Structure versus Function in Glaucoma: An Application of a Linear Model

Donald C. Hood,¹,² Susan C. Anderson,³ Michael Wall,³ and Randy H. Kardon⁵

PURPOSE. To evaluate a linear model that relates the glaucomatous loss in retinal nerve fiber (RNFL) thickness, measured with optical coherence tomography (OCT), to the loss in sensitivity, measured with standard automated perimetry (SAP).

METHODS. Fifteen patients with asymmetrical glaucoma, whose better eye was normal or near normal (mean deviations better than −3 dB) on SAP, were tested. SITA 24-2 standard and OCT RNFL thickness measures were made on three to five different occasions and the mean values were obtained. For each eye, the mean SAP loss was calculated for an upper and lower arcuate field region by averaging the loss in relative sensitivity on a linear scale. The average RNFL thickness for corresponding arcuate sectors of the lower and upper optic disc was obtained for each eye. A linear model was fitted to the plots of RNFL thickness versus SAP loss. According to the linear model, the RNFL thickness $R = (\sigma_o + b)$, where $T$ is the SAP sensitivity loss relative to age-matched normal eyes (linear scale), $(\sigma_o + b)$ is the RNFL thickness in the healthy/normal state ($T = 1$), and $b$ is the residual RNFL thickness measured when all sensitivity and all axons are lost.

RESULTS. The model provided a reasonable fit to the data with best fitting values of $(\sigma_o, b)$ of (upper field: 80.6 μm; 50.5 μm) and (lower field: 67.4 μm; 50.5 μm) and (upper field: 78.8 μm; 54.9 μm; $r = 0.82$) and (lower field: 59.2 μm; 61.5 μm; $r = 0.70$) for two different methods of best fit.

CONCLUSIONS. A linear model that relates RNFL thickness to losses in SAP sensitivity describes the results for arcuate regions of glaucomatous visual fields. The linear model provides a framework for assessing the relative efficacy of structural and functional tests throughout the course of the disease. (Invest Ophthalmol Vis Sci. 2007;48:3662–3668) DOI:10.1167/iovs.06-1401

The relationship between structure and function is important in glaucoma. Knowing the relationship between a structural and functional test can aid in assessing the relative efficacy of the two tests in detecting glaucomatous damage¹ and in more accurately determining the stage of the disease in an individual eye.

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The advent of automated, noninvasive techniques for measuring retinal nerve fiber layer thickness (RNFL) has sparked renewed interest in the relationship between structural and functional glaucomatous losses. In the past 6 years, a large number of empiric studies have related functional losses measured with static automated perimetry (SAP) to RNFL losses measured with these automated techniques. The analyses of these data have been largely descriptive, and there is a debate about the form of the function relating functional and structural losses. (For references, see the review by Garway-Heath and a recent article by Bowd et al.⁵) However, the theoretical treatment of these data has been relatively limited.² Recently, Hood⁴ proposed a simple model that predicts the relationship between RNFL thickness and loss of SAP sensitivity. This model, based on a model⁵ proposed to explain the relationship between multifocal visual evoked amplitudes and SAP losses, assumes that the local loss in RNFL thickness is linearly related to the loss in SAP sensitivity, when SAP sensitivity loss is expressed on a linear scale. However, a complete loss in sensitivity does not result in an RNFL thickness of zero; rather, it is associated with a finite RNFL thickness. In particular, there is some minimum value beyond which the thickness cannot be reduced because glial cells or other factors do not contribute to the number of axons. According to this model, the portion of the RNFL thickness due to retinal ganglion cell (RGC) axons is linearly related to the proportion of RGC axons ("response") remaining.

Hood⁴ reviewed the data from published studies⁶–¹¹ that used optical coherence tomography (OCT) to measure RNFL thickness and concluded that these data were consistent with the proposed model. However, there are problems with evaluating this model with the published data. First, the results from both OCT and SAP may vary from day-to-day, due to measurement variability. Existing studies typically present the cross-sectional results for a single OCT and SAP test. Second, the best way to evaluate the model is to compare local sensitivity to local RNFL loss. Most of the studies in the literature present the SAP data averaged over a large region (e.g., hemifield or full-field of 24-2 SAP). Finally, in existing studies, the SAPs value for a region of the visual field are usually expressed as an arithmetic average of dB units for each location within the region considered, but, as detailed in the Methods section, according to the model, these values should be antilogged before averaging and then logged again after averaging.¹⁵,¹¹

In the current study, we fit the linear model to data from patients with asymmetrical glaucoma tested on multiple occasions with RNFL thickness (OCT) and SAP. To minimize the effects of measurement variability, multiple measures of OCT retinal nerve fiber layer thickness recorded on different test days were averaged, as were the antilog values of the SAP measures for the same days. Regional changes were examined by using the mapping between SAP arcuate regions and corresponding retinal nerve fiber layer sectors proposed by Garway-Heath et al.¹² The data have been presented in abstract form (Hood DC, et al. IOVS 2007;48: ARVO E-Abstract 490).
METHODS

Subjects

Fifteen patients with glaucoma (primary open-angle glaucoma, \( n = 5 \); normal tension glaucoma, \( n = 7 \); pigmentary glaucoma, \( n = 2 \); pseudoexfoliative glaucoma, \( n = 1 \)) were participants in a larger prospective study and were chosen on the basis of interocular asymmetry of glaucoma. In particular, the least-affected eye was normal or had mild damage (better than a mean deviation of \(-3\) dB). These patients were judged to be stable by visual field testing and disc appearance over the period during which each was studied. The patient characteristics are summarized in Table 1. Procedures adhered to the tenets of the Declaration of Helsinki, and the protocol was approved by the committee of the Institutional Board of Research Associates of Columbia University and the University of Iowa Institutional Review Board (IRB) for Human Use.

Visual field testing was performed using automated perimetry ( Humphrey Field Analyzer, program 24-2 SITA, Carl Zeiss Meditec, Inc., Dublin, CA). In addition, RNFL thickness was measured with optical coherence tomography (OCT3, Stratus, fast RNFL circular scan, Carl Zeiss Meditec, Inc.). The circular scan RNFL data consisted of the average of three circular scans in the set and only sets with a signal greater than 6 were used. Repeat visual field testing and RNFL determinations were performed on the most damaged eye on five different test days in most patients (\( n = 10 \) patients for five determinations; \( n = 4 \) patients for four determinations; \( n = 1 \) patient for three determinations). The average time between the first and last test was 19.3 ± 4.8 months. As mentioned earlier, the SAP fields and disc appearance of each patient were stable over the testing period. For the arcuate field regions studied (described later), the change in mean deviation between the first and last test averaged \(-0.45 \pm 2.39\) dB (lower field) and \(-1.06 \pm 2.60\) dB (upper field), where a negative number is an improvement in sensitivity.

For each test date, the visual field threshold data and the OCT RNFL data were divided into six sectors, based on the schema proposed by Garway-Heath et al.2 (Fig. 1). For visual field threshold data, the decibel levels in each location of the total deviation field were converted to a linear scale (e.g., 0 dB converted to 1.0 and \(-30\) dB to 0.001) before averaging the data within each sector.1,5,11 To understand the rationale for averaging the values on a linear scale rather than on the log (decibel) scale, one must consider a region of the retina in which the left half is normal (0 dB total deviation and a normal complement of RGCs) and in which the right half has no RGCs remaining and a maximum loss in sensitivity (a total deviation of \(-30\) dB). If we take the average of the decibel levels, we get \(-15\) dB, which is \(1/30\) on a linear scale. In contrast, if we take the average on the linear scale, we get \(0.5\) (1.001/2), which is \(-3\) dB on the decibel scale. The model predicts that the OCT RNFL thickness due to RGC axons for the entire region should be one half the normal thickness.

The averaged data (linear scale) in each sector were either kept in relative linear units or converted back to decibel units, depending on the presentation of the data. For multiple test dates, the arithmetic average of all test dates was used for each sector. To test the linear model used in this study, we used only the superior (red) and inferior (blue) arcuate field regions in Figure 1 (top right panel) in the analysis. These regions, closest to the horizontal midline, were chosen because they fall within the 24-2 field, contain a significant proportion of the RNFL thickness, and show the earliest signs of damage. The 256 OCT RNFL values for the RNFL profile (black curve in Fig. 1, bottom) were exported for each eye and averaged for the multiple test dates. The RNFL thicknesses within the superior (blue) and inferior (red) sectors of Figure 1 (top left), were averaged. These disc sectors correspond to the inferior and superior field regions (Fig. 1, top left), according to the map in Garway-Heath et al.2

RESULTS

Figure 2 shows the data for the superior (Fig. 2A) and inferior (Fig. 2B) arcuate fields for the more affected and better eyes. Each data point represents the results in a single eye. In each panel, the mean RNFL thickness in the arcuate disc sectors in Figure 1 is plotted against the mean field loss in the corresponding arcuate field region.

The curve in Figures 2A and 2B is the fit of the linear model.4 In particular, RNFL thickness

\[
R = s_O 10^{-0.13\cdot D} + b \quad \text{for} \quad D \leq 0, \tag{1}
\]

where \(D\) is the total SAP deviation from normal sensitivity in decibels (the 0.1 in the exponent term converts from decibels to relative linear units or converted back to decibels to log units); \(s_O\) is the RNFL thickness attributable to the RGC fibers in the healthy normal state; and \(b\), the base level, is the residual response \(R\) (RNFL thickness) obtainable when a patient has lost all sensitivity to light and all RGC axons. Note that when the total deviation, \(D\), is 0 dB and the region on average is normal, then \(R\) equals \((s_O + b)\). When the total deviation is very abnormal (e.g., \(D = -30\) dB), then \(R\) is approximately equal to \(b\). So, the predicted curve goes from \((s_O + b)\) to \(b\) as the field goes from normal sensitivity (0 dB field loss in Figs.

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<th>Table 1. Patient Characteristics</th>
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Mean deviations are shown for one test date.
2A, 2B) to a total loss in light sensitivity (\(-30\) dB). To derive a predicted curve from equation 1, we estimated the starting (\(s_o\)) and ending (\(b\)) points of the curve.

In particular, a curve was fitted to the data by setting (\(s_o\)) equal to the median of the arcuate RNFL thickness for the better eye. (\(s_o\)) was calculated separately for the superior (131.1 \(\mu m\)) and inferior (117.9 \(\mu m\)) fields. \(b\) was set equal to the median (50.5 \(\mu m\)) of the RNFL thickness for field loss greater than \(-10\) dB for both superior and inferior field regions. (For field losses worse than \(-10\) dB, the RNFL thickness reaches an asymptotic value.)

Figures 2C and 2D show the same data on linear coordinates. RNFL thickness is plotted against the antilog of the total SAP deviations (Fig. 2D). The straight lines are the fit of

\[
R = s_o T + b \quad \text{for} \quad T \leq 1.0,
\]

where \(T\), the relative sensitivity, equals \(10^{0.1 \times D}\). \(T\) equals 1.0 when there is no loss (0 dB difference from normal) and approaches 0 for large losses in sensitivity. For example, total deviations (\(D\)) of \(-3\) dB and \(-30\) dB, yield \(T\) of 0.5 and 0.001, respectively. For the solid lines, the \(s_o\) and \(b\) were the same as in Figures 2A and 2B. For the dashed straight lines, the best-fitting linear regression was obtained by allowing both \(s_o\) and \(b\) to vary. The parameters, expressed as (\(s_o\) \(+\) \(b\)), of best fit were 135.7 \(\mu m\); 54.9 \(\mu m\) (superior field) and 120.7 \(\mu m\); 61.5 \(\mu m\) (inferior field), with \(r = 0.82\) and 0.70, respectively. The parameters for the two methods were similar with those of the best-fitting line, tending to be slightly larger. When the data from only the last test date were analyzed, the results were very similar. The best-fitting parameters (\(s_o\) \(+\) \(b\)) were similar (123.6 \(\mu m\); 57.5 \(\mu m\), superior field; and 116.7 \(\mu m\); 57.8 \(\mu m\), inferior field) as were the correlations (\(r = 0.81\) and 0.69, respectively).

The structural–functional analysis is based on a mapping of specific visual field locations to a particular sector of the circular RNFL scan, namely the Garway-Heath et al. map in Figure 1. To get a measure of whether this map was optimal for the eyes in this study, the following analyses were performed. First, the width of the Garway-Heath et al. arcuate disc sector was held constant (40°) and rotated in 5° steps around the optic disc. For each sector location, a correlation coefficient (\(r\)) between the SAP field loss and the RNFL for that location was determined with our linear model. Figure 3 shows the \(r\)-value for each sector location.
on the y-axis as a function of the position of the center of the
40° sector for correlations with the superior arcuate SAP field
values and inferior arcuate SAP field values. The best correla-
tions are close to the center of the sectors in the map by
Garway-Heath et al. For the superior arcuate field region, the
best correlations are centered approximately 5° nasal from the
center of the inferior arcuate disc sector in Garway-Heath et al.
The agreement with the map of Garway-Heath et al. is excel-
lent.

Although the group data showed good agreement with the
map by Garway-Heath et al., it would not be surprising to find
that an individual eye deviates from this map. If so, this would
contribute to the scatter of the data around the predicted
curves in Figure 2. The data in Figure 2A are shown again in
Figures 4A, with an outlier indicated with a red arrow. Figure
4B shows the RNFL profiles associated with this value. The gray
curve is the average profile of the RNFL thickness for the better
eye (two test days), the black curve is the average profile for
the affected eye (five test days), and the red curves are the five
individual profiles associated with the average black curve. The
region between the vertical blue lines represents the superior
RFNL sector in Garway-Heath et al. associated with the lower
arcuate field, and the region between the vertical red lines
represents the inferior RFNL sector associated with the upper
arcuate field. The solid horizontal red line in Figure 4B is the
average inferior arcuate RFNL thickness (83 μm) that is plotted
in Figure 4A. The small red crosses in Figure 4A show the
results for the five repeat measures in this eye. The agreement
among the measurements assures us that this point is not an
outlier due to random measurement variability, but is displaced
vertically from the predicted curve fit by approximately the
same amount for each test date. Suppose the superior arcuate
field projected to a more nasal disc region, shifted by 15 points
on the 256 point scale (21.1°), as shown by the dashed vertical
lines in Figure 4B. Under these conditions, the RNFL thickness
would be only 53 μm (dashed horizontal black line) and the
point in Figure 4A would fall near the predicted curve as
shown by the tip of the red arrow and the open red square.
The RNFL profile (1 day) of the better eye, shown as the solid
black, RNFL profile line in Figure 4C, is consistent with this
explanation. Note that the profile (black curve) for this eye
appears to be shifted to the left relative to the normal profile
shown as the green band. In general, given the steepness of the
RNFL profiles in the vicinity of the arcuate nerve fiber bundles,
relatively small deviations in the actual distribution pattern of
the bundle of retinal nerve fibers can produce noticeable
variations in the data from the line predicted by the model.
Therefore, anatomic variation in the location of specific nerve fiber bundles correlating to a specific arcuate visual field region may help to explain some of the scatter of points about the predicted curve (see the Discussion section).

A similar explanation only partially explains the outlier (filled black square) with the open black square above it in Figure 4A. It is not clear why this point falls well below the predicted curve. Perhaps, for reasons we do not understand, the RNFL damage exceeded that expected from the field in this patient.

DISCUSSION

To a first approximation, the data relating RNFL thickness to SAP loss (linear units) are described by a simple linear model.\(^4\) This model has been shown to describe the relationship between local multifocal VEP amplitude and local SAP field loss.\(^5\) While the fit of our data to the model was reasonably good, there are still outlier points and some scatter of points about the predicted curve. Before discussing the clinical implications of these findings, we will consider the possible sources of the scatter of the data points.

First, the model does not predict a single curve, but rather it predicts that there will be a family of curves. Figure 5 shows the same data as in Figure 2, with the dashed curves representing the boundaries of a family of predicted curves. To understand how these boundaries were obtained, one must recall that the model assumes that the measure of RNFL thickness has two components, one, \(s_o T\), which represents the thickness of the retinal axons associated with a given relative sensitivity, \(T\), and the other, \(b\), which is the residual RNFL thickness measured when all the axons are lost. This residual portion includes glial cells and perhaps limitations imposed by the algorithm that determines the RNFL layer. In individuals with normal visual sensitivity \((T = 1.0)\), the RNFL thickness is the sum of \(s_o + b\), where \(s_o\) is the thickness of the axon portion in the normal healthy eye. There is a wide range of values for \((s_o + b)\) as defined by the 95% confidence interval for normal RNFL thickness as shown by the green region in Figure 4C. Assuming for the moment that \(b\) is the same in different eyes, this confidence interval provides a range of normal \((s_o + b)\) values. (For the purposes of this example, the effects of age on \(s_o\), and thus on the confidence interval, were not taken into consideration.) The upper and lower boundaries of the confidence interval each provide the parameter \((s_o + b)\) for a theoretical curve. Figure 5 shows the data from Figure 2 with the predicted curves associated with the upper and lower limits of \((s_o + b)\) estimated from the green region in Figure 4C.

In particular, the upper curve describes the predicted course of glaucomatous progression in a patient who started with a relatively large \(s_o\), whereas the lower curve shows the predicted curve in a patient with an \(s_o\) that was relatively small when normal. Regardless of the initial RNFL thickness, all curves have the same common shape, meaning that there is a loss in SAP sensitivity that is proportional to RNFL thickness attributable to RGC axons. Note that the linear model, combined with the normal confidence interval, predicts that most of our data points should fall between these curves.

Several factors could contribute to the scatter of the points in Figure 2 and provide possible explanations for those falling outside the dashed lines in Figure 5. We delineate four of these possible factors. First, although we averaged the results from multiple measurements, there will be some measurement variability of both SAP threshold and RNFL thickness. Second, we assumed that the residual RNFL thickness \(b\) is the same in different individuals, whereas in fact there may be a variation in \(b\) due to a variety of factors. In particular, individuals may have different amounts of glial contributions to the RNFL thickness in the normal eye, and this contribution may increase or decrease with progressive losses in RGC axons due to disease. Third, as detailed earlier, there may be interindividual variations in the map between a particular region of the SAP field and the corresponding sector of the optic disc.\(^12\) If we know the mapping for an individual patient, we suspect that a sub-
stantial portion of the scatter could be reduced. Finally, there may be sources of SAP sensitivity loss that are not associated with RNFL loss. For example, sensitivity loss due to disease occurring before the RGCs (e.g., media opacities, photoreceptor disease) would result in data points falling above the predicted curves. In isolated glaucoma, there may be cases in which SAP sensitivity loss precedes a loss of axons. In such cases, the associated data points also should fall above the predicted curve. In fact, the model provides a framework for identifying these so-called sick as opposed to dead RGCs.

Although the model (equations 1 and 2) explicitly relates RNFL thickness to SAP loss, there is an implicit assumption that the local RNFL thickness is directly proportional to the number of RGC axons. That is, if local RNFL thickness is reduced by one half, then the number of RGC axons is reduced by one half. If we assume that the local number of axons is proportional to RNFL thickness, then the model predicts that the loss in the relative number of local RGCs is linearly related to local sensitivity loss (in linear terms). On the one hand, this assumption is in apparent contradiction with the conclusions in the monkey and human studies in which RGCs were counted in postmortem tissue. On the other hand, it is in agreement with theoretical treatments of the human data that argue for a linear relationship. For example, the best articulated model of the human data by Swanson et al. predicts that the relationship is linear for eccentricities beyond 5° to 10°. There are several differences among the methodologies in these studies and further work is needed before we can account for the differences in conclusions.

A related question is the relationship between RNFL thickness and SAP sensitivity in individuals with normal vision. The linear model articulated in this study is specified only for losses in sensitivity (i.e., Δ ≤ 0 dB or T ≤ 1.0); it makes no prediction about individuals who may have greater than normal sensitivity. We know that both SAP sensitivity and OCT RNFL thickness decrease with age. What remains to be determined is the quantitative relationship between these changes in the arcuate regions, as well as the nature of the changes, if any, within groups of normal individuals of the same age.

Clinical Implications

The model provides a framework in which to determine the stage of a diseased eye. In particular, as glaucoma progresses, the data points associated with a particular eye should move along a single theoretical curve. We intend to test this prediction by observing the patients over time. In addition, at any given time point, the model combined with information about the variability of the SAP and RNFL thickness measures provides a forum for considering the optimal use of these tests in the clinic. For detecting early glaucomatous damage, it is often said that SAP does not show a statistically significant defect until structural changes have taken place. For example, Kerri-gan-Baumrind et al. reported that a loss of 25% to 35% of the RGCs was associated with a statistically significant SAP field loss. According to our model, a loss of 25% to 35% of the RGCs would result in a loss in local sensitivity between −1.2 and −4.6 dB, within the 5% confidence interval (≈ −5 dB for local SAP points). However, this assumption does not necessarily mean that the RNFL measure is more sensitive than SAP for detecting early damage. In practice, test which is more sensitive to early damage will depend on the relative variation of each normal control measure and the initial RNFL thickness (s_o + b) when the eye is healthy.

Consider two patients, each with a 50% RGC loss, but with different s_o values. According to the linear model, each patient would show a proportional −3-dB field loss and normal SAP test results. In contrast, a 50% RGC loss and the consequent 50% decrease in s_o in the patient with the smaller s_o would result in a much smaller RNFL thickness than that in the patient with the larger s_o. Thus, the patient with the smaller initial RNFL thickness may show an abnormal RNFL thickness, whereas the other is still in the normal range. Thus, a significant change in the OCT RNFL thickness may occur before a significant change in the SAP in the patient with the smaller initial RNFL thickness. Conversely, the patient with the thicker initial RNFL may show abnormalities on the SAP before the RNFL thickness drops below the 5th percentile of the normal range. In general, to determine which of two tests is the more sensitive, one must know both the function that relates the two tests and the variability in test scores in healthy individuals.

The model also has implications for the use of the OCT RNFL thickness to detect progression of glaucoma. The model indicates that the RNFL thickness approaches the asymptotic value, s_b, as the SAP loss approaches −10 to −15 dB. The value of s_b, approximately 50 μm, provides an estimate for the lower bound of the OCT RNFL thickness. On average, the thickest part of the RNFL profile is <200 μm (Fig. 1, bottom). Thus, the largest range typically encountered spans a factor of less than 4. According to the model, a −15-dB loss would reduce a 200-μm thickness to 54.7 μm (150 μm × 0.03 (antilog of −15 dB) + 50 μm). This value is within the measurement error of the lower bound of 50 μm. Further, this is close to a best-case scenario; in practice, local SAP losses of more than −10 dB will not yield an RNFL thickness detectably different from the base level, b. Thus, the RNFL thickness is of limited use for observing regions with extensive damage. In contrast, the SD of SAP under conditions of a −10-dB loss is very large. For both tests, progression is probably best observed by examining relatively healthier regions of the same eye.

SUMMARY

A linear model that relates RNFL thickness to losses in SAP sensitivity has been applied to OCT and SAP data from arcuate regions of human glaucomatous visual field loss. The agreement with the data supports a linear relationship between RNFL thickness and the relative loss in SAP sensitivity at all stages of the disease. The model provides a framework for assessing the relative efficacy of structural and functional tests throughout the course of the disease.

Acknowledgments

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