Aspects of Frequency Doubling Perimetry in the Detection of Early Glaucoma

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ABSTRACT

Background: Frequency Doubling Perimetry (FDP) is a recently developed form of perimetry, which may be more sensitive for detecting visual field loss from glaucoma than conventional Achromatic Automated Perimetry (AAP). This thesis was undertaken to study aspects of FDP for the detection of early glaucoma.

Method: FDP was compared with other forms of perimetry at one point in time using one dataset (n=83) and longitudinally over a four-year period with another dataset (n=62). Several aspects were studied: (1) the ability of FDP to detect visual field loss earlier than AAP, (2) its ability to detect early functional abnormality in the presence of mild glaucomatous structural abnormality (3) visual field topography compared with other perimetry and (4) its ability to predict future field loss when only the nasal quadrants were considered.

Results: When subjects at risk of glaucoma with initial visual field loss on FDP were followed over a three-year period, a significant proportion developed field loss with AAP, whilst those without initial FDP loss did not. FDP detected cases of early glaucomatous optic disc damage, which had not been detected using AAP; however, there was still a proportion of those with abnormal optic discs which remained normal on FDP. FDP field topography was hill-shaped with the most sensitive point centrally; however, it was considerably flatter and more sensitive than AAP. Finally, if FDP field loss was only considered significant when it occurred within the nasal step location of the visual field, then this may improve the accuracy of glaucoma diagnosis.

Conclusion: This thesis has demonstrated that FDP is not only more sensitive than AAP in the detection of glaucomatous optic disc damage, but it is able to predict future field loss on AAP. FDP may therefore be useful in the early detection and management of glaucoma.

SUMMARY

Background:

Glaucoma is a potentially blinding condition, characterized by a progressive optic neuropathy with corresponding changes in the visual field. The diagnosis is made, not only from the clinical assessment of the optic nerve head appearance, but also on characteristic and typical patterns of visual field loss seen on achromatic automatic perimetry (AAP). The Humphrey Field Analyzer mark II (HFA II) has traditionally been considered as the 'gold standard' for visual field examination. However, increasing evidence suggests that visual field loss may not become apparent using this method of testing until up to 50% of retinal ganglion cells (RGCs) are lost, implying that the retina has a significant amount of redundancy for a non-selective, achromatic stimuli.

Theoretical and empirical evidence suggested that larger RGCs may be lost first in glaucoma and tests which selectively target them may be able to detect visual field loss earlier. Larger RGCs may be more likely to be damaged first in glaucoma, or may be under-represented in the retina and therefore may have less redundancy. One such type of RGC is the koniocellular line which responds maximally to blue light (Blue-on cells). These may be targeted by a form of testing called short wavelength automated perimetry (SWAP), which is available on the HFA II, and can detect visual field loss earlier than AAP. Another type of RGC which may be lost early in glaucoma is the magnocellular cell line (M cells), which respond maximally to a flickering stimulus. Flicker perimetry has been shown to be able to detect visual field loss earlier than AAP and although all of this research used perimeters that were specifically designed for each study, there is a commercial model, the Medmont Perimeter; however, very little work has been published using it and this has not included longitudinal studies.

More recently a new form of visual field testing, Frequency Doubling Perimetry (FDP), was developed as a screening test for glaucoma. It is a small, compact portable unit, which uses a flickering stimulus and was designed to target a non-linear (Y-like) subset of the magnocellular cell line (My pathway), which may therefore have less redundancy than the other previously mentioned cell lines and may be more sensitive for detecting field loss for glaucoma screening than AAP.

Aims of Thesis

This thesis was undertaken to investigate the properties of FDP, with respect to its utility in early glaucoma. In order to do this I recruited a group of subjects with ocular hypertension and normal visual fields (n=62) attending an urban glaucoma clinic, performed AAP, SWAP and FDP and then followed them over 4 years to determine if those with early FDP field loss subsequently developed AAP field loss. At the same time my colleague Dr Alok Sharma recruited a separate group of subjects who were either normal, were glaucoma suspects or had glaucoma (n=83) and performed 6 visual field tests including Flicker perimetry, AAP, SWAP and FDP, in order to compare the properties of all these tests among the same group of subjects. After this second sample was selected and his data collected, Dr Sharma passed on his data to me.

During the project, the following hypotheses were tested:

Hypothesis 1: In early glaucoma subjects, FDP can detect visual field loss which has not become manifest on AAP and may perform superiorly to SWAP.

Hypothesis 2: In early glaucoma subjects, the results of FDP will reflect more closely optic nerve head appearance compared with AAP.

Hypothesis 3: In normal and glaucoma subjects, FDP will produce results which do not depend on the My pathway.

Hypothesis 4: In normal subjects, the topography of the visual field produced by FDP will differ from that produced by SWAP or AAP.

Hypothesis 5: In early glaucoma subjects, the visual field loss within the nasal quadrants will be more indicative of pathology.

Papers:

Landers J, Goldberg I, Graham S. A Comparison of Short Wavelength Automated Perimetry with Frequency Doubling Perimetry for the Early Detection of Visual Field Loss in Ocular Hypertension. *Clin. Exp. Ophthalmol.* 2000; **28**: 248-52

Summary: Among patients at risk of developing glaucoma, but with normal AAP visual fields, compared with SWAP, FDP has a sensitivity of 90% and a specificity of 96% for the detection of early visual field loss. Therefore FDP produced comparable results to another test which had previously been shown to be able to detect field loss not seen on AAP.

Landers J, Goldberg I, Graham S. A Comparison of Optic Disc Examination with Tests of Early Visual Field Loss. *Clin. Exp. Ophthalmol*. 2002; **30**: 338-42

Summary: On comparing FDP with clinical optic disc assessment as the 'gold standard', the sensitivity, specificity, positive predictive value and negative predictive value were 25%, 89%, 43% and 79% respectively. FDP fields detected visual field loss in glaucoma suspects who appeared to have normal optic discs and as such produced a certain rate of false positives results. It detected cases of early glaucoma which had not been detected using AAP, however there was still a proportion of those with abnormal optic discs which remained normal on FDP, indicating that the retina still has some redundancy for the testing stimulus used in FDP.

Landers J, Sharma A, Goldberg I, Graham S. A Comparison of Perimetric Results with Medmont and Humphrey Perimeters. *Brit. J. Ophthalmol*. 2003; **87**: 690-4

Summary: Among a typical heterogenous group of patients who may present to an urban glaucoma clinic, comparing flicker perimetry with FDP yielded a kappa correlation statistic of 0.85 and an area under the receiver operator curve of 0.96. This indicated that FDP and flicker perimetry were comparable tests. The inference being that possibly FDP was not targeting a subset of magnocellular cells, but was a general stimulus for the magnocellular pathway.

Landers J, Goldberg I, Graham S. Detection of Early Visual Field Loss in Glaucoma Using Frequency Doubling Perimetry and Short Wavelength Automated Perimetry. *Arch. Ophthalmol*. 2003; **121**: 1705-10

Summary: When patients at risk of developing glaucoma, but with normal visual fields were followed longitudinally, 5 of the 10 subjects with initial FDP field loss had developed field loss on AAP 3 years later, however no patients with normal initial FDP fields went on to develop AAP field loss. Furthermore, only those with FDP field loss involving the nasal step position of the visual field, developed AAP field loss during the testing period.

Landers J, Sharma A, Goldberg I, Graham S. The Topography of the Frequency Doubling Perimetry Visual Field Compared with that of Short Wavelength and Achromatic Automated Perimetry Visual Fields. *Brit J Ophthalmol.* 2006; **90**: 70-4

Summary: FDP field topography is hill-shaped with the most sensitive point centrally, however it is flatter and more sensitive than AAP and SWAP fields. There was also no significant decrease in sensitivity with age, as there was seen for AAP and SWAP.

Landers J, Sharma A, Goldberg I, Graham S. A Comparison of Diagnostic Protocols for Interpretation of Frequency Doubling Perimetry Visual Fields in Glaucoma. *J Glaucoma.* 2006; **15**: 310-4

Summary: A conventional diagnostic protocol, which considered FDP field loss significant regardless of its position in the visual field, had a sensitivity of 92%, a specificity of 81%, a positive predicted value of 75% and negative predicted value of 94% compared with AAP. However, a diagnostic protocol which considered FDP field loss significant only if it occurred within the nasal step position of the visual field, showed a substantial decrease in false positive results with only a minimal increase in false negative results and yielded a sensitivity of 88%, a specificity of 88%, a positive predicted value of 82% and negative predicted value of 93%.

Conclusion:

The findings from this project have shown that FDP has comparable properties to SWAP, a testing method which has previously been shown to be able to detect field loss not seen on AAP. Those subjects with initial abnormal FDP fields, which on later analysis were found to have affected the nasal step location of the visual field, went on to develop AAP field loss over a 3 year period, whilst those with normal FDP fields did not. This demonstrated that FDP may have more than just a screening role in glaucoma and that it may be useful for earlier diagnosis of glaucoma than is possible with current testing modalities. This research is the first to show the early diagnosis properties of FDP, having been acknowledged as such and validated by later research from other authors. This provides evidence supporting Hypothesis 1.

FDP detected visual field loss in glaucoma suspects who appeared to have normal optic discs and as such produced a certain rate of false positives results. It detected cases of early glaucoma which had not been detected using AAP; however, there was still a proportion of those with abnormal optic discs which remained normal on FDP, indicating

that the retina still has some redundancy for the testing stimulus used in FDP. However, there is some evidence that Hypothesis 2 should not be rejected.

Whilst originally thought to be targeting a specific subset of magnocellular cells, FDP was found to have similar properties to flicker perimetry and therefore may target the magnocellular pathway as a whole. As such this would provide evidence in support of Hypothesis 3.

FDP topography is hill-shaped with the most sensitive point centrally; however, it is flatter and more sensitive than AAP and SWAP fields. Hypothesis 4 should therefore not be rejected.

Finally, if FDP field loss was only considered significant when it occurred within the nasal step location of the visual field, then this may improve the accuracy of glaucoma diagnosis. Whilst the results of paper 6 did not reach statistical significance, they provided a trend in favour of Hypothesis 5.

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PUBLICATIONS RELEVANT TO THIS THESIS

- Landers J, Goldberg I, Graham S. A Comparison of Short Wavelength Automated Perimetry with Frequency Doubling Perimetry for the Early Detection of Visual Field Loss in Ocular Hypertension. *Clin Exp Ophthalmol.* 2000; **28**: 248-52

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- Landers J, Sharma A, Goldberg I, Graham S. The Topography of the Frequency Doubling Perimetry Visual Field Compared with that of Short Wavelength and Achromatic Automated Perimetry Visual Fields. *Brit J Ophthalmol.* 2006; **90**: 70-4

- Landers J, Sharma A, Goldberg I, Graham S. A Comparison of Diagnostic Protocols for Interpretation of Frequency Doubling Perimetry Visual Fields in Glaucoma. *J Glaucoma.* 2006; **15**: 310-4

DECLARATION

This work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

I give consent to this copy of my thesis, when deposited in the University Library, being available for loan and photocopying.

John A Landers November 2006

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LIST OF SPECIAL NAMES OR ABBREVIATIONS

AAP	Achromatic Automated Perimetry
CPSD	Corrected Pattern Standard Defect
GHT	Glaucoma Hemifield Test
GON	Glaucomatous Optic Neuropathy
FDI	Frequency Doubling Illusion
FDP	Frequency Doubling Perimetry
HFA	Humphrey Field Analyzer
IOP	Intraocular Pressure
MD	Mean Defect
NTG	Normal Tension Glaucoma
OHT	Ocular Hypertension
POAG	Primary Open Angle Glaucoma
PSD	Pattern Standard Defect
RGC	Retinal Ganglion Cell
SITA	Swedish Interactive Thresholding Algorithm
SWAP	Short Wavelength Automated Perimetry