Approach for Identifying Glaucomatous Optic Nerve Progression by Scanning Laser Tomography

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PURPOSE. To describe and test an analytical approach for identifying glaucomatous optic nerve change by scanning laser tomography.

METHODS. The approach (1) analyzed 30° sectors of rim area by (2) a novel and reproducible experimental reference plane, (3) estimated and accounted for measurement variability in each sector, and (4) required that any change exceeding variability in a single (positive) test should be confirmed as repeatable by a criterion requiring two of three consecutive tests to be positive. The sensitivity and false-positive rate of a single positive test and the two-of-three criterion were assessed in image series of one eye each of 20 ocular hypertension patients who converted to glaucoma (referred to as converters) who had unambiguous disease progression, and in one eye each of 20 normal control subjects.

RESULTS. Eighteen of 20 (90% sensitivity) converters and 7 of 20 (35% false-positive responses) control subjects had single positive test results, but with confirmation by the two-of-three criterion, the false-positive rate improved to 5% (1/20) whereas sensitivity was relatively preserved at 85% (17/20).

CONCLUSIONS. Estimates of rim area variability in each sector of each nerve allowed change consistent with disease progression to be distinguished from measurement variability. Confirming that change is repeatable by the criterion used in the study resulted in considerably fewer false-positive responses than did testing without confirmation, but with sensitivity not significantly compromised in the former. By this approach, eyes with progressive glaucoma could be distinguished from unchanging normal control eyes. (Invest Ophthalmol Vis Sci. 2003;44:2621–2626) DOI:10.1167/iovs.02-0850

The course of glaucoma has conventionally been evaluated by serial perimetry and disc photography, but both have considerable measurement variability that can make interpreting progression difficult.1–5 A promising alternative to conventional tests is the newer quantitative and more objective technique of scanning laser tomography for measuring optic nerve head (ONH) topography. By this method, the surface height of the ONH and its surrounding retina is measured reproducibly6–8 and in great detail over a grid of more than 60,000 points represented in the pixels of digital topography images. Glaucma physically changes the surface of this region, and being able to ascertain such change reliably could provide a useful means of identifying disease progression.

Although scanning laser tomography appears to be reproducible, analyzing and interpreting the vast information in each image is complex, and consensus remains to be reached on how best to approach these data. This difficulty is evident, for example, in the variety of reference planes proposed to describe anatomic parameters such as the neuroretinal rim and cup in the nerve’s three-dimensional architecture.9–15 Identifying change requires topography to be assessed in the extra dimension of time. To do this, some advocate directly analyzing surface height for change,16,17 whereas others have analyzed summary parameters such as rim area.9,18,19 Paramount to such assessment is the need to rule out measurement variability as a confounder before glaucomatous change can be judged to truly have occurred.

The parameter rim area has been suggested to be useful as a marker of progression in disc photographs20–25 and tomographic images9,19 (Heidelberg Retina Tomograph; Heidelberg Engineering GmbH, Heidelberg, Germany). In tomographic image analysis, we have found that rim area is reproducible compared with other parameters.24 Relating rim area loss to disease behavior is also a familiar task to clinicians. We have previously described a novel experimental reference plane that allows the parameter of rim area to be analyzed more reproducibly than reference planes conventionally used in tomographic analysis.25 Herein, we describe an approach that incorporates the experimental reference plane in evaluating progressive rim area loss. We describe how measurement variability can be estimated and accounted for in small regions of the neuroretinal rim in a way that is individualized to each ONH. The approach requires that any detected change be confirmed as repeatable before being attributed to disease progression. We show that this scheme is useful in distinguishing eyes with progressive glaucoma from the unchanging eyes of normal control subjects. Finally, we demonstrate how the technique may be applied clinically.

METHODS

Overview of Approach

We devised and tested an analytical approach for identifying progression: (1) An experimental reference plane was used for analysis, and (2) the rim area was measured in 30° sectors. (3) Measurement variability was estimated and accounted for in each sector so that true regional change due to glaucoma could be distinguished from variability. (4) Any apparent change had to be repeatable before being attributed to progression. (5) The approach was applied clinically.

Experimental Reference Plane. This reference plane25 is customized to the morphology of each ONH. The position of the reference plane (REFpos) relative to each ONH is kept constant in any image series and is defined as

\[ \text{REF}_{\text{pos}} = \text{MHC} + \text{LOW}_{\text{yr}} + R \]  

(1)

where MHC is mean height of the contour line, LOWyr is the average of the ONH contour line’s lowest 5% of heights calculated from the
constituent topographies of a baseline mean image, and $R$ is the level of the reference plane below $LOW_{5\%}$, where variability is least, previously determined in longitudinal data as $R = 100 \mu m$. Figure 1 illustrates the positioning of the experimental and standard reference planes.

Briefly, the experimental reference plane has the following characteristics:

1. It is devised to lie entirely beneath the margin of the ONH because a reference plane lying above parts of the contour line would underestimate the calculation of adjacent rim tissue. Together, $LOW_{5\%}$ and $R$ indicate the position of the reference plane below the contour line: $LOW_{5\%}$ estimates the lowest level of the contour line, and $R$ is the distance of the reference plane below $LOW_{5\%}$. To calculate $LOW_{5\%}$ heights $1^{\circ}$ apart (360 values) on the contour lines of single-topography images at baseline (usually three) are ranked, from which the mean of the lowest 5% of heights is calculated for each image. Means of the lowest 5% of heights from each of the three single-topography images are averaged to give $LOW_{5\%}$ for that image series.

2. It maintains a fixed $z$-axis distance below the ONH throughout the image series in any eye, with the position of the ONH on the $z$-axis represented by the mean height of its contour line (MHC). We have previously found that the $z$-axis position of the ONH can fluctuate considerably and affect its relationship with the reference plane. In keeping the $z$-axis distance between the ONH and reference plane constant in each eye’s image series, we have found that rim area variability is less than when analysis by conventional HRT (Heidelberg Engineering, GmbH) reference planes is used. We have also found that variability is less affected by testing involving different operators and visits and glaucomatous morphology (compared with normal ONHs).

3. The experimental reference plane’s position is calculated from heights across the whole contour line and does not rely on localized regions or presume selectivity in the pattern of change. Data are also used from multiple single-topography images to help minimize the effect of random outliers.

Analysis of Rim Area. Thirty-degree rim area sectors were evaluated for change. The parameter of rim area was calculated within a longitudinal image series, using the experimental reference plane to define the inner edge of the rim. The outer extent of the rim coincided with the contour line marking the inner margin of the scleral ring of Elschning, outlined by the same observer (JCHT) in each subject’s baseline mean-topography image. Contour lines were exported to other mean and single-topography images in each series. Mean-topography images were derived from triplets of single-topography images using the software provided by the manufacturer (HRT ver. 2.01; Heidelberg Engineering, GmbH). Only images with a mean pixel standard deviation of less than 50 µm were used. Grainy images having a honeycombed appearance were excluded. Data from the mean-topography image of a test visit were used as the point estimate of rim area for that visit. Single-topography images from within a visit provided the data with which to derive mean-topography images by the tomograph software, as instructed by the manufacturer, and to estimate variability (described later). Topographical height was measured by the reference ring, the tomograph’s default referencing region in the image periphery used to establish zero in the $z$-axis. The reference plane differs from the reference ring in that it defines a level in topography by which parameters are defined and measured.

Estimating and Accounting for Sector Rim Area Variability. Intra-Visit Difference Estimates for Calculating Limits of Variability. Measurement variability in each sector of an image series was estimated and accounted for by way of limits of variability. Limits were modeled from intravist difference estimates (denoted $\delta$), calculated as the area difference in each rim sector between a pair of same-visit single-topography images. By this method, three single-topography images per visit yielded three $\delta$ per sector, but the more images acquired per visit, the greater the number of $\delta$. Hence, four intravist images yielded six $\delta$ per visit, five images per visit yielded 10 $\delta$, six images per visit yielded 15 $\delta$, and so on. The possible number of $\delta$ per visit can be calculated by

$$nC_2 = \frac{m!}{(m-r)!r!}$$

This gives the number of ways in which $m$ single-topography images from a visit can be combined to calculate $\delta$ for the visit, with $r$ the number of images used in each combination (in this case, $r = 2$). The number of $\delta$ in any image series equates the total of all $\delta$ from all visits; all are used to calculate limits of variability. The $\delta$ is taken to be free from glaucomatous change, being derived from data from within a visit, not between visits. Using experimental reference plane analysis, we did not expect $\delta$ to be appreciably affected by glaucoma or testing involving different operators and visits.

Limits of Variability to Account for Sector Variability in an Image Series. Limits of variability were the confidence limits for each sector’s range of $\delta$, calculated by multiplying the standard deviation of $\delta$ by the appropriate point of the $t$-distribution for $n-1$ df. This allowed for better estimates of the limits of variability when dealing with relatively small samples (say, of 50). ONH can fluctuate considerably and affect its relationship with the reference plane. In keeping the $z$-axis distance between the ONH and reference plane constant in each eye’s image series, limits of variability can be considered a measure of agreement between repeated measures of the same sector and can be derived as described by Altman and Bland.

In this study, the limits of variability define the extent to which measurements vary when compared with baseline rim area.

For an image series, limits of variability for each sector (VARLIM) can be expressed as

$$VARLIM = Y \cdot \sqrt{\frac{1}{n} \sum (\delta_i - X)^2 / (n - 1)}$$

where $a$ is the sector number (corresponding to the order of a sector’s location on the ONH circumference between 0° and 360°), $\delta$ is the sector rim area difference between pairs of intravist single-topography images, $t$ is the $t$ value of $\delta$, $X$ is the mean of observations of $\delta$, and $n$ is the number of observations of $\delta$. $Y$ is the $t$ statistic for degrees of freedom for $\delta$, corresponding to a chosen two-tailed probability such as $P = 0.05$. The distribution of $\delta$ in sectors was examined on computer with previously found, normal plots, and Shapiro-Wilk significance testing (SPSS ver. 9 for Windows; SPSS, Inc, Chicago, IL) and found to approximate normality in more than 95% of sectors tested. It is expected that the distribution of differences would tend to be normal, but any departures from normality were log transformed. After transformation where needed, more than 99% of all tested sectors had normal distributions. Limits of variability can be expected to narrow with increasing degrees of freedom for $\delta$. For this study, limits of
variability were defined by $P = 0.05$, compatible with a 95% confidence limit.

**Criterion for Confirming Change.** The limits of variability defined the smallest amount of change we could expect to detect above test variability. In addition, we wanted to establish criteria to help ensure that identified change is consistent with glaucomatous progression and not variability. Our criterion took the form of a system of duplicate testing, as espoused by Schulzer et al. for assessing visual fields in the Collaborative Normal Tension Glaucoma Study. Sequential rim area data for each sector were assessed for change exceeding limits of variability wherein a single observation of change was not accepted as disease progression but only regarded as tentative. To be attributed to progression, tentative change had to be verified as repeatable in at least two of three consecutive tests. After an initially positive result, there are three possible outcomes: (1) the subsequent second test result is positive (confirmed), (2) the second result is negative but the third is positive (confirmed), and (3) both subsequent test results are negative (not confirmed).

We empirically assessed the two-of-three criterion’s sensitivity and false-positive rate for identifying change in a reference data set. The data set comprised longitudinal image series of (1) eyes with progressive glaucoma—that is, eyes with ocular hypertension that convert to glaucoma (referred to as converters) and that had reproducible visual field defects—and (2) unchanged eyes of normal control subjects. These results were compared with other plausible criteria for confirming change: two-of-two, requiring two consecutive positive test results; three-of-three, requiring three consecutive positive results; two adjacent sectors on a single test; and two adjacent sectors on two consecutive tests.

**Clinical Application of Approach. Identifying and Confirming Progression.** Sequential rim area data were plotted as rim area profiles. Spatial and temporal information could thus be integrated simply. Profiles were plots of rim area by angular location round the ONH (0°-360°, with 0° temporal, 90° superior, 180° nasal, and 270° inferior) from the same image series. This represented rim area at different points in time in a common graph. Limits of variability for each sector were plotted in relation to the baseline profile, with the region beneath the lower limits termed the zone of change. Rim area in a sector that diminished, exceeded its lower limit of variability, and entered the zone of change was taken to have changed more than measurement variability alone. A single positive result occurred if at least one sector exceeded its limit of variability on a single test. The repeated exceeding of a limit of variability to meet a chosen criterion meant that change was no longer regarded as tentative but to represent disease.

**Evaluation in Progressive and Unchanging Eyes.** The approach for detecting progressive rim area loss was tested in the longitudinal image series of 40 eyes of 40 subjects: 20 normal control subjects and 20 age-matched ocular hypertension converters. In each subject only one eye was analyzed: a randomly selected eye in control subjects and the eye that had converted to glaucoma in the converters. Converters and control subjects regularly attended the Ocular Hypertension and Early Glaucoma Research Clinic at Moorfields Eye Hospital and had received imaging on at least six separate occasions over a minimum of 3 years. This study adhered to the tenets of the Declaration of Helsinki, having received appropriate institutional review board approval and the subjects’ informed consent.

Eyes of normal control subjects were taken to be unchanged. Normal subjects were volunteers comprising spouses or friends of hospital patients, hospital staff, or members of external nonmedical social organizations. They had (1) intraocular pressure (IOP) repeatedly less than 22 mm Hg, (2) serially normal and reliable visual fields (program 24-2; Humphrey Instruments, Inc., Palo Alto, CA) with Advanced Glaucoma Intervention Study (AGIS) visual field scores of 0, (3) no concurrent ocular disease or previous intraocular surgery, (4) no family history of glaucoma, (5) refractive errors less than ±6 D, and (6) age of more than 40 years. ONH appearance was not taken into account for entry into the study.

Converters were assumed to have progressive glaucoma in the eye that converted. They initially had a diagnosis of ocular hypertension with (1) IOP consistently 22 mm Hg or more in one or both eyes without IOP-lowering treatment, (2) open angles on gonioscopy, (3) initial normal visual fields (program 24-2; Humphrey Instruments) with AGIS scores of 0, determined after a learning period of three consecutive tests, (4) refractive errors ±6 D, (5) no concurrent ocular disease or previous intraocular surgery, (6) were aged more than 40 years, and (7) had development of visual field abnormality during the course of monitoring, according to AGIS criteria (score >0) that was reproducible on three consecutive tests. A glaucoma expert independently confirmed this. Other possible causes of visual field defects were excluded. Those on topical IOP-lowering treatment did not receive intervention that altered IOP during the period of monitoring reported in this study. ONH appearance was not part of the criteria for inclusion.

**RESULTS**

Image series from one eye each of 20 converters and 20 age-matched normal control subjects were analyzed. Table 1 shows the subjects’ demographics. Figure 2 shows the rim area profiles of two different normal control eyes. Regional or global depression in progressive disease when the groups were compared sector for sector (all $P > 0.05$) that was not significant when comparing age of the converters and normal control subjects.

**Table 1. Demographic Data for Converters and Normal Control Subjects.**

<table>
<thead>
<tr>
<th></th>
<th>Converters</th>
<th>Normal Control</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>20</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>66.2 ± 10.8</td>
<td>63.6 ± 4.79</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Visual field MD (dB)</td>
<td>−2.82 ± 1.88</td>
<td>+0.35 ± 1.18</td>
<td>=0.001</td>
</tr>
<tr>
<td>Visual field CPSD (dB)</td>
<td>4.02 ± 1.27</td>
<td>0.96 ± 0.51</td>
<td>=0.000</td>
</tr>
</tbody>
</table>

Perimetric indices relate to the visual field at final follow-up. Data are expressed as the mean ± SD.

Eighteen (90%) of 20 converters had single positive test results in which at least one sector of rim area was reduced and exceeded its limit of variability a minimum of once. Seven of 20 (35%) normal control subjects had single positive results. Hence, for the single-test strategy, sensitivity was 90% and the false-positive rate was 35%, corresponding to a specificity of 65%. When assessed by our two-of-three criterion of duplicate testing, repeatable change was found in 17 (85%) of 20 converters and 1 (5%) of 20 normal control subjects, giving a
sensitivity of 85% and false-positive rate of 5%. Table 2 compares the two-of-three criterion with other criteria for confirming change.

**DISCUSSION**

Various innovative methods of analyzing topography for glaucomatous change have been proposed. Chauhan et al.\textsuperscript{16,17} described a technique for detecting statistical change in clusters of HRT (Heidelberg Engineering, GmbH) image pixels (superpixels) so that triplets of images from between pairs of visits—a baseline and a follow-up visit—could be compared. The probability that change in superpixels exceeded variability was evaluated by analysis of variance and expressed as probability maps. Criteria were introduced requiring repeatable significant change in clusters of at least 20 superpixels on three consecutive tests. The technique has been tested against computer simulations and against visual field change analysis (Statpac II; Humphrey Instruments) of normal and glaucomatous eyes and reported to be useful. Quigley and Pease\textsuperscript{29} and Yamada et al.\textsuperscript{30,31} have also applied the concept of probability maps to analyzing glaucoma-scope disc images.

Burgoyne et al.\textsuperscript{9} reported a method for detecting change in ONH parameters defined by a reference plane fixed 150 μm below zero of the z-axis. Parameters were analyzed singly and in groups by univariate and multivariate analysis of variance, respectively, to tell whether change had occurred between baseline and follow-up visits. Analysis was based on six single-topography images per visit. The method was tested in image series of 12 monkey eyes. Using a criterion requiring two positive test results in a row, multivariate analysis showed confirmed change in 11 eyes having experimental glaucoma but also in four contralateral normal eyes. The method has been reported to be at least as good as expert subjective assessment of stereoscopic disc photographs.\textsuperscript{18}

The approach we have described tests discrete rim area sectors for change and allows the discerning of patterns of loss. A new experimental reference plane was used that facilitates reproducible analysis of rim area. Variability is accounted for in each sector of each ONH by way of limits of variability. This is significant change in clusters of at least 20 superpixels on three consecutive tests. The technique has been tested against computer simulations and against visual field change analysis (Statpac II; Humphrey Instruments) of normal and glaucomatous eyes and reported to be useful. Quigley and Pease\textsuperscript{29} and Yamada et al.\textsuperscript{30,31} have also applied the concept of probability maps to analyzing glaucoma-scope disc images.

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**FIGURE 2.** Rim area profiles from one eye each of two different normal subjects, (A) and (B). The lower limits of variability are represented by the superior extent of the shaded zone of change. As may be expected in normal eyes, no rim area sectors exceeded their limits of variability. Limits of variability were (1) specific to each eye: In the eye in (A), sequential rim area profiles were more dispersed and associated with wider limits of variability than in the eye in (B), in which data were more reproducible; (2) specific to each region within each eye: In the eye in (A), limits of variability were wider where data were variable (example at 120–150°) and narrower where data were more reproducible (example at 180–210°).

**FIGURE 3.** Rim area profiles from a converter’s eye. Top: There was localized change in rim area inferotemporally at 270° to 300° where a single sector exceeded its limit of variability, thereby entering the zone of change. This change was repeatable on three consecutive tests. Bottom (top row) sequential tomograph intensity images corresponding to the rim area profiles; (middle row) description of sequential rim area by the experimental reference plane; (bottom row) the sector that changed (270°–300°) is highlighted, together with an adjacent sector in which change was highly suggestive of disease progression (300°–330°).
calculated from intravisit image data from across all test visits. Mean-topography images, each from one visit in time, provide the point estimates of rim area. In judging progression, data from any number of visits can be simultaneously assessed and weighed against variability. Only change repeatedly exceeding variability in two of three tests is attributed to progression. By this approach we found that eyes having unambiguous glaucoma progression could be distinguished from unchanging normal control eyes.

Measurement variability had to be rigorously accounted for, and we dealt with it in several ways. First, we introduced a novel reference plane that allows rim area to be analyzed reproducibly. By this, variability is expected to be significantly less and not appreciably affected by glaucoma or testing involving different operators and visits, compared with other conventional HRT (Heidelberg Engineering, GmbH) reference planes.\(^2\) Variability was thus simpler to account for. Second, we did not presume that variability is uniform across the ONH and so estimated variability in each sector separately. Third, estimation of variability was unique to each eye—necessary because, apart from ONH morphology, individual factors, such as media opacity\(^3\) and ability to maintain fixation,\(^4\) may affect variability differently in each eye. Fourth, only change that was repeatable in two of three tests was attributed to disease progression. This confirmation test strategy had fewer false-positive results than the single-test strategy, and sensitivity in confirming change was not significantly compromised. Hence, confirming change by this criterion resulted in fewer eyes being misidentified as having progressive glaucoma. The two-of-three criterion also had a favorable balance between sensitivity and the false-positive rate compared with other tested criteria. Fifth, variability was estimated using all image data from each series, with limits of variability updateable to factor in data from subsequently acquired images. This is desirable because the estimation of variability can be expected to improve with more \(\delta\) values. Higher degrees of freedom of \(\delta\) would result in narrower limits of variability, with the \(\delta\) statistic decreasing as degrees of freedom increase (equation 5). Sixth, although obtaining three single topographies per visit is advised, more images could be acquired per visit if the number of \(\delta\) has to be increased quickly. This is possible because the number of \(\delta\) increases exponentially according to \(\binom{n}{k}\) (equation 2). For example, three images per visit yield \(3 \delta\), but six images yield 15 \(\delta\) (a 5-fold increase) and nine images yield 36 \(\delta\) (a 12-fold increase). Thus, robust estimates of variability can be obtained rapidly, giving flexibility in clinical situations where indicated. However, fatigue of the patient and its consequences on variability must be considered when many images are acquired at a single sitting.

To verify progression, we constructed a rigorously defined reference data set based on converters with unambiguous visual field progression and normal control subjects. Ascertainment progression in converters—defined as the development of persistent defects in previously normal fields—is simpler than doing so in established glaucomatous fields. The latter can be an uncertain measure for external validation, because perimetric variability\(^1\)–\(^3\)–\(^5\)–\(^34\) and inconsistency in interpreting change\(^35\)–\(^36\) make ascertaining true change difficult. Also, perimetric variability in ocular hypertension is expected to be less than in glaucomatous fields.\(^37\) We assessed visual field conversion by a rational and accepted visual field template (AGIS), required that defects be repeatable in exactly the same locations in three consecutive tests, and sought expert independent verification. It was reasonable to assume that eyes in which disease progressed to field conversion had coexisting morphologic change.\(^20\)–\(^23\) Age-matched normal eyes with similar follow-up acted as the controls.

We have described an analytical approach for identifying rim area loss in sequential scanning laser tomography images. We arbitrarily defined measurement variability by 95% confi-

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**Table 2. Sensitivity and False-Positive Rates for Various Criteria for Confirming Disease Progression**

<table>
<thead>
<tr>
<th>Criteria for Duplicate Testing</th>
<th>1 of 1 (20/20)</th>
<th>2 of 3 (17/20)</th>
<th>2 of 2 (15/20)</th>
<th>3 of 3 (12/20)</th>
<th>Two Adjacent Sectors on a Single Test (16/20)</th>
<th>Two Adjacent Sectors on Two Consecutive Tests (4/20)</th>
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<tr>
<td>Sensitivity</td>
<td>90 (18/20)</td>
<td>85 (17/20)</td>
<td>75 (15/20)</td>
<td>55 (11/20)</td>
<td>80 (16/20)</td>
<td>50 (10/20)</td>
</tr>
<tr>
<td>False-positive rate</td>
<td>55 (20/20)</td>
<td>5 (1/20)</td>
<td>5 (1/20)</td>
<td>0 (0/20)</td>
<td>20 (4/20)</td>
<td>0 (0/20)</td>
</tr>
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Data are expressed as percentages with the number of subjects in a total of 20 tested shown in parentheses.
dence limits, tested the approach in two suitable groups of subjects, and found that the approach could distinguish eyes with progressive glaucoma from the unchanging eyes of normal control subjects. In a future study, we will further investigate the clinical significance and accuracy of various limits of variability and criteria for confirming glaucoma-induced change in a larger group of subjects.

References