The Spatial Pattern of Neuroretinal Rim Loss in Ocular Hypertension

Nicholas G. Strouthidis,¹,² Stuart K. Gardiner,² Christos Sinapis,¹ Claude F. Burgoyne,² and David F. Garway-Heath¹

PURPOSE. To assess the spatial pattern of rim area (RA) decline in ocular hypertension (OHT) as measured with the Heidelberg Retina Tomograph (HRT; Heidelberg Engineering, Heidelberg, Germany).

METHODS. One hundred ninety-eight OHT subjects were examined with the HRT from 1993 to 2001. One eye per subject was selected for analysis, with a median of 10 (range, 5–16) mean topographies, analyzed using the Moorfields Reference Plane. Linear regression of RA/time was performed for each sector; temporal (T), superotemporal (ST), inferotemporal (IT), nasal (N), superonasal (SN), and inferonasal (IN). The mean slope of RA loss (expressed as square millimeters per year and the percentage of baseline RA/year) and the frequency of significant negative slopes were compared in each sector.

RESULTS. The steepest mean slopes of RA loss were observed in the IT sector (−1.43%/y) followed by ST (−1.05%/y), SN (−0.52%/y), IN (−0.46%/y), N (−0.31%/y), and T (0.33%/y). Significant negative slopes (P < 0.01) were observed most frequently in the ST sector (12%) followed by IN (10%), IT (10%), N (7%), SN (6%), and T (2%).

CONCLUSIONS. The rate of RA loss (%/y) was greatest in the IT and ST sectors. However, because the nasal sectors contain more blood vessels (included in the HRT RA measurement), the percentage loss of neural tissue is underestimated in these sectors, to an unknown extent. The frequency of significant negative RA loss slopes was greatest in the ST, IN, and IT sectors. The finding suggests that all disc sectors should be evaluated for glaucomatous change in ocular hypertensive eyes. (Invest Ophthalmol Vis Sci. 2009;50:3737–3742) DOI: 10.1167/iovs.08-2844

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The clinical interpretation of structural changes at the optic nerve head (ONH) in ocular hypertension (OHT) and glaucoma may be influenced by the observer’s preexisting expectation of the spatial pattern of neuroretinal rim loss. Histologic studies have demonstrated that glaucomatous damage has a predilection for the superior and inferior poles of the disc, where arcuate nerve fibers enter the nerve head.¹,² Careful planimetric examination of optic disc stereophotographs has established a widely accepted sequence of sector rim area (RA) loss in glaucoma—specifically, inferotemporal (IT) followed by the superotemporal (ST), temporal (T), inferonasal (IN), and superonasal (SN) sectors.³ The nasal (N) sector is regarded as the final neuroretinal remnant in advanced glaucoma, corresponding to the preservation of a temporal island of vision. Much of the evidence supporting these studies has been cross-sectional, with a relative paucity of longitudinal studies.¹—⁶ When considering these reports, one should evaluate the selection criteria for the studied patients for potential biases that may influence the outcome. For instance, clinically discernible glaucomatous RA loss may be more readily apparent in some regions of the ONH than others—for instance, where there are fewer large blood vessels, where there is less interindividual variation in morphology, and where the cup/rim border is better defined (least sloping). Furthermore, the Humphrey Field Analyzer (Carl Zeiss Meditec, Inc., Dublin, CA) test grid relatively oversamples regions of the visual field (VF) associated with retinal ganglion cells axons exiting the eye at the ST and IT regions of the ONH,¹ making VF loss easier to identify when glaucomatous damage has occurred in these ONH sectors.

The accepted spatial pattern of rim loss in glaucoma has largely been established before the introduction of semiautomated ONH and retinal nerve fiber layer imaging devices into clinical practice. In particular, one device, the Heidelberg Retina Tomograph (HRT; Heidelberg Engineering, Heidelberg, Germany), has been available for a sufficient duration to accrue considerable longitudinal data. That the HRT operational software is backwards-compatible (meaning that images acquired with older devices can be analyzed with the newest available software) has ensured that there is the potential to analyze all images available in a lengthy data set, regardless of which iteration of the HRT hardware is used to acquire the image. Several studies assessing longitudinal HRT-defined RA change have been published.⁸—¹³ RA has been selected as a good potential candidate for monitoring HRT change, as it is a highly repeatable parameter and has an obvious clinical correlate, the ophthalmoscopically visible neuroretinal rim.¹⁴,¹⁵ There is great potential for establishing whether the accepted pattern of RA loss is supported by longitudinal data acquired with the HRT. The purpose of this study was to investigate the spatial pattern of HRT-defined RA loss in OHT subjects observed over time.

MATERIALS AND METHODS
Subject Selection
This study was a retrospective analysis of 198 OHT subjects originally recruited to take part in a prospective randomized trial of betaxolol
versus placebo.\textsuperscript{16} The trial took place at Moorfields Eye Hospital between 1992 and 1997; however, subjects continue to receive regular follow-up examinations until the present day. ONH imaging using the HRT Classic (Heidelberg Engineering, Heidelberg, Germany) was introduced into the testing protocol in 1994. Subjects underwent HRT imaging at yearly intervals for the first 2 years of the study and then imaging frequency was increased to every 4 months. Three single topography images (10\textsuperscript{th} acquisitions) were obtained at each imaging session and were used to generate a mean topography image. For the purposes of the present study, only HRT Classic images were included until September 2001, regardless of VF progression status. No HRT-II images were included in the present study. All subjects included in the present study had a minimum of five HRT mean topographies available for analysis. Subjects also underwent VF testing (Humphrey Field Analyzer; Full threshold 24-2 Program; Carl Zeiss Meditec, Inc.) at each visit.

Initial recruitment criteria included an IOP of greater than 21 mm Hg and less than 35 mm Hg, without prior IOP-lowering treatment, on two or more occasions within a 2-week period and with a baseline Advanced Glaucoma Intervention Study (AGIS) VF score of 0.\textsuperscript{17} Clinical ONH appearance was not considered a criterion for recruitment. In addition, subjects had best corrected visual acuity of 6/12 or better and no coexistent ocular or neurologic disease.

The same eye as had been randomized in the original betaxolol versus placebo study was included in the present study. In brief, OHT eyes were randomized according to risk of glaucomatous conversion, derived from baseline pattern electroretinogram measurements, cup-to-disc ratio, and level of IOP.\textsuperscript{18}

An additional 21 healthy subjects, examined over the same study period, were included. Healthy subjects were recruited from senior citizens groups or were the spouses or friends of subjects in the OHT cohort. They were not attending the eye clinic as patients and were not seeking care or undergoing checkups. Healthy subjects had a baseline IOP of less than 21 mm Hg, normal baseline VF test results (same criteria as in the OHT group), and were excluded if there was a self-reported family history of glaucoma or any coexistent ocular or neurologic disease.

The study adhered to the tenets of the Declaration of Helsinki and had local ethics committee approval as well as the subjects’ informed consent.

HRT Analysis

HRT Classic single topographies were exported as HRTport files into a beta version of the Heidelberg Eye Explorer (ver. 3.1.2.0; Heidelberg Engineering), with which mean topographies were generated. The beta version incorporated a novel reference plane, the Moorfields Reference Plane (MRP) which has recently been described by our group.\textsuperscript{18} The MRP applies the standard reference plane at baseline (located at 50 \textmu m posterior to the temporal disc margin). The height difference between the reference ring (a ring located at the retinal surface in the image periphery) and the standard reference plane is kept constant for follow-up images (Fig. 1). In our previous report, we demonstrated that the MRP has a better signal-to-noise ratio (measured as ratio of RA slope to RA variability), suggesting that it may be particularly useful for the identification of longitudinal RA change.\textsuperscript{16}

Contour lines were drawn onto the baseline mean topographies by an experienced observer (NGS) and were then automatically exported to follow-up images. To maximize the amount of available data, images of all quality (as measured by mean pixel height SD) were included for analysis, except when satisfactory contour line position could not be achieved by manual repositioning, when double imaging (whereby the image is duplicated within the same mean topography) was present, or when the image was sufficiently grainy or honeycombed to prevent adequate visualization of the disc. A total of eight mean topographies were excluded for these reasons.

RA values were calculated for each of the six HRT Explorer software-defined disc sectors: temporal (T), superotemporal (ST), inferotemporal (IT), nasal (N), supronasal (SN), and inferonasal (IN).

Assessing the Pattern of RA Loss

Linear regression of RA over time was performed for each HRT sector in all 198 patients. The slopes of RA over time were expressed as square millimeters per year. As the HRT sectors vary in size and the baseline RA in each sector varies, RA loss was also calculated as the percentage of the baseline sector RA/year. Linear regressions were performed with commercial software (Medcalc ver. 7.4.2.0; Medcalc Software, Mariakerke, Belgium). Variability of the RA measurements around the regression slopes was assessed for each sector using the mean residual SD (RSD). To ascertain whether the spatial pattern of rim loss differed in OHT subjects who went on to develop primary open angle glaucoma, we compared the sector RA slopes in the eyes that had progressed according to VF results, compared with eyes with no evidence of VF progression. Progression was identified in VF series which satisfied the three omitting criteria for point-wise linear regression of sensitivity over time, with slopes exceeding −1 dB/y and \( P < 0.01 \).\textsuperscript{12,19}

A Friedman test was used to test the null hypothesis that there is no difference in RA slopes between sectors. RA slopes/time were compared between sectors by the nonparametric Mann-Whitney test. This was performed with slopes expressed as percentage RA/year, to re-

Table 1. Characteristics of the Ocular Hypertensive and Control Subjects

<table>
<thead>
<tr>
<th></th>
<th>OHT</th>
<th>CONTROL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects, n</td>
<td>198</td>
<td>21</td>
</tr>
<tr>
<td>Age, y</td>
<td>60 (32–79)</td>
<td>65 (41–77)</td>
</tr>
<tr>
<td>Follow-up, y</td>
<td>6.0 (2.3–7.2)</td>
<td>5.3 (3.1–6.8)</td>
</tr>
<tr>
<td>HRT examinations, n</td>
<td>10 (5–16)</td>
<td>9 (8–11)</td>
</tr>
<tr>
<td>Baseline mean defect, dB</td>
<td>+0.1 (+2.7–+3.0)</td>
<td>+0.1 (+2.6–2.4)</td>
</tr>
<tr>
<td>Baseline global RA, mm\textsuperscript{2}</td>
<td>1.24 (0.63–2.51)</td>
<td>1.35 (0.86–2.51)</td>
</tr>
<tr>
<td>Image quality throughout study (mean pixel height standard deviation), ( \mu m )</td>
<td>20 (7–186)</td>
<td>23 (9–80)</td>
</tr>
</tbody>
</table>

Data are expressed as the median (range).

FIGURE 1. The location of the MRP. The height of the reference plane in the baseline image is the same as for the standard reference plane, located 50 \( \mu m \) posterior to the temporal disc margin (white disc with black outline). The height difference between the baseline reference plane and the reference ring (black circle with gray outline) is then kept constant for follow-up images.

Figure 1.
duces the effect of baseline RA. To account for the effect of baseline RA and age on the results, a regression model was constructed. The rate of RA change (expressed as square millimeters per year) was predicted by disc sector, baseline RA value, and age. To remove the effect of intrasubject correlations (since there are six data points, one per sector, from each eye), the generalized estimating equation (GEE) technique was used. This analysis was repeated to compare variability between sectors, and (using logistic regression) the probability of a statistically significant \( P < 0.01 \) negative slope. Comparisons between sectors were made using R (R Foundation for Statistical Computing, Vienna, Austria).

### Results

The baseline demographics and characteristics of the subjects included in the study are shown in Table 1. The mean slopes of RA loss over time across the six HRT sectors for the OHT subjects are depicted in Table 2. Table 3 compares the mean slopes of RA loss over time in subjects with OHT who had progressed according to VF results at the end of the study period (total, 37 eyes) with subjects who had not progressed according to VF results (total, 161 eyes). The spatial pattern of RA loss does not appear to differ between progressing and nonprogressing groups and for this reason all analyses were performed using the full cohort (total, 198) of OHT eyes. The sector RA slopes for the healthy subjects are depicted in Table 4. The frequency distribution of RA slopes (expressed as millimeters per year) within each sector for the 198 subjects with OHT is displayed across the six histograms shown in Figure 2. It is apparent from these histograms that in all sectors the majority of slopes are between 0 and \(-0.05 \text{ mm}^2/\text{y} \), except in the temporal sector where the greatest frequency is between 0 and \(-1.05 \text{ mm}^2/\text{y} \).

When RA slopes in the OHT group were compared, regardless of the direction of slope, a Friedman test rejected the null hypothesis that the slopes were the same across all sectors \( P < 0.0001 \). Table 5 shows the probabilities obtained from a Mann-Whitney comparison of RA slopes between each pair of sectors in the OHT subjects, when expressed as percentages per year.

To account for the effects of age and baseline RA, while also taking account of correlations between sectors for the same eye, GEE regression was performed (two-tailed tests in all cases) to compare slopes between sectors (regardless of direction) in the OHT subjects. Compared with the IT sector, RA slopes were significantly shallower in the T \( ( P = 0.003) \), N \( ( P = 0.005) \), SN \( ( P = 0.0154) \), and IN \( ( P = 0.005) \) sectors but not in the ST sector \( ( P = 0.5622) \). Compared with the ST sector, RA slopes were significantly shallower in the T \( ( P = 0.0020) \), N \( ( P = 0.0146) \), SN \( ( P = 0.0304) \), and IN \( ( P = 0.0081) \) sectors, but not in the IT sector (as before, \( P = 0.5622 \)). In both cases, the slopes were significantly steeper, with increased baseline RA \( ( P = 0.0304) \) and younger age \( ( P = 0.0467) \). The T sector was significantly more variable (as estimated by the residual SD) than any other sector \( ( P < 0.0001 \) in all cases). Variability was higher with increased baseline RA \( ( P = 0.0038) \), but was not affected by age \( ( P = 0.4760) \). The SN sector was the least variable, followed by the IN sector.

Table 6 shows the number of significant \( P < 0.01 \) negative and positive RA slopes within each HRT sector for the OHT and control eyes. Using the same GEE model among the OHT eyes, taking into account baseline RA, age, and correlations between sectors, the ST sector had a higher probability of obtaining a statistically significant negative RA slope than did the T \( ( P = 0.0002) \), N \( ( P = 0.0432) \), and SN \( ( P = 0.0354) \) sectors. The IT sector had more statistically significant negative RA slopes than the T sector \( ( P = 0.0019) \). Other comparisons between sectors did not reach \( P < 0.05 \) age \( ( P = 0.9697) \) and baseline sector RA \( ( P = 0.1228) \) had no significant effect on these results.

After accounting for differences caused by age, baseline sector RA, and differences between sectors, poorer image quality (as measured by an increased mean pixel height SD, averaged over all tests in the series) significantly increased the

### Table 2. Mean RA Slopes/Time for Each HRT Sector in the Subjects with OHT

<table>
<thead>
<tr>
<th>Sector</th>
<th>Mean RA Slope (mm²/y)</th>
<th>SD (mm²/y)</th>
<th>Mean RA Slope (%/y)</th>
<th>SD (%/y)</th>
<th>Mean RSD* (mm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T</td>
<td>-0.0007</td>
<td>0.0067</td>
<td>0.33</td>
<td>4.19</td>
<td>0.024</td>
</tr>
<tr>
<td>ST</td>
<td>-0.0015</td>
<td>0.0037</td>
<td>-1.05</td>
<td>2.53</td>
<td>0.009</td>
</tr>
<tr>
<td>IT</td>
<td>-0.0018</td>
<td>0.0047</td>
<td>-1.43</td>
<td>4.41</td>
<td>0.010</td>
</tr>
<tr>
<td>N</td>
<td>-0.0010</td>
<td>0.0036</td>
<td>-0.31</td>
<td>1.21</td>
<td>0.011</td>
</tr>
<tr>
<td>SN</td>
<td>-0.0008</td>
<td>0.0025</td>
<td>-0.52</td>
<td>1.59</td>
<td>0.007</td>
</tr>
<tr>
<td>IN</td>
<td>-0.0007</td>
<td>0.0022</td>
<td>-0.46</td>
<td>1.41</td>
<td>0.010</td>
</tr>
</tbody>
</table>

* An estimate of the measurement variability in each sector, with higher values equating to greater variability.

### Table 3. The Mean RA Slopes/Time for Each HRT Sector in the Subjects with OHT

<table>
<thead>
<tr>
<th>Sector</th>
<th>Mean RA Slope (mm²/y)</th>
<th>SD (mm²/y)</th>
<th>Mean RA Slope (%/y)</th>
<th>SD (%/y)</th>
<th>Mean RSD* (mm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T</td>
<td>-0.0019</td>
<td>0.0005</td>
<td>-0.63</td>
<td>3.56</td>
<td>0.027</td>
</tr>
<tr>
<td>ST</td>
<td>-0.0029</td>
<td>-0.0012</td>
<td>-2.11</td>
<td>2.17</td>
<td>0.009</td>
</tr>
<tr>
<td>IT</td>
<td>-0.0042</td>
<td>-0.0015</td>
<td>-2.98</td>
<td>3.58</td>
<td>0.012</td>
</tr>
<tr>
<td>N</td>
<td>-0.0024</td>
<td>-0.0006</td>
<td>-0.82</td>
<td>1.36</td>
<td>0.013</td>
</tr>
<tr>
<td>SN</td>
<td>-0.0018</td>
<td>-0.0007</td>
<td>-1.18</td>
<td>1.97</td>
<td>0.009</td>
</tr>
<tr>
<td>IN</td>
<td>-0.0020</td>
<td>-0.0005</td>
<td>-1.22</td>
<td>2.06</td>
<td>0.008</td>
</tr>
</tbody>
</table>

* As defined in Table 2.
variability as measured by residual SD \( (P < 0.0001) \). Poorer image quality reduced the probability of achieving a significant negative RA slope.

**DISCUSSION**

The results of this study appear to concur with the expected pattern of rim loss.\(^3\) The mean RA slopes in the ST and IT sectors were steeper than the other sectors, and this relationship was maintained in a mixed-effects model that took into account the potential influence of age, baseline RA, and the relationships between sectors within the same eye. Likewise, the highest probability of observing a significant negative slope was in the ST sector. However, there are various factors that should be considered when interpreting the results.

When RA loss is measured in absolute units (square millimeters per year), the fact that sectors vary in size and the amount of baseline neural tissue varies between sectors makes comparison between sectors difficult. When RA loss is measured in relative units (percent per year), the fact that some sectors contain more non-neural tissue (principally large blood vessels) than others confounds the interpretation. And when the frequency of statistically significant RA loss is measured, the fact that measurement variability is greater in some sectors than others confounds the interpretation.

When considering the measurement of RA using the HRT, it is important to take into account that a proportion of the measured RA will comprise non-neural tissue. Most of the non-neural rim tissue in each disc sector may be accounted for by blood vessels. The central retinal vessel trunk exits the optic nerve head, most frequently nasally, in both normal and glaucomatous eyes,\(^{21}\) indicating that the bulk of the vasculature is located in nasal regions of the disc. It is therefore likely that the degree of rim area loss in the nasal sector of the disc may be underestimated and that a more accurate estimate will be achieved if the proportion of vascular tissue is accounted for.

There is also evidence from experimental models of glaucoma in primate eyes that the degree of neuroretinal rim loss in the nasal sector may be underappreciated.\(^ {22,23} \)

In a clinical observational study of optic disc photographs from 1357 glaucoma subjects and 649 normal subjects, Jonas and Budde\(^ {24} \) reported that the nasal sector—either alone, or in combination with other sectors—had the lowest glaucoma diagnostic precision. It is important to note that glaucoma diagnosis in that study was based on the presence of glaucomatous VF loss (as well as a separate classification of preperimetric glaucoma, based on ONH appearance). It is therefore likely that the relative oversampling of the nasal VF compared with the temporal VF accounts for the observed underperformance of the nasal disc sector. The authors noted the paradox that despite the nasal sector containing a high proportion of larger diameter fibers, nasal sectoral damage was infrequently discernible clinically. The results of our study do not support the recommendation of their study, which suggested that the nasal sector could effectively be omitted or ignored in the quantification of optic nerve images in glaucoma.

In this study, we assumed that RA loss is linear. In a longitudinal study of 123 eyes, Airaksinen et al.\(^6\) identified four broad patterns of RA change over time: linear, episodic, accelerating curvilinear, and decelerating curvilinear. Of these, the
linear pattern was the most frequently observed, occurring in approximately 50% of subjects with glaucoma or OHT. The curvilinear pattern differs from the linear pattern, in that the rate of change alters over time, whereas the linear pattern presupposes a fixed rate of change. In episodic damage, the overall trend between successive episodes may be linear. Given the higher incidence of a linear pattern of rim loss, it was reasonable to adopt a linear model for the purposes of this study although measurement variability largely precludes identification of the true pattern.

There is no consensus in the existing literature regarding the degree of, and indeed the existence of, age-related optic nerve damage.25–28 Moya et al.29 were unable to identify a statistically significant change of rim area/disc area (i.e., greater than the reproducibility limits of the planimetry techniques used) in 100 normal subjects followed longitudinally for a mean of 13 years. A recent longitudinal study investigated RA loss by digital planimetry of optic disc photographs acquired 5 and 10 years after a baseline image.30 A rate of RA loss of 0.36%/y was estimated in normal subjects, compared with 0.54%/y in OHT subjects and 0.95%/y in OHT subjects with evidence of conversion to early glaucoma. These estimates are not directly comparable to those of the present study as sector rim loss was not calculated, and only three time points were available. Although we have included data from a cohort of control subjects, there is a large discrepancy in the number of subjects compared to the OHT cohort. In the absence of a similarly sized cohort of age-matched controls, it is not realistic to estimate the degree of age-related loss in the cohort of OHT subjects examined in the present study. One must therefore accept that the sector rim loss observed in this study most likely includes a proportion of age-related, non-glaucomatous, tissue in each RA sector that will result in an underestimation of the true pattern.

The spatial pattern of rim loss in this study should be interpreted with the understanding that RA measurement variability differs in each sector. The mean RSDs suggest that measurement variability is very similar between most sectors, except the T sector, which was found to be the most variable sector in the GEE model. We have reported RA repeatability coefficients derived from an HRT test-retest study using the 320 reference plane.13 The 320 reference plane is located 320 μm posterior to a reference ring located in the image periphery. This study identified RA in the T sector as being the least repeatable across all degrees of image quality, consistent with the finding of the lowest frequency of significant negative slopes in the T sector. In this study we have included images of all quality so as to maximize the amount of available data. Poor-quality images were associated with increased sector RA variability, which in turn decreased the probability of observing a statistically significant negative RA slope. Another factor that may have influenced the results is the possibility that there was a posterior drift of the reference plane as glaucomatous damage progressed. The neuroretinal rim slope is shallowest in the temporal region of the disc and so this area would be more sensitive to changes in reference height position. This finding may help to explain the presence of a mean positive slope of RA change in the T sector.

In this study a propensity for a steeper rate of RA loss in the ST and IT sectors was observed compared with that in other sectors. However, the interpretation of these results must take into account the varying proportion of non-neural vascular tissue in each RA sector that will result in an underestimation of RA loss in the nasal sectors of the disc.

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