Detection of Early Visual Field Loss in Glaucoma Using Frequency-Doubling Perimetry and Short-Wavelength Automated Perimetry

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Objective: To investigate whether frequency-doubling perimetry (FDP) predicts future visual field loss with achromatic automated perimetry (AAP), just as it may be predicted with short-wavelength automated perimetry (SWAP).

Methods: We recruited 62 patients selectively from an urban glaucoma practice. At the commencement of the study, each patient had ocular hypertension with normal visual fields on AAP. Baseline SWAP and FDP were performed to determine whether underlying earlier visual field loss was present. Patients were then followed up prospectively for 3 years with annual AAP, SWAP, and FDP.

Main Outcome Measure: The development of visual field loss on AAP.

Results: Nine subjects had abnormal SWAP findings and 10 had abnormal FDP findings. At the conclusion of the study, field loss on AAP developed in 5, all of whom had preexisting abnormal SWAP and FDP results. No AAP visual field loss developed in patients with a normal SWAP or FDP. The rate of development of visual field loss on AAP was therefore significantly greater for those with abnormal SWAP ($\chi^2=40.83; P<.001$) and abnormal FDP findings ($\chi^2=32.76; P<.001$) than for those with normal SWAP and FDP findings.

Conclusion: In the same way that SWAP may predict AAP visual field loss, FDP may also detect field loss earlier than AAP.

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OPEN-ANGLE GLAUCOMA (OAG) is a potentially blinding ocular condition that is characterized by a progressive optic neuropathy with or without characteristic visual field loss.1 It may be associated with raised intraocular pressure.2,3 However, to diagnose glaucoma at the optic disc or on the visual field, ganglion cell loss needs to occur. Up to 50% of local ganglion cell concentration may be lost to glaucoma before visual field abnormalities are detected using conventional achromatic automated perimetry (AAP).4,5 Using the theoretical models of selective loss and reduced redundancy,6 tests of early visual field loss were developed. In the early stages of glaucoma, large-diameter ganglion cells may be lost selectively,7,8 although this concept remains controversial.5,10-13 Furthermore, a ganglion cell population, which has relatively few numbers, will have little reserve when loss occurs.6 Ganglion cell axons projecting from blue-on cells within the koniocellular14,15 pathway are about 50% larger than those in red- or green-sensitive pathways and are fewer in number.16 Tests that target them (eg, short wavelength automated perimetry [SWAP]) can therefore detect glaucomatous damage several years earlier than AAP.17,18

Magnocellular cells are larger than parvocellular or koniocellular cells and make up only 15% of total ganglion cell numbers.9,19 A subset of these with nonlinear (Y-like) properties (My cells) make up approximately 15% of magnocellular cells.20,21 Although evidence of this subset may be disputed,22,23 the magnocellular line itself, having larger and fewer numbers of cells, may still be subject to selective loss and reduced redundancy. Tests that target them, such as frequency-doubling perimetry (FDP),24-26 should be able to detect glaucomatous loss before it becomes manifest on AAP.27-30

We conducted a study to investigate whether subjects with ocular hypertension and normal AAP findings who have abnormal SWAP and FDP results will develop similar AAP abnormalities.
Table 1. SWAP Results Compared With FDP Results

<table>
<thead>
<tr>
<th>FDP Result</th>
<th>Swan</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Normal</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Abnormal</td>
<td>1</td>
<td>51</td>
</tr>
<tr>
<td>Normal</td>
<td>0</td>
<td>52</td>
</tr>
<tr>
<td>Total</td>
<td>10</td>
<td>52</td>
</tr>
</tbody>
</table>

Abbreviations: AAP, achromatic automated perimetry; FDP, frequency-doubling perimetry; SWAP, short-wavelength automated perimetry.

METHODS

SUBJECTS

A sample of 62 patients with ocular hypertension and normal AAP visual fields (ie, not manifesting a glaucomatous scotoma, as defined later for SWAP) were recruited selectively from a private glaucoma practice. Inclusion criteria were an intraocular pressure of at least 21 mm Hg when not receiving medication, visual acuity of 6/12 or better, 5 diopeters (D) or less of sphere and 3 D or less of cylinder in refractive error, no previous intraocular surgery, no other systemic illness, and no history of color vision deficit. Optic disc structure was not considered. After obtaining informed consent in accordance with the requirements of the South Eastern Sydney Area Health Services Clinical Research Ethics Committee, Sydney, New South Wales, each patient initially underwent AAP, SWAP, and FDP in random order. They were then followed up prospectively in a longitudinal fashion for 3 years. Testing was performed annually, each time in random order. The main outcome measure was the development of visual field loss on AAP.

PROCEDURE

The right eye underwent testing unless it did not meet the criteria. The Humphrey Field Analyzer II (Carl Zeiss Meditec, Inc, Dublin, Calif) was used to perform central 24-2 SITA standard (AAP) and central 24-2 SWAP tests. We performed SWAP using a background illuminated with a yellow light at 100 candela (cd)/m² and a blue target stimulus (440 nm), size V (1.72°). The determination of an abnormal AAP or SWAP finding was based on the pattern deviation of the Humphrey Field Analyzer II probability plot and was established before the commencement of the study. Visual field loss was considered significant if it had a pattern typical of glaucoma and occurred in a field with 5 or more points of P<.05, with a cluster of 3 or more abnormal points of P<.05% or 2 or more points of P<.1%.

We performed FDP using a Humphrey-Zeiss frequency-doubling technology perimeter (Carl Zeiss Meditec, Inc) with a full-threshold C-20 program. This test uses a square target, 10° wide, consisting of alternating light and dark stripes (spatial frequency, 0.25 cycles per degree). The stripes were reversed at a rate of 25 Hz, and the contrast of the stripes was changed to determine the patient’s contrast threshold. The target was presented in 17 zones (4 per quadrant) up to 20° from fixation, with a central 10°-wide circular zone. For FDP, visual field loss was considered significant if there were 2 or more adjacent zones of P<.05 or 1 zone of P<.1% on the FDP pattern deviation. The AAP, SWAP, and FDP fields were considered reliable if there were less than 30% false-negative and false-positive errors and less than 25% fixation losses.

For a subject to be classified as having an abnormal AAP, SWAP, or FDP finding, as previously described, significant visual field loss needed to have been seen on 2 consecutive visual field tests, with the scotoma involving the same quadrant in each case.

STATISTICAL ANALYSIS

At the conclusion of the study, we analyzed the results to determine the rate at which visual field test results became abnormal. This analysis was stratified for abnormal SWAP and FDP findings that occurred before the development of field loss on AAP. We also compared global indices and test times. We used SAS version 6.12 software (SAS Institute Inc, Cary, NC) for statistical analysis, including Mantel-Haenszel log-rank test, unpaired 2-tailed t test, and simple linear regression. In the log-rank testing, the development of visual field loss on AAP was considered a survival analysis failure. Mean defect (MD), pattern standard defect (PSD), and test time were used as linear variables. Test statistics and P values are presented.

RESULTS

Our sample included 26 men (42%) and 36 women (58%). At the beginning of the study, their average age was 58 years (SD, 12 years). Average follow-up time was 1137 days (minimum, 891 days; maximum, 1545 days). Nine subjects had abnormal SWAP findings and 10 had abnormal FDP findings on 2 consecutive testing times (Table 1). At the conclusion of the follow-up period of the study, field loss on AAP had developed in 5 subjects. All of these had preexisting abnormal SWAP and FDP results (Table 1). The results from 2 of these subjects are illustrated in Figure 1 and Figure 2. From the time of entering the study, the median time to development of an abnormal AAP for those with initial abnormal SWAP or FDP findings was 2 years and 3 months. When the rate of the development of abnormal AAP visual fields was analyzed, there was a significant difference for those with preexisting abnormal SWAP findings vs those without (Mantel-Haenszel log-rank test statistic, $\chi^2 = 40.83; P < .001$) (Figure 3). A similar result was found for those with preexisting field loss on FDP (Mantel-Haenszel log-rank test statistic, $\chi^2 = 32.76; P < .001$) (Figure 4). On analysis of global indices, the MD correlated significantly between all tests (Table 2). The PSD correlated well between field tests using the Humphrey Field Analyzer (ie, AAP and SWAP). However, it correlated poorly when comparing FDP with AAP or SWAP (Table 2). This was found to be due to 5 FDP field tests performed during the duration of the study, in which there were test points with exceedingly high sensitivity. None of these tests had field loss considered abnormal. If these tests were excluded from the analysis, the FDP PSD correlated significantly with AAP ($r^2 = 0.121; P < .001$) and SWAP ($r^2 = 0.114; P < .001$).

During the period of the study, our subjects with normal SWAP or FDP findings demonstrated a decrease in AAP MD of 0.06 dB/y and an increase in AAP PSD of
However, those who had visual field loss on SWAP had a decrease in AAP MD of 0.75 dB/y and an increase in AAP PSD of 0.49 dB/y, which was statistically significant compared with those with a normal SWAP visual field (\(t = 2.94\) \([P = .004]\) for MD; \(t = 4.26\) \([P < .001]\) for PSD). A similar finding was seen for those with visual field loss on FDP, who had a decrease in AAP MD of 1.01 dB/y and an increase in AAP PSD of 0.46 dB/y. This too was significantly different from those with a normal FDP finding (\(t = 4.06\) \([P < .001]\) for MD; \(t = 4.15\) \([P < .001]\) for PSD).

Furthermore, the mean FDP test time was 4 minutes 50 seconds, which was not significantly different from that of the AAP at 4 minutes 59 seconds (\(t = 1.92; P = .06\)), but was significantly shorter than that of the SWAP at 11 minutes 55 seconds (\(t = 55.69; P < .001\)).

**COMMENT**

The diagnosis of open-angle glaucoma based on visual field loss may be significantly delayed, owing to the amount of redundancy the visual field has for an achromatic stimulus. Achromatic automated perimetry uses a white stimulus on a white background. Short-wavelength automated perimetry targets the koniocellular pathway, whose small bistratified ganglion cells possess large dendritic fields. They are fewer in number than those of the parvocellular pathway, resulting in
Sparse retinal coverage. The combination of low spatial frequency and high temporal frequency that FDP uses stimulates the My cellular pathway, which responds in a nonlinear fashion to changes in contrast. This property of the My cellular pathway results in a greater response to a change in stripe contrast than may be seen with the parvocellular or koniocellular pathway and thus an earlier detection of glaucomatous damage.

Short-wavelength automated perimetry may be able to detect visual field loss 2 to 3 years earlier than AAP. However, the combination of the yellow background and blue target used can be affected by lens nuclear sclerosis, resulting in diffuse loss of visual field sensitivity, although this may be overcome by the use of the pattern deviation plot for the determination of visual field loss. Furthermore, we found maximum test times to be as long as 17 minutes 19 seconds per eye. This compares with the maximum test time for FDP of 6 minutes 31 seconds per eye.

Just as SWAP may predict future AAP visual field loss, FDP may be similarly predictive. However, the testing pattern for FDP presents targets in 17 zones (4 per quadrant) up to 20° from fixation with a central circular zone 10° wide. Because of this, FDP may lack the resolution for visual field loss that AAP and SWAP possess.

Figure 2. Pattern deviations from patient 098 for achromatic automated perimetry (AAP), short-wavelength automated perimetry (SWAP), and frequency-doubling perimetry (FDP) during the 4-year study period.
There was a significant correlation for MD between all tests and for PSD between AAP and SWAP. However, this was not the case for PSD when comparing FDP with AAP or SWAP. There were 5 cases that had test locations with significantly high sensitivities. This affected the FDP PSD, thus affecting the linear regression relationship with the AAP or the SWAP PSD. A poor relationship between FDP and AAP PSD has been noted in past work. It has been attributed to a different retinal distribution for different cell types. Other factors such as type of test, stimulus size, stimulus duration, or number of stimuli may be responsible. The correlation between the FDP and AAP or SWAP PSD may not be an appropriate outcome factor in comparing these perimetric tests.

Visual field loss needed to occur within the same field quadrant on 2 consecutive fields in order for the subject to be considered to have abnormalities. Fields with an abnormality that initially developed during year 3 were confirmed in year 4. There were no fields in which new abnormalities developed during year 4.

The main limitation of this study was the sample size. It was performed in an urban glaucoma practice with no external financial subsidy. Despite the small sample numbers, we believe the statistical significance of the study findings should allow conclusions to be drawn. The methodology, including the determination of a significant visual field scotoma, was based on previous publications on SWAP. Several patients in our study who exhibited abnormal SWAP and FDP findings showed a few points of decreased sensitivity on AAP at baseline (Figures 1 and 2). However, these did not meet the criteria for a significant scotoma, and thus the field was considered normal. Only 1 eye underwent testing, as testing of both eyes in a longitudinal study could artificially double the rate of conversions. As glaucoma is a bilateral disease, when one eye shows progression, there is a high likelihood that the fellow eye also shows progression. The decision to select the right eye preferentially unless contraindicated was made before the commencement of the study. The survival analysis performed in this study was a Mantel-Haenszel log-rank test, which describes the difference between the rates of failure (development of an abnormal AAP finding) over time, in terms of a test statistic and a P value. To perform a Cox proportional hazards regression and generate a hazard ratio and 95% confidence limits, both groups (those with normal and those with abnormal SWAP or FDP findings) need to have failures. Without this, the rate of failure cannot be compared. At the end of the third year of follow-up, there were still no failures in the normal SWAP or the normal FDP group.

Our study confirmed previous work by showing that future AAP visual field loss may be detected by SWAP at least 2 years earlier. Furthermore, we have shown that, like SWAP, FDP can detect the same visual field loss, which then became manifest on AAP. Consequently, FDP can predict future AAP visual field loss in patients with ocular hypertension. In our study, no abnormal AAP findings developed in patients with normal FDP or SWAP results. Global indices of FDP correlated with SWAP and AAP, and the test could be performed in a significantly shorter time than SWAP.

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**Table 2. Comparison of Global Indices Among AAP, SWAP, and FDP Throughout the Study**

<table>
<thead>
<tr>
<th>Tests Compared</th>
<th>MD</th>
<th>PSD</th>
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<tbody>
<tr>
<td>AAP and SWAP</td>
<td>0.084</td>
<td>0.122</td>
</tr>
<tr>
<td>AAP and FDP</td>
<td>0.113</td>
<td>0.021</td>
</tr>
<tr>
<td>SWAP and FDP</td>
<td>0.108</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Abbreviations: AAP, achromatic automated perimetry; FDP, frequency-doubling perimetry; MD, mean defect; PSD, pattern standard deviation; SWAP, short-wavelength automated perimetry.

*Global indices include MD and PSD.