Glaucoma is one of the most common eye diseases, affecting about 2% of the population older than 50 years. It is characterised by progressive optic nerve damage and retinal ganglion cells loss. Perimetry is considered the fundamental method in the diagnosis and follow up of glaucoma.

Previous studies have demonstrated that the standard achromatic perimetry (SAP), considered as the gold standard in visual field (VF) examination, cannot detect damage until about 20–50% of the ganglion cells have been lost, and that the optic disc and retinal nerve fibre layer (RNFL) alterations, caused by ganglion cell axons loss, commonly occur before the perimetric defects.

In order to detect VF damage before it can be seen with SAP, other perimetric techniques have been developed including frequency doubling technology (FDT), motion perimetry, flicker perimetry, high pass resolution perimetry (HRP), and short wavelength automated perimetry (SWAP).

Rarebit perimetry (RBP) is a new perimetric method, developed by Frisén, which has given promising preliminary results in the early detection of VF damages in patients with neurological disorders, and medications altering the VF.

In this consecutive comparative observational study, the SAP and RBP data of patients with ocular hypertension (OH), and early primary open angle glaucoma (POAG), and of controls, were compared and discussed.

**METHODS**

The study included 43 patients affected with OH, 39 patients with early POAG, and 41 age matched controls. After obtaining informed consent, all subjects underwent an ophthalmological examination (including best corrected visual acuity (BCVA) evaluation, slit lamp examination, Goldmann applanation tonometry, gonioscopy, fundus biomicroscopy). VF examination with SAP and RBP was then performed within 1 month. One eye per patient was randomly selected for analysis, except when only one eye met our inclusion criteria.

Inclusion criteria were age range of 35–72 years, BCVA ≥0.8, open anterior chamber angle, absence of ocular pathology other than glaucoma, mild nuclear sclerosis, and rare drusen.

Exclusion criteria included ametropia more than plus or minus 5 dioptries, pupils diameter <3 mm, anterior angle alterations, presence of secondary causes of glaucoma, history of intraocular surgery, diabetes mellitus, neurological disorders, and medications altering the VF.

Controls were screened to have a normal intraocular pressure (IOP) and to exclude glaucoma family history and ocular pathologies. VF were assessed with SAP using the Humphrey field analyser (HFA) II 750 (Carl Zeiss Meditec Inc, Dublin, CA, USA) program 30-2, with Swedish Interactive Threshold Algorithm (SITA) strategy.

SAP tests were classified as glaucomatous according to the Anderson criteria, in which at least one of the following was present:

1. A cluster of ≥3 points in the pattern deviation probability plot, located in areas typically observed in glaucoma, having a probability level of <5%, with at least one point having a probability level of <1%; none of the points could be edge points unless they were located immediately above or below the nasal horizontal meridian;
2. PSD probability level of <3%;

**Abbreviations:** BCVA, best corrected visual acuity; FDT, frequency doubling technology; HFA, Humphrey field analyser; HRP, high pass resolution perimetry; IOP, intraocular pressure; MD, mean deviation; MHR, mean hit rate; OD, ocular hypertension; POAG, primary open angle glaucoma; PSD, pattern standard deviation; RBP, rarebit perimetry; RNFL, retinal nerve fibre layer; SITA, Swedish Interactive Threshold Algorithm; SWAP, short wavelength automated perimetry; VF, visual field.
Reliable criteria for HFA tests included false positive and false negative responses of <33% and fixation losses of <20%. Glaucomatosus VF defects were classified using the Glaucoma Staging System, which classifies severity in five stages. Stages 0, 1, and 2 were considered, which included tests having a mean deviation (MD) of >-9.0 and a pattern standard deviation (PSD) of <8.0 dB.

Optic disc and RNFL appearance were analysed by an expert ophthalmologist with slit lamp biomicroscopy using a +7BD Volk lens, and classified utilising the European Glaucoma Society (EGS) guidelines (table 1).

All eyes having both an IOP >21 mm Hg and normal SAP results were evaluated with a scanning laser polarimeter having a variable corneal compensator (GDx-VCC) (Laser Diagnostic Technologies, Inc, San Diego, CA, USA). The GDx images were judged by an expert ophthalmologist based on the software provided parameters.

The patients were classified into three groups according to the EGS criteria:

(1) OH group (43 eyes): IOP >21 mm Hg; optic disc and RNFL appearance, and SAP results all normal;
(2) POAG group (39 eyes): IOP >21 mm Hg before medication, typically glaucomatous optic disc or RNFL changes, either with reproducible glaucomatous SAP VF defect (perimetric POAG, 33 eyes) or without (pre-perimetric POAG, six eyes);
(3) control group (41 eyes): IOP, optic disc and RNFL appearance and SAP results all normal.

The RBP procedure has already been described elsewhere. In brief, the RBP test is performed on any standard PC with a liquid crystal display; the software (in Microsoft Windows format) is available free of charge from the author.

The test stimulus is composed of two microdots, having a diameter set at half of the minimum angle of resolution (approximately 1/100 the size of the SAP stimulus), separated by 4° of the visual angle and simultaneously exposed for 200 ms. Paired dots appear on the screen at random positions within a 5° circular diameter area centred on each of four central and 26 peripheral test locations. A total of 30 areas, separated by 10° (centre to centre), are tested, covering a horizontal eccentricity of 27.5° and a vertical eccentricity of 20° upwards and of 22.5° downwards (fig 1). The tested area distribution is the same for both the right and left eye.

The first test phase involves one pass (=2 microdots presentation) over each of the tested areas; a minimum of five runs is recommended, for a total of 10 presentations per area; 10% of presentations, containing either only one dot or none at all, are used as a control. Target and background luminances are set at 150 cd/m² and 1 cd/m² respectively. The room illumination required is 1 lux.

A fixation mark is moved at a preset sequence by the computer. Subjects are instructed to fixate it on the monitor, to indicate the number of microdots seen during each presentation (0, 1, or 2) by not clicking, clicking, or double clicking a mouse button, and to refrain from gazing at eccentric stimuli.

The test was first performed at 0.5 metres of distance, to test the 26 peripheral areas, and repeated at a distance of 1 metre, for the four central locations.

Total refractive error and proper test distance were corrected with the spherical equivalent. The RBP results are provided as a hit rate, expressing the total number of dots seen divided by the total number of dots shown, calculated as a percentage. The printout provides a mean hit rate (MHR), which is calculated over all the tested locations (except for the one closest to the blind spot). 30 non-hit rate values, plotted separately for each of the tested areas, are also provided.

The error statistic value represents the sum of the responses to control presentations, and it should come close to 0. Reliability of RBP testing was defined as an error statistic value of <2. Left eye results were converted in a right eye format for the results analysis.

The following parameters were considered:

- for the HFA test: MD, PSD, testing time;
- for the RBP test: MHR, number of tested areas with a non-hit rate of 10 groups of misses (one group for each 10% miss level), testing time, percentage of eyes having the following patterns of distribution of missed hit rates:

<table>
<thead>
<tr>
<th>Average number of dots per eye</th>
<th>Controls</th>
<th>OH</th>
<th>POAG</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
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<tr>
<td>2</td>
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<tr>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Non-hit rate miss level (%)</td>
<td>0–10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>11–20</td>
<td>1–2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>21–30</td>
<td>2–3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>31–40</td>
<td>3–4</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>41–50</td>
<td>4–5</td>
<td>4</td>
<td>4</td>
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<tr>
<td>51–60</td>
<td>5–6</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>61–70</td>
<td>6–7</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>71–80</td>
<td>7–8</td>
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<td>81–90</td>
<td>8–9</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>91–100</td>
<td>9–10</td>
<td>9</td>
<td>9</td>
</tr>
</tbody>
</table>

Figure 1 Representation of size and distribution of the 30 test areas in rarebit perimetry with the corresponding test points used in the Humphrey field analyser program 30-2.

Figure 2 Histogram showing the mean number of areas per eye with a non-hit rate of 10 groups of misses (one group for each 10% miss level) obtained by the three groups in the rarebit perimetry test.

Table 1 Glaucomatous characteristics of optic disc and retinal nerve fibre layer (RNFL) as stated by the European Glaucoma Society (at least 1)

| (1) Optic disc excavation—that is, undermining of the neural rim |
| (2) Notching involving >2 clock hours |
| (3) Focal or diffuse atrophy of neural rim area involving >2 clock hours |
| (4) Vertical cup to disc ratio >0.6 |
| (5) Cup to disc asymmetry between fellow eyes >0.2 |
| (6) Disc haemorrhage |
| (7) Baring of circumlinear blood vessels |
| (8) Focal or generalised atrophy of the RNFL |

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The control subjects were significantly younger than patients with both OH and POAG (Kruskal-Wallis test, p < 0.02, table 2).

The average HFA-MD and HFA-PSD values were significantly higher in the POAG than in control and OH eyes (S-N-K test, p < 0.01, table 2). The mean RBP-MHR of control, OH, and POAG groups was respectively 88.6% (SD 4.8%) (range 78–98%), 79.1% (10.9%) (range 44–95%), and 64.3% (13.8%) (range 37–96%) (and 71.2% (10.4%), range 44–95%, and 64.3% (13.8%) (range 37–96%), with at least one area with a non-hit rate of >50%.

Areas with a non-hit rate between 11% and 30% were equally distributed within the groups; areas with a non-hit rate between 31% and 60% were significantly more frequent in the POAG group; areas with a non-hit rate of >60% appeared significantly less in the controls and more in the POAG group (S-N-K test, p < 0.01).

Areas with a non-hit rate between 11% and 30% were equally distributed within the groups; areas with a non-hit rate between 31% and 60% were significantly more frequent in the POAG group; areas with a non-hit rate of >60% appeared significantly less in the controls and more in the POAG group (S-N-K test, p < 0.01).

The percentage of eyes having at least one of the patterns of distribution of missed hit rates were the lowest in the controls (9.8%), intermediate in the OH (48.8%), and the highest in the POAG eyes (84.6%), showing significant differences among the groups for all of the pattern types (χ² test, p < 0.01, fig 3).

Figure 3 Histogram showing the number of eyes in the three groups having one of the following patterns of distribution of missed hit rates in the rarebit perimetry test: pattern 1: ≥2 adjacent areas with a non-hit rate of >50%, with at least one area with a non-hit rate of >50%; pattern 2: ≥3 adjacent areas with a non-hit rate of >50%, with at least one area with a non-hit rate of >50%; pattern 3: ≥2 adjacent areas with a non-hit rate of >50%.

Figure 4 Scatter plot illustrating the relation between Humphrey field analyser-mean deviation (HFA-MD) and rarebit perimetry-mean hit rate in the glaucomatous eyes.

Table 2 Patient demographics and Humphrey field analyser (HFA) data

<table>
<thead>
<tr>
<th>Groups (no of eyes)</th>
<th>Age (years)</th>
<th>M/F</th>
<th>MD</th>
<th>PSD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Controls (41)</td>
<td>54 (9.0)</td>
<td>13/28</td>
<td>−0.4 (1.2)</td>
<td>1.6 (0.2)</td>
</tr>
<tr>
<td>OH (43)</td>
<td>61 (8.1)</td>
<td>15/28</td>
<td>−0.8 (1.2)</td>
<td>1.6 (0.3)</td>
</tr>
<tr>
<td>POAG (39)</td>
<td>61 (10.1)</td>
<td>19/20</td>
<td>−2.0 (1.6)</td>
<td>3.1 (1.4)</td>
</tr>
</tbody>
</table>

| OH, ocular hypertension; POAG, primary open angle glaucoma; SD, standard deviation; MD, mean deviation; PSD, pattern standard deviation. |
Optimal Sp was found when the presence of “at least one area with a non-hit rate of &gt;70%” was used as cut-off criterion.

Largest AROC and optimal Se were obtained when RBP tests were defined as abnormal if having at least one of the following: MHR &lt;80%; &gt;15 areas with a non-hit rate of &gt;10%; &gt;2 areas with a non-hit rate of &gt;50%; at least one area with a non-hit rate of &gt;70%.

The percentage of abnormal eyes tested with RBP in the OH group ranged from 44.2 to 65.1%. The average RBP testing time was slightly, but not significantly, less (405 (49.3) seconds/patient) than SAP testing time (416 (54.8) seconds/patient).

DISCUSSION

The detection of early glaucomatous VF damage is of great clinical interest. Many new perimetric techniques have been developed with this purpose, one of the newest being the RBP. RBP utilises a spatially and temporally minimised test stimulus in order to avoid the simultaneous stimulation of many retinal receptive fields, with the risk of underestimating a defect.

The purpose of the RBP is to calculate the percentage of the visual system integrity by analysing the proportion of observed responses to microdots presentations. The basic concept that lies behind the RBP is that all normal eyes, although differing in the total number of ganglion cells, have a complete neuroretinal architecture, permitting the detection of pairs of dots of opportune size, contrast and separation, everywhere in the VF. A depleted neural matrix may give rise to the detection of just one or none of the target dots. Some misses can be expected on physiological grounds (the blind spot, angioscotomata, age related neuroretinal architecture depletion, blinks, attention lapses).

In the present study, differences in MHR and non-hit rates within control, OH, and POAG groups were evaluated in order to establish if these parameters could effectively reflect the functional integrity of the retinal ganglion cells; a complete neuroretinal architecture, permitting the detection of pairs of dots of opportune size, contrast and separation, everywhere in the VF. A depleted neural matrix may give rise to the detection of just one or none of the target dots. Some misses can be expected on physiological grounds (the blind spot, angioscotomata, age related neuroretinal architecture depletion, blinks, attention lapses).

The RBP-MHR progressively significantly decreased from the controls to the POAG group. Our controls were significantly younger than the glaucomatous patients. We believe, however, that this difference would not practically affect our results, since the age related reduction of RBP-MHR was very small compared to the decrease induced by glaucoma.

The number and magnitude of missed hit rates appeared significantly lower in the controls and higher in the POAG group (fig 2). Adjacent areas having a high non-hit rate were more frequently observed in the OH and POAG groups rather than in the controls (fig 3). These results are interesting because our POAG group comprised only patients having either an early or pre-perimetric POAG.

The high number of abnormal RBP tests found in the OH (table 3) and in pre-perimetric POAG eyes, coupled with the tendency of observed higher values using RBP as opposed to SAP (fig 4), strongly suggests that RBP may depict a more advanced stage of glaucoma, improving the detection of low degrees of damage. This advantage in RBP can be attributed to various causes: the simplification of the target content; the replacement of the threshold procedure with a probe of the percentage of the visual system integrity; the possible lower inter-individual variability in the test results.

The good correlation between HFA-MD and RBP-MHR in the glaucomatous eyes (fig 4) suggests that both values are probably related to the number of functioning retinal ganglion cells, and that counting the misses on the RBP test may determine the presence and severity of glaucoma.

Our best AROC value, of 0.95, showing a Se and Sp respectively of 97.4% and 92.7% (table 3), indicates that the ability of RBP in differentiating between normal and early POAG is comparable, if not better, than that obtained by other non-conventional perimetry: in a cohort of mild to moderate glaucomatous patients, FDT showed a Se and Sp respectively of 93% and 100%: the HRP performances were respectively 82.5% and 85%, and decreased to 61% and 90% with SWAP.

Our patients did not experience any problem in performing RBP, except for the advanced elderly, who were not familiar with the PC mouse; moreover, the RBP test appeared slightly faster than the HFA 30-2 SITA test. In conclusion, RBP appeared to be a rapid and easily administered perimetric test, able to detect early glaucomatous VF defects. With some improvements (a more accurate screen calibration, a designed patient head rest, a better fixation control), we think that RBP may become useful in both the screening and assessment of glaucoma and other neuro-ophthalmological pathologies, providing a quantitative VF testing method which is easily available in every medical office (since it only requires a PC), even when ordinary perimetry is impracticable—for example, at the bedside.

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Probing glaucoma visual damage by rarebit perimetry

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*Br J Ophthalmol* 2005 89: 180-184
doi: 10.1136/bjo.2003.041178

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