Asymmetry in Optic Disc Morphometry as Measured by Heidelberg Retina Tomography in a Normal Elderly Population: The Bridlington Eye Assessment Project

Matthew J. Hawker,1 Stephen A. Vernon,1 Gerard Ainsworth,1 Jonathan G. Hillman,2 Harmish K. MacNab,2 and Harminder S. Dua1

PURPOSE. To define the normal range of asymmetry in optic disc parameters measured by the Heidelberg Retina Tomograph (HRT II: Heidelberg Engineering GmbH, Dossenheim, Germany) in a normal elderly population.

METHODS. Optic disc analysis of 918 eyes of 459 normal elderly patients was performed. All patients were consecutive in a cohort screened for eye disease. Normality was defined with a normal visual field on automated suprathreshold screening, intraocular pressure less than 22 mm Hg, and minimum corrected visual acuity of 6/12. Asymmetry measures were calculated by subtracting the values of the smaller disc from those of the larger disc.

RESULTS. Subjects’ mean age (262 female and 197 male) was 72.6 years (range, 65.5–89.3). There was no significant difference in disc area or rim area between the right and left eyes. Neither rim-to-disc area ratio asymmetry nor rim measurement asymmetries were significantly affected by age or sex. Rim-to-disc area ratio asymmetry was much less affected by the increasing difference in disc size than was absolute rim asymmetry. The 2.5th and 97.5th percentile limits of normality for the rim-to-disc area ratio asymmetry in the global and temporal–inferior analyses were −0.212 and 0.154, and −0.331 and 0.261, respectively.

CONCLUSIONS. The normal range of parameter asymmetry in an age group relevant to glaucoma may be useful in the discrimination of normal from early glaucoma. Asymmetry analysis may improve discriminatory ability by reducing parameter variability based on disc size. The rim-to-disc area ratio asymmetry measure is likely to be the most useful parameter in describing normality with consistency. (Invest Ophtalmol Vis Sci. 2005; 46:4153–4158) DOI:10.1167/iovs.05-0423

From the 1Department of Ophthalmology, Queen’s Medical Centre, Nottingham, United Kingdom; and 2The Medical Centre, Bridlington, United Kingdom.

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Corresponding author: Stephen A. Vernon, Department of Ophthalmology, Queen’s Medical Centre, University Hospital, Derby Road, Nottingham, NG7 2UH, UK; stephen.vernon@qmc.nhs.uk.

The evaluation of neuroretinal rim morphology is key in the diagnosis of glaucoma. For glaucoma screening to be successful, an objective, reproducible evaluation of the neuroretinal rim would be required to achieve sufficiently high sensitivity and specificity. The Heidelberg Retina Tomograph (HRT; Heidelberg Engineering GmbH, Dossenheim, Germany) is a semi-automated confocal scanning laser system that provides reliable and reproducible three-dimensional imaging data on the optic nerve head (ONH).1 However, previous studies in which diagnostic criteria were developed for glaucoma based on HRT parameters have failed to generate sufficient sensitivity and specificity for the purposes of mass screening.2-6 In a population setting, sensitivity and specificity must be very high, to avoid a significant number of false-positive and false-negative results. Although specificities of more than 95% can be achieved, sensitivities are universally lower, due largely to the wide overlap in HRT parameters between normal and glaucomatous optic discs.7 In addition, variability in ONH parameters due to factors other than disease creates background noise, reducing diagnostic facility. Variation in age,8-10 sex,11 disc area,5,9 refraction,10 image acquisition,12 and contour placement on the optic disc13 have all been shown to influence ONH parameters.

Asymmetry of neuroretinal rim configuration is a well-recognized component in the diagnosis of glaucoma.14 It is also a risk factor for progression of ocular hypertension to glaucoma.15 Determining the asymmetry between the eyes of each patient has the potential to reduce parameter variability by providing a measure that accounts for interindividual variation due to patient factors such as age, sex, and disc size. Thus, interindividual comparisons in cross-sectional (diagnostic) studies may become more valid. Despite this potential, we found only one study in which the usefulness of asymmetry measures was examined in glaucoma diagnosis with the Heidelberg Retinal Tomograph (HRT).16 Those investigators constructed the RADAAR measure (rim area-to-disc area asymmetry ratio) and found that it correlates significantly with intraocular pressure and degree of glaucomatous optic nerve damage in patients with glaucoma. However, they were unable to test the ability of RADAAR to discriminate between normal and glaucomatous eyes in the absence of development of a suitable reference range in normal patients.

We present data obtained from patients screened by the Bridlington Eye Assessment Project (BEAP). The project systematically invited residents over the age of 65 years in the town of Bridlington, United Kingdom, to attend a full screening examination for eye disease. HRT II imaging was performed as part of the examination. The purpose of this study was to generate reference range data for asymmetry of HRT II ONH parameters in a population-based sample of elderly patients.

PATIENTS AND METHODS

BEAP Subjects

The methodology of the BEAP has been described.11 Briefly, the project is a screening exercise for eye disease in patients older than 65...
years. Patients registered with a general practitioner in the town of Bridlington were systematically invited to attend an eye examination by one of four optometrists trained specifically for the project. Each of the four optometrists provided their services to the project on a daily rotational basis. Patients registered blind or partially sighted, bed-bound or with dementia and those who moved into or out of the area during the study were excluded. Patients underwent a comprehensive eye examination, logMAR (logarithm of the minimum angle of resolution) visual acuity testing (Bailey–Lovio Chart 4, National Vision Research Institute of Australia), and automated suprathreshold visual field testing with a perimeter (Henson Pro 5000 perimeter; Tinsley Instruments, Croydon, UK). A single stimulus, suprathreshold central 26-point test was used. This was automatically extended to a 68-point test if a defect was detected. After instillation of 1% tropicamide into both eyes, systematic slit lamp biomicroscopy was performed, with specific disc, macular, and periphery findings noted. Assessment of the clinical vertical cup-to-disc ratio was performed by all examiners with a 90-D lens (Volk). Finally, HRT II images (HRT II, software ver. 1.4.1.0; Heidelberg Engineering GmbH) were obtained.

The first patient examined in the BEAP was seen on November 5, 2002, and 1246 patients were examined by the start of the present study in January 2004. Patients were invited in ascending numerical order of postal code. Informed consent was obtained from all participants, and a local ethics committee approved all methodology. All methods adhered to the tenets of the Declaration of Helsinki guidelines for research in human subjects.

Assessment by Confocal Scanning Laser Ophthalmoscope

In this study, data from the first 1246 patients were examined. Of those, 576 patients were defined as normal, with an intraocular pressure less than or equal to 21 mm Hg, a normal visual field determined by suprathreshold automated examination, and corrected logMAR acuity of at least 0.3 (Snellen equivalent 6/12) in both eyes. Patients with a history of glaucoma or use of ocular pressure-lowering treatment were excluded. Of the 576 normal patients, a further 15 were excluded because of absent or unacceptable disc images, and 11 more were excluded because of anomalous discs or discs with splinter hemorrhages present clinically. No attempt was made to exclude patients on the basis of an optic disc with neuroretinal rim morphology raising clinical suspicion of glaucoma. Patients were imaged with HRT II, with the scanner’s focus being adjusted according to the patient’s refraction, and to obtain the best image. One mean topographic image was acquired per eye. Much of the acquisition process using HRT II is automated. If the machine stated that astigmatism was significantly impairing the image, then the image was obtained through the patients’ spectacles. If the image acquired was visually unacceptable, then the process was repeated to obtain an acceptable image, although in a minority of patients we did not acquire an acceptable image. The optic disc contour line was drawn separately by two investigators (GA, MJH) to mark the edge of the optic disc and mean parameters analysed. The HRT II then calculated disc area (in square millimeters) and 12 other stereometric parameters. The parameters were cup and rim areas (both in square millimeters), cup-to-disc and rim-to-disc area ratios, cup and rim volume (in cubic millimeters), mean maximum cup depths (in millimeters), height variation contour (in millimeters), cup shape measure, mean retinal nerve fiber layer (RNFL) thickness (in millimeters), and RNFL cross-sectional area (in square millimeters). Each of these parameters was expressed for the global disc and for six individual disc sectors (temporal, temporal superior, temporal inferior, nasal, nasal superior, and nasal inferior). The average variability (standard deviation) of the three HRT images comprising the mean topographic image was 34 μm. Because of the large range of average variability (0–258 μm) discs with the largest 10% of average variability were excluded on a patient-wise (eye pair) basis (a further 91 patient exclusions). The maximum average variability was then 68 μm, with a mean ± SD of 26.8 ± 13.3 μm. This result was comparable to the average variability in previous investigations and gave acceptable data quality for the purposes of generating a reference range. 3

Analysis

HRT II parameters for this study were derived as the mean of parameters generated by the two investigators. Parameter asymmetries were generated for all global parameters by subtracting the value of the smaller disc from that of the larger. Rim-to-disc area ratio asymmetries were also calculated by the same method for the global and six sectoral measures.

ONH HRT II parameters were analyzed on computer (SPSS for Windows version 12.0.2; SPSS, Inc., Chicago, IL). Parameter indices were assessed visually for normality by generating histograms and objectively with the Kolmogorov-Smirnov test. As expected, all parameters produced a bell-shaped distribution, though nearly all parameters showed significant departure from normality, according to the Kolmogorov-Smirnov test. This is likely, in part, to be related to the large number of data points. However, for this reason and with a large dataset, we quote the 95th and 99th percentile limits of normality (reference range) for our data. The Mann-Whitney test was used to assess significance of differences in parameters between men and women. To examine the effects of age on asymmetry, the sample was divided into age quartiles. The groups were divided at 68.5, 71.8, and 76.1 years. To examine the relationship between the magnitude of difference in the disc area and the asymmetry parameters, the sample was divided into quartiles based on disc area difference. The groups were divided at 0.07, 0.14, and 0.25 mm² difference. The Kruskal-Wallis test was used to assess the significance of differences in parameters between the four age and disc area difference quartile groups. Spearman’s rank correlation coefficient was calculated to investigate the relationship between mean intraocular pressure and central corneal thickness with each asymmetry parameter. Two-tailed tests were used throughout. Statistical significance was set at P < 0.05.

RESULTS

Demographics

A total of 918 eyes of 459 patients were included in the study. The mean age of the subjects (262 women and 197 men) was 72.6 ± 5.1 years (SD; range, 65.5–89.3). The mean ages of the men and women were not significantly different (72.9 and 72.4 ± 5.4 years, respectively; P = 0.41).

Asymmetry Parameters

Mean (±SD) and 5% percentile limits of normality for the right and left eyes of 459 normal elderly patients are shown in Table 1. Rim volume, cup shape measure, and height variation contour reached statistically significant levels of difference between eyes. The differences, however, were very small and clinically insignificant.

Figure 1 illustrates the distribution of values for the global rim-to-disc area ratio asymmetry parameter. The normal curve (with the same mean and SD) is shown for reference. The data display a bell-shaped distribution, with significant positive kurtosis and departure from the normal distribution. The 5% and 1% limits of normality for the global and sectoral rim-to-disc area ratio asymmetry measures are given in Table 2. Figure 2 depicts global rim-to-disc area ratio asymmetry in the subjects. The distribution of differences was similar in both sexes. There was no significant difference in any global or sectoral rim-to-disc area ratio asymmetry measure between the sexes or the four age quartiles (P > 0.05). Figure 3 shows data distributions (box-and-whisker plots) for other selected global HRT II parameter asymmetries. The differences in data dispersion largely reflect differences in the data range of HRT II global parameters. No significant difference in disc area asymmetry or any of the other global HRT II parameter asymmetries was found between the sexes or the four age quartiles.

The median difference in disc area was 0.14 mm² (minimum and maximum differences were 0.00 and 0.64 mm²).
respectively). Increases in the difference in disc area (larger disc minus smaller disc) were significantly related to increases in the difference in global rim area \((P < 0.001; \text{Fig. 4})\). However, increasing disc area difference was related to only a small change in the magnitude of global rim-to-disc area ratio asymmetry of marginal significance \((P = 0.055)\). Table 3 compares the magnitudes of association between the difference in disc area and various asymmetry parameters by means of Spearman’s rank correlation. The magnitude of asymmetry of rim area and cup area was positively associated with increasing disc area asymmetry. This relationship was a negative one for all rim-to-disc area ratio asymmetries. The magnitude of association with disc area asymmetry was much greater for the raw rim area and cup area asymmetries than for the rim-to-disc area ratio asymmetry.

Mean \((\pm \text{SD})\) intraocular pressure and central corneal thickness (CCT) in the sample were 16.1 \(\pm 2.5\) mm Hg and 543.5 \(\pm 35.9\) \(\mu\)m, respectively. No statistically significant correlation existed between any of the asymmetry measures presented and mean IOP/CCT \((P > 0.05)\).

Figure 5 shows the distribution of vertical cup-to-disc ratio asymmetry graded clinically during the screening examination. There is a positive skew in the data indicating disproportionately larger cup-to-disc ratios in larger discs. The median asymmetry value was 0 with 2.5th and 97.5th percentile limits of normality of \(-0.2\) and \(+0.25\), respectively. There was no significant difference in the amount of clinical cup-to-disc ratio asymmetry based on sex or between the difference in disc area quartile groups. In addition, no significant difference in clinical cup-to-disc ratio was found between the sexes or the age quartiles.

**DISCUSSION**

It has been demonstrated that HRT classification techniques and stereophotograph assessment can detect optic disc topography abnormalities in glaucoma-suspect eyes before the development of standard achromatic perimetry abnormalities. Thus, optic disc examination is very important in detecting early glaucoma. However, variation due to patient factors such as disc size, patient sex, and age can have a significant effect on the quoted normal range of ONH parameters. Thus, the specificity of various diagnostic functions based on HRT scanning has been found to decrease significantly with increasing disc size. However, these factors seem to have much

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Right Eye</th>
<th>Left Eye</th>
</tr>
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<tbody>
<tr>
<td>Disc area (mm²)</td>
<td>1.98 (0.35)</td>
<td>1.97 (0.36)</td>
</tr>
<tr>
<td>Cup area (mm²)</td>
<td>0.46 (0.34)</td>
<td>0.44 (0.36)</td>
</tr>
<tr>
<td>Rim area (mm²)</td>
<td>1.52 (0.31)</td>
<td>1.53 (0.31)</td>
</tr>
<tr>
<td>Cup-to-disc area ratio</td>
<td>0.22 (0.14)</td>
<td>0.21 (0.14)</td>
</tr>
<tr>
<td>Cup volume (mm³)</td>
<td>0.09 (0.10)</td>
<td>0.09 (0.11)</td>
</tr>
<tr>
<td>Rim volume (mm³)</td>
<td>0.39 (0.15)</td>
<td>0.41 (0.15)</td>
</tr>
<tr>
<td>Mean cup depth (mm)</td>
<td>0.19 (0.08)</td>
<td>0.19 (0.09)</td>
</tr>
<tr>
<td>Maximum cup depth (mm)</td>
<td>0.51 (0.21)</td>
<td>0.53 (0.22)</td>
</tr>
<tr>
<td>Height variation contour (mm)</td>
<td>0.36 (0.09)</td>
<td>0.39 (0.10)</td>
</tr>
<tr>
<td>Cup shape measure</td>
<td>(-0.17(0.06))</td>
<td>(-0.18(0.06))</td>
</tr>
<tr>
<td>Mean RNFL thickness (mm)</td>
<td>0.22 (0.07)</td>
<td>0.25 (0.07)</td>
</tr>
<tr>
<td>RNFL cross-sectional area (mm²)</td>
<td>1.10 (0.33)</td>
<td>1.13 (0.34)</td>
</tr>
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</table>

* 95th percentile (lowest value = 0).

**FIGURE 1.** Difference in global rim-to-disc area ratio (larger disc minus smaller disc) in 918 eyes of 459 normal elderly patients.
less of an effect on the normal limits of asymmetry than on the direct measurements in individual eyes. We could find no significant effect of variation in age or sex on asymmetry of cup or rim area or volume. Similarly, asymmetry of rim-to-disc area ratio was not affected by variation in age or sex. The major advantage of rim-to-disc area ratio asymmetry was in its relative immunity to the effects of variation in disc area asymmetry, compared with the absolute rim and cup measurements. We found increasing disc area asymmetry to be much more strongly associated with changes in rim and cup measurements. We found increasing disc area asymmetry to be much more strongly associated with changes in rim and cup asymmetry compared with rim-to-disc area ratio asymmetries. On this basis, rim-to-disc area ratio asymmetry is likely to be the most useful parameter in defining normality and perhaps in discriminating normal from glaucomatous eyes.

The choice of method in calculating asymmetry measures is important. In most of the previous studies calculating asymmetry parameters, data were recorded on a left–right basis, though in a recent study, Harasymowycz et al. used a larger disc-smaller disc comparison. It has been demonstrated that cup area increases to a larger degree than rim area with increases in disc size. In our own sample, comparison of the largest and smallest quartiles of disc size showed a relative increase in rim area of 1.30 with a corresponding relative increase in cup area of 2.91. This difference must be handled consistently to generate well defined limits of normality for asymmetry. We found no systematic difference in ONH measurements between right and left eyes. Asymmetry measures should therefore be calculated by comparing eyes on the basis of disc size, rather than laterality. The standard deviations of asymmetry measures in our sample, calculated by subtracting the left eye value from the right eye value, were up to 8% higher compared with the larger disc-minus-smaller disc method (data not shown). In contrast with the RADAAR measure, we chose to compare eyes not on a relative scale, but on an absolute one. Comparing the results between eyes by division rather than subtraction results in a loss of potentially useful information.

Using a 90-D Volk lens, we found the 95% limits of clinical vertical cup-to-disc ratio asymmetry to be 0.2 to 0.25. These tolerances are similar to those in previous studies. The slight asymmetry in the limits may indicate that estimation

### Table 2. Difference in Rim-to-Disc Area Ratio (Larger Disc Minus Smaller Disc) for Global and Sectoral Measures of 918 Eyes of 459 Normal Elderly Patients

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
<th>Median</th>
<th>2.5th/97.5th Percentiles</th>
<th>0.5th/99.5th Percentiles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global</td>
<td>-0.021 (0.097)</td>
<td>-0.016</td>
<td>-0.212/0.154</td>
<td>-0.431/0.379</td>
</tr>
<tr>
<td>Temporal</td>
<td>0.019 (0.155)</td>
<td>-0.011</td>
<td>-0.351/0.324</td>
<td>-0.614/0.420</td>
</tr>
<tr>
<td>Temporal–superior</td>
<td>-0.028 (0.151)</td>
<td>-0.020</td>
<td>-0.341/0.252</td>
<td>-0.672/0.507</td>
</tr>
<tr>
<td>Temporal–inferior</td>
<td>-0.025 (0.151)</td>
<td>-0.010</td>
<td>-0.331/0.261</td>
<td>-0.568/0.473</td>
</tr>
<tr>
<td>Nasal</td>
<td>-0.021 (0.104)</td>
<td>-0.001</td>
<td>-0.260/0.144</td>
<td>-0.484/0.439</td>
</tr>
<tr>
<td>Nasal–superior</td>
<td>-0.026 (0.126)</td>
<td>-0.008</td>
<td>-0.277/0.213</td>
<td>-0.643/0.418</td>
</tr>
<tr>
<td>Nasal–inferior</td>
<td>-0.012 (0.115)</td>
<td>0.000</td>
<td>-0.251/0.216</td>
<td>-0.407/0.299</td>
</tr>
</tbody>
</table>
of the cup-to-disc ratio is biased by disc size, or it may simply reflect the finding that disc cups are proportionately larger in larger discs (as found with the HRT).

The quality of the HRT image was a limitation in our study. Even by excluding patients with the greatest SD, the maximum SD in our study was 68 μm. Heidelberg Engineering recommends that images of low quality (SD of the mean topographic image greater than 50 μm) should not be used in a follow-up (change) analysis. We have discussed this problem in a previous communication.11 In a study involving the use of HRT II in the elderly, this finding is not unexpected. Previous studies have found that image variability increases with age22 and with the presence of cataract,23 though the effect of cataract was much reduced by acquiring images through a dilated pupil. We found similar relationships in our subjects (data not shown). Thus, if we were to exclude patients with SDs over 50 μm, we would preferentially exclude more elderly patients and limit one of the main novelties of our study as an analysis of HRT II imaging in the elderly. However, we anticipate that in a cross-sectional study the effect of mean topographic image SD is less critical than in longitudinal studies, because of the principal of regression to the mean. Indeed, when we reanalyzed the sample with patients with an SD >50 μm excluded, all global parameter means and SDs remained essentially unchanged, with no significant differences caused by the new exclusion criteria. We have therefore excluded patients with the greatest 10% of image SD, to remove outlying patients with SDs not representative of the group as a whole. The relationship between image SD and patient variables in our sample is to be the subject of a further communication.

Our definitions of normality excluded most of the 1246 patients examined in the BEAP. This limitation of our study arises mainly from the lack of best corrected visual acuity determined in a contemporary refraction and a large number of abnormal suprathreshold visual field test results. Generating a reference range for normality necessarily requires strict entry

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<tr>
<th>Asymmetry Parameter</th>
<th>$r_s$</th>
<th>$P$</th>
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<tbody>
<tr>
<td>Global rim area</td>
<td>0.41</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Global cup area</td>
<td>0.29</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Global cup volume</td>
<td>0.24</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Temporal-superior rim/disc area ratio</td>
<td>-0.15</td>
<td>0.002</td>
</tr>
<tr>
<td>Global rim/disc area ratio</td>
<td>-0.13</td>
<td>0.004</td>
</tr>
<tr>
<td>Temporal-inferior rim/disc area ratio</td>
<td>-0.10</td>
<td>0.03</td>
</tr>
</tbody>
</table>

![Figure 4](image-url) Box-and-whisker plots showing the differences in global rim area and global rim-to-disc area ratio (larger disc minus smaller disc) in relation to the difference in disc area (quartiles), in 459 normal elderly patients.

![Figure 5](image-url) Difference in clinically graded cup-to-disc ratio asymmetry (larger disc minus smaller disc) in 459 normal elderly patients. The normal curve is displayed for comparison.
criteria, and it is likely that we falsely rejected a significant number of normal eyes to maintain as pure a dataset as possible. It is very difficult to predict the effect of these exclusion criteria on the tolerances of normality for asymmetry parameters. However, to our knowledge, this is the first study to generate a reference range for normal asymmetry based on HRT parameters in a large sample of normal, elderly patients. We have shown that the rim-to-disc area ratio asymmetry measure is likely to be the most useful parameter in describing normality with consistency. Whether it achieves sufficient precision in discriminating normal from glaucomatous eyes for the purposes of screening requires further research.

Acknowledgments

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References