship was found in the temporal segment; there are a number of possible explanations for this. No adjustment for spatial summation in the central field was made. As the size of the stimuli remains unchanged across the VF, at early stages of damage this results in less change in the DLS in the central (within 15° of fixation), compared with peripheral, VF locations. In the temporal sector, there was a wide range of RNFL thickness measurements but no consistent associated change in VF sensitivity. The lack of relationship could also be explained by an apparent variation of tissue birefringence around the optic nerve head due to underlying structural differences among nerve bundles that serve different retinal regions (Huang X, et al. IOVS 2003;44:ARVO E-Abstract 3365).

There appeared to be an offset of RNFL measurements below 20 μm, and so the RNFL never appeared to be zero. It is not clear whether this was due to inaccuracies in measuring a thin RNFL or another source of retardation arising from unrecognized structures that had not previously been considered.

The results obtained in this study regarding the decline in RNFL thickness with age of 0.25% per year are consistent with previous imaging11 and histologic studies,9,22,23 and provide support to the notion that the GDx VCC measures ganglion cell axons or a correlate of these axons.9,9 Histologic studies have reported an age-related decline in optic nerve axon count, with the estimated rate of decline ranging from around 0.56%22 to 0.62%23 per year, similar to the rate of RNFL loss found in this study.

In summary, the strength of the structure/function relationships compared well with previous reports in the literature. The relationships were curvilinear with the dB scale and linear with the 1/L scale, and were much stronger with VCC than with FCC RNFL thickness measurements. Functional measurements in a linear scale should reflect disease progression more accurately and correlate better with structural measurements of disease progression. This study contributes to a better understanding of the relationship between structure and function, and may lead to an improved staging of the disease by means of a more appropriate measurement scale.

Acknowledgments

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References

17. Zhou Q, Weinreb RN. Individualized compensation of anterior

<table>
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<tr>
<th>Table 6. Coefficient of Determination ($R^2$) of Regression between Visual Field Sensitivity and Retinal Nerve Fiber Layer Thickness</th>
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<tbody>
<tr>
<td>dB Sensitivity</td>
</tr>
<tr>
<td>Linear Regression ($R^2$)</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Global</td>
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<tr>
<td>Temporal</td>
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Derived with FCC setting, using linear and logarithmic regression analysis.