Use of high spatial resolution perimetry to identify scotomata not apparent with conventional perimetry in the nasal field of glaucomatous subjects

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Aim: To examine whether high spatial resolution perimetry (HSRP) could identify fine scale scotomata which may not be apparent with conventional perimetry. The HSRP was performed in the nasal field, as this location is a recognised site for the early occurrence of glaucomatous defects.

Method: 16 early glaucoma eyes, 17 glaucoma suspect eyes, and 20 age matched healthy control eyes underwent conventional automated perimetry using the 24-2 program of the Humphrey field analyser (HFA) and HSRP. The HSRP was performed in the nasal field by testing 9 × 9 degrees of 100 tested points separated by 1 degree and the results compared with the HFA 24-2 program.

Results: Mean HSRP thresholds were significantly abnormal in the suspect and glaucoma eyes, with elevated levels of asymmetry between the superior and inferior nasal field. Overall, 7/17 (41%) suspect eyes (95% confidence interval 5/17 (29%) to 7/17 (41%)) had nasal scotomata on HSRP, although their HFA 24-2 fields failed to identify any defects. In glaucomatous eyes, 15/16 (94%) eyes had HSRP scotomata (95% CI 14/16 (88%) to 15/16 (94%)). In 12 these coexisted with HFA 24-2 defects at the same location, while in three eyes only HSRP identified scotomata in the nasal field.

Conclusion: HSRP can identify scotoma in glaucomatous eyes in the nasal field which may be missed with the lower spatial resolution of conventional perimetry.
number of locations other than the nasal field, with good reproducibility and within a clinically acceptable test time.

The purpose of this study was to examine whether HSRP could identify fine scale scotomata which may not be apparent with conventional perimetry. The HSRP was performed in the nasal field, as this location is a recognised site for the early occurrence of glaucomatous defects.

METHODS

The study was approved by the Moorfields Hospital ethics committee and followed the tenets of the Helsinki agreement.

Eligibility criteria

Healthy control subjects

Twenty healthy subjects comprised the control group. These were recruited from an established cohort of normal subjects (spouses, volunteers) used as the control group for a number of prospective studies in the ocular hypertension clinic of Moorfields Eye Hospital.

Inclusion criteria were normal ocular examination with an IOP less than 21 mm Hg, visual acuity better than 6/12, refraction less than 7 dioptres (D) ametropia, and a normal HFA 24-2 field test, repeated on at least three occasions. For this study we defined a normal HFA 24-2 field as a normal or borderline glaucoma hemifield test in the absence of any clusters of depressed locations in either hemifield. The cluster definition of a scotoma on the HFA 24-2 required a minimum of three adjacent points within a hemifield depressed by at least 5 dB from normal age expected values, with one point depressed by 10 dB. This definition has been widely used in previous studies.

Exclusion criteria were previous ocular surgery, diabetes, family history of glaucoma in a first degree relative, or systemic β blocker medication.

Glaucoma suspects

Twenty glaucoma suspects were recruited from the Moorfields ocular hypertension clinic. Inclusion criteria were visual acuity better than 6/12, refraction less than 7 D ametropia, documented intraocular pressure >21 mm Hg in the presence of a normal HFA 24-2 field test according to the above definition, repeated on at least three occasions.

Exclusion criteria were previous ocular surgery or history of diabetes.

Early primary open angle glaucoma eyes

Sixteen patients with early primary open angle glaucoma (POAG) were recruited from the glaucoma clinic or the ocular hypertension clinic. The latter were patients in whom a reproducible field defect had developed while under review.

Inclusion criteria were visual acuity better than 6/12, refraction less than 7 D ametropia, documented intraocular pressure >21 mm Hg on at least one occasion in the presence of an open angle, and a glaucomatous visual field defect on the HFA 24-2 field test reproducible on at least three consecutive occasions. All 16 eyes had early arcuate scotomata. In 12 these extended to the nasal field on the HFA 24-2 test.

Exclusion criteria

Significant ocular pathology other than glaucoma, previous ocular surgery or trauma, history of diabetes, or topical miotic agents.

All study participants contributed only one eye to the study, chosen at random if both were eligible. The characteristics of the study population are summarised in Table 1.

Visual field testing

All subjects underwent conventional perimetry with the HFA 24-2 program, followed by HSRP using the Humphrey field analyser model 630. Tests were performed on the same day using the same machine, with the tests separated by a suitable rest period. All perimetry was performed using the full threshold algorithm with standard 4·2 double reversal strategy. Eye movements were continuously monitored using a closed circuit camera in the standard fashion. All fields were reliable, defined as fewer than 30% fixation losses, 30% false negatives and 15% false positives. All subjects were practised perimetric observers.

High spatial resolution perimetry

The technique for performing HSRP has been extensively described in previous publications. To perform HSRP, the “custom grid” program of the HFA was used to define four custom test programs, each consisting of 5×5 locations separated by 2 degrees, with the coordinates of each custom test program offset to the other by 1 degree in the x, y, or x and y axis. Subjects were tested using the four custom test programs applied in succession in a randomised order with a short standardised rest period between each. The test time was approximately 20 minutes, excluding the brief rest between grids, and was tolerated by all subjects.

A size III stimulus was used on a standard HFA bowl illumination of 31.5 apostilbs. Software was used to merge the four custom test programs to generate a single fine matrix map (FMM) of the thresholds of 100 test locations separated by 1 degree covering an area of 9×9 degrees in the nasal field. This extends from the HFA 24-2 coordinates –19, –4 to –28, 5 for a right eye, and extends above and below the horizontal midline. The test location overlaps four test points on the HFA 24-2 program (including the two locations in the nasal field at –27, 3, and –27, –3). Accuracy of fixation is monitored in the same way as conventional perimetry.

HSRP was performed without near correction in accordance with the protocol of our previous studies. The refraction at this eccentricity is difficult to ascertain and near correction could induce prismatic and edge effects which would be difficult to standardise during the test procedure. However, the distribution of refractive errors was comparable between the groups of eyes tested and did not differ significantly (Table 1).

Analysis

The data were imported to software (SPSS for Windows, release 10, SPSS Inc, Chicago, IL, USA) for statistical analysis. All variables were tested for normality, and analysis of variance (ANOVA) followed by post hoc testing was used to identify
significant differences between pairs of groups. If data distributions were non-parametric, equivalent non-parametric tests were used. The level of statistical significance was set to \( p < 0.05 \).

**High spatial resolution perimetry**

The method of analysis of the threshold data from HSRP has been reported in previous publications.\(^{11,12}\) Firstly, the mean threshold of the 100 test locations was calculated to obtain a global summary measure of the thresholds. Two additional measures were calculated to describe the uniformity of thresholds within each FMM, called the uniformity index and the asymmetry index.

The uniformity index is the standard deviation (SD) of the threshold values and gives an overall measure of the degree of uniformity, similar to the pattern standard deviation of the HFA 24-2 test.

The asymmetry index was derived to quantify the degree of threshold difference for each test location in the superior nasal field and its corresponding equivalent location in the inferior nasal field. This index was calculated as the mean of the pairwise threshold differences (superior − inferior) between corresponding locations in the superior and inferior nasal field. In control eyes, differences between the superior and inferior nasal fields were minimal (superior − inferior mean (1 SD) difference = −0.4 (0.4) dB). The negative mean value indicates a minimally higher threshold sensitivity in the inferior field. This difference is a physiological reflection of the anatomical and functional asymmetry of the retina and has been reported previously.\(^{10}\) To allow scores to be compared between groups we calculated the “normalised asymmetry index” for each subject, expressed as the absolute difference normalised with respect to the mean difference of the controls.

The normative ranges of the HSRP summary measures (mean threshold, uniformity index, asymmetry index) were investigated for the possible influence of factors such as age and refraction by performing linear regression on the control data. Forward stepwise linear regression was performed separately with each summary measure as the dependent variable using factors such as age, refraction, sex, and eye side as independent variables. Factors that contributed significantly to a linear relation were taken as those with a significance level <0.05 and \( R^2 > 0.1 \).

**Table 2** Summary statistics of HSRP thresholds by group. Values shown are mean (1 SD) in dB. Figures in parentheses indicated minimum and maximum values

<table>
<thead>
<tr>
<th></th>
<th>Normal eyes (20 eyes)</th>
<th>Suspect eyes (17 eyes)</th>
<th>Glaucoma eyes (16 eyes)</th>
<th>Normal v suspect</th>
<th>Normal v glaucoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean threshold (MT)</td>
<td>28.0 (1.7) [24.2–30.4]</td>
<td>25.9 (3.2) [18.8–30.5]</td>
<td>22.1 (4.1) [12.4–27.1]</td>
<td>( p &lt; 0.03^* )</td>
<td>( p &lt; 0.001^* )</td>
</tr>
<tr>
<td>Uniformity index (UI)</td>
<td>1.5 (0.2) [1.1–2.1]</td>
<td>2.4 (1.4) [1.2–7.4]</td>
<td>3.8 (1.9) [1.3–8.6]</td>
<td>( p &lt; 0.001^* )</td>
<td>( p &lt; 0.001^* )</td>
</tr>
<tr>
<td>Asymmetry index (AI)</td>
<td>0.4 (0.2) [0.0–0.7]</td>
<td>1.2 (2.2) [0.2–8.4]</td>
<td>2.2 (2.3) [0.0–7.5]</td>
<td>( p &lt; 0.009^* )</td>
<td>( p &lt; 0.001^* )</td>
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*\(^{Mann-Whitney U test.}\)

The presence of scotomata on the HSRP was assessed in relation to the presence or absence of scotoma on the HFA 24-2 field at the test site. This was defined as the presence of at least one of the four HFA 24-2 locations depressed by at least 5 dB from normal age expected values, directly adjacent or within a cluster of a scotoma according to our definition (see Methods). The HFA 24-2 fields were further analysed for the presence of scotoma according to a probabilistic definition, defined as at least one depressed nasal HFA 24-2 location within a hemifield cluster of three or more abnormal points on the pattern deviation plot, with at least one location having a probability of abnormality at \( p < 0.01 \), and two locations at \( p < 0.05 \).

Quantitative analysis was performed on the raw data. However, for display purposes, spatial image processing of the HSRP thresholds was performed using a Gaussian filter to generate three dimensional surface plots in accordance with previous studies.\(^{16,24}\)
RESULTS

Table 2 shows summary data of the HSRP by group. The mean threshold was significantly lower in the glaucomatous eyes (p <0.001) and suspects (p = 0.03) compared with controls.

In controls, threshold plots were uniform and as a consequence the uniformity indices were low (Fig 1). This non-uniformity of the visual field is shown in the HSRP threshold plots from suspects. Scotoma is shown by elevations and is not apparent at the lower spatial resolution of the HFA 24-2 (Figs 2 and 3).

The threshold asymmetry between the superior and inferior fields, expressed as normalised asymmetry index, was significantly higher in the glaucomatous eyes (p = 0.001) and the suspects (p = 0.009) (Table 2). This can be seen graphically in the HSRP threshold plot of Figure 3B: the elevations represent reduced threshold sensitivity in the superior compared to inferior nasal field. This represents an abnormally high degree of asymmetry in sensitivity between the superior and inferior fields.

In glaucomatous eyes, 15/16 (94%) eyes had HSRP scotomata (95% CI 14/16 (88%) to 15/16 (94%)).

HSRP results were analysed in terms of whether there was a scotoma on the HFA 24-2 field at the test site using the conventional 5 dB definition. The HSRP overlapped an area unaffected by scotoma on the HFA 24-2 at the test site in 4/16 eyes. Of these, three eyes had scotoma on the HSRP with summary measures outside normal limits. An example is shown in Figure 4: one eye had scotoma on the HFA 24-2 pattern deviation plot according to the probabilistic definition.

The remaining 12 eyes had scotoma extending to the nasal field on the HFA 24-2.

All had abnormal HSRP with at least one summary measure outside normal limits An example is shown in Figure 4: one eye had scotoma on the HFA 24-2 pattern deviation plot according to the probabilistic definition.

Eleven of 12 eyes had two or more abnormal summary measures.

For the controls, 19/20 had summary measures within normal cut-offs. One had an uniformity index outside control mean +1.96 SD with normal mean threshold and asymmetry index.

HSRP test times for the suspect and glaucoma groups were 21.6 (4.2) and 23.5 (4.1) minutes (mean (1 SD)) respectively. These were significantly prolonged compared to the control group mean of 17.7 (1.6) minutes (p <0.01). For comparison, HFA 24-2 mean test times were 13.4 (2.6) (suspect group), 13.4 (1.9) (glaucoma group), and 12.5 (1.9) minutes (control group).
Scotomata in the peripheral nasal field (>30 degrees) have been reported in glaucoma in suspects who appear to have normal central fields, as tested using conventional automated perimetry. Our findings provide further evidence that the inadequate spatial resolution of conventional perimetry is a principal limitation in detecting early glaucoma.

Our findings also suggest that the nasal field is a worthwhile location to investigate for the early occurrence of visual field loss, and it is worth considering the possible reasons that may account for this.

One factor to consider is the sector of the optic nerve head represented by the nasal field. A recent study has produced a map relating the HFA 24-2 visual field test locations to the corresponding regions of the optic nerve head (ONH). According to this map, the paracentral area of the visual field (which includes the nasal region tested in our study) would be represented by sectors nearer the poles of the ONH than previously thought. Thinning of the neuroretinal rim at the ONH poles is characteristic of glaucoma, and several authors have reported that vertical enlargement of the cup may be an early sign of glaucoma. Vertical expansion of the cup is often noted to be asymmetric. This may result in notching of the neuroretinal rim if marked asymmetry of expansion occurs towards one of the poles. The frequent occurrence of thinning of the neuroretinal rim in early glaucoma provides a rationale for detailed testing of the nasal field in the absence of overt loss on the 24-2 program of the HFA.

Furthermore this asymmetry of rim thinning is likely to account for the high asymmetry of threshold identified between the inferior and superior nasal fields in glaucomatous eyes. Other researchers have reported high degrees of threshold asymmetry in the nasal field in glaucoma.

**Potential sources of bias and error**

The sample sizes in this study were relatively small and consequently the cut-off values used to define the normal control limits are likely to be significantly dependent on the sample sizes and the exclusion and inclusion criteria used. This must be recognised as a potential source of bias. Both control and glaucoma groups were enrolled from an ongoing study (the Moorfields Ocular Hypertension study) and the controls would have been selected on the basis of a repeatedly normal field. Selecting controls on the basis of a normal field is a possible source of selection bias that may overemphasise the true differences between the groups. Bias could have been minimised if an independent measure, such as the optic disc, had been used to classify the normal, suspect, and glaucomatous groups. However this is still problematic because of the lack of any agreed standard for reliably classifying subjects into normal or abnormal using quantitative disc analysis.

A further source of bias to consider is sampling bias. In our study, HSRP sampled the area of field many more times than the 24-2 program of the HFA (100 versus 4). Testing many more locations in areas where there is likely threshold variability associated with early disease increases the likelihood of discovering defects.

The final potential source of error is the influence of refractive error on the HSRP thresholds in the nasal field. While the influence of refractive error cannot be excluded, there are reasons to suppose that it is unlikely to be a major factor in accounting for the differences between the groups. Firstly, the refractive errors of the subject groups were equivalent. Secondly, our analysis did not identify any relation between HSRP thresholds and the degree of refractive error in the controls. Thirdly, previous studies have shown that in general, the effect of refractive error is to globally suppress field sensitivities. However, two of the HSRP indices this study used reflect focal sensitivity differences, either within the entire area of field tested (uniformity index) or across the superior and inferior fields (asymmetry index). Refractive...
errors would not be expected to account for these localised threshold abnormalities, as in general the effect of refractive error is to smear out localised abnormalities.

In summary, a substantial proportion (88%) of glaucomatous eyes and 41% of glaucoma suspects had fine scale scotomata in the nasal field identified with our technique. These may be missed by the low spatial resolution of conventional perimetry. Longitudinal follow up is under way to identify whether those eyes with fine scale scotomata are more likely to develop enlargement of scotomata which can be detected with conventional perimetry.

ACKNOWLEDGEMENTS

The authors thank Mr Ian Thrasher of Moorfields Eye Hospital for his assistance in performing the perimetry.

Grant support: This work was supported by grants from the Frost Charitable Trust, the Friends of Moorfields, the Medical Research Council, and the International Glaucoma Association.

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