Fluctuation of intraocular pressure and glaucoma progression in the early manifest glaucoma trial.

Bengtsson, B; Leske, M C; Hyman, L; Heijl, Anders

Published in:
Ophthalmology

DOI:
10.1016/j.ophtha.2006.07.060

2007

Title: Fluctuation of Intraocular Pressure and glaucoma progression in the Early Manifest Glaucoma Trial

Authors:
Boel Bengtsson, PhD[1]
M Cristina Leske, MD, MPH[2]
Leslie Hyman, PhD[2]
Anders Heijl, MD, PhD[1]
The EMGT Group

This material has not previously been presented at any meeting.

Financial Support: The EMGT was supported by grants from the National Eye Institute (Bethesda, MD, USA) U10EY10260 and U10EY10261, and from the Swedish Research Council (Stockholm, Sweden).

None of the authors have any conflict of interest.

Running head: Intraocular pressure fluctuation and glaucoma progression in EMGT

[1] Department of Clinical Sciences, Ophthalmology, Lund University, Malmö University Hospital, SE-20502 Malmö, Sweden
[2] Department of Preventive Medicine, Stony Brook University School of Medicine, Stony Brook, New York, USA

Abstract

Purpose: To investigate whether increased fluctuation of intraocular pressure (IOP) is an independent factor for glaucoma progression.

Design: Cohort of patients followed in a randomized clinical trial.

Participants: Two hundred and fifty-five glaucoma participants of the Early Manifest Glaucoma Trial (EMGT; 129 treated and 126 control patients.)

Methods: Study visits, conducted every three months, included ophthalmologic examinations, IOP measurements and standard automated perimetry, with fundus photography every six months. IOP values were included only until the time of progression, in those eyes that showed such progression. Individual mean follow-up IOP and IOP fluctuation, calculated as the standard deviation of IOP at applicable visits, were the variables of main interest. Cox regression with time-dependent variables was used to evaluate the association between IOP fluctuation and time to progression, both with and without IOP mean in the models. These analyses also controlled for other significant variables.

Main Outcome Measures: Glaucoma progression, as defined by a predetermined visual field criterion, and/or worsening of the disk, assessed by an independent disk reading center.

Results: Median follow-up time was 8 years (ranging from 0.1 to 11.1 years). Sixty-eight percent of the patients progressed. When considering mean follow-up IOP and IOP fluctuation in the same time-dependent model, mean IOP was a significant risk factor for progression. The hazard ratio (HR) was 1.11 (95% confidence interval: 1.06, 1.17; $p<0.0001$). IOP fluctuation was not related to progression, with a HR=1.00 (0.81, 1.24; $p=0.999$).

Conclusion: These results confirm our earlier finding that elevated IOP is a strong factor for glaucoma progression, with the HR increasing by 11% for every mmHg of higher IOP. IOP fluctuation was not an independent factor in our analyses, a finding that conflicts with some earlier reports. One explanation for the discrepancy is that our analyses did not include post-progression IOP values, which would be biased towards larger fluctuations because of more intensive treatment. In contrast, in this EMGT report, no changes in patient management occurred during the period analyzed.

Elevated intraocular pressure (IOP) is an indisputable risk factor for glaucoma,[1,2,3] and glaucoma progression.[4,] As is well-known, IOP fluctuation is proportional to IOP levels.[5,6] Diurnal IOP fluctuation has been reported to be a risk factor, independent of IOP level, for development of glaucoma[7] or glaucoma progression,[8,9] but these studies compared IOP measurements at different times, e.g., baseline IOP fluctuation vs. follow-up IOP levels, or before vs. after a glaucoma intervention. Other reports studying various IOP parameters, measured during the same period and the same conditions, have been unable to show that large IOP fluctuation is an independent risk for glaucoma,[10] or glaucoma progression.[11] On the other hand, results from the Advanced Glaucoma Intervention Study (AGIS)[12] indicated that a larger long-term IOP fluctuation at follow-up,[13] defined as inter-visit fluctuations of IOP, was associated with visual field progression. Mean follow-up IOP was not a significant risk factor when included in the same multivariate analysis. These analyses, however, also included IOP values after progression, which could have affected the results.

The role of IOP fluctuation as an independent predictive factor for glaucoma or glaucoma progression thus remains in doubt. Results from earlier studies are conflicting, and research designs were perhaps not always optimal. More studies investigating the independent effect of IOP fluctuation are needed to resolve this question.

The aim of our article is to report on the role of IOP fluctuation as an independent factor for glaucoma progression among patients included in the Early Manifest Glaucoma Trial (EMGT).[14] The EMGT is a randomized controlled clinical trial designed to compare the effect of IOP reduction with treatment, vs. no treatment, on glaucoma progression. The study population consists of glaucoma patients, mainly (85%) identified by a large population screening,[15] who have been followed for up to 11 years.

METHODS

EMGT overview

The EMGT design and methods have been described in detail elsewhere[15] and are here summarized. Patients with newly detected, previously untreated glaucoma, including primary open-angle glaucoma, normal tension glaucoma, and exfoliation glaucoma were recruited. Eligible patients were between 50 and 80 years of age, with reproducible glaucomatous visual field loss in at least one eye, but no advanced visual field loss, i.e. Mean Deviation (MD) values better than –16 dB, visual acuity (VA) equal to or better than 0.5 (corresponding to 20/40), mean IOP less than 31mm Hg or any IOP less than 35 mm Hg. The study was conducted according to the tenets of the Declaration of Helsinki. All patients gave informed consent, and the Ethics Committee of Lund University, Sweden, and the Committee on Research involving Human Subjects at the State University of New York at Stony Brook approved the study. Eligible patients were randomized evenly to treatment and no initial treatment. All eyes randomized to treatment received a full 360° trabeculoplasty plus betaxolol eye drops at a dose of 5mg/ml twice daily. All patients stayed in their allocation arm unless significant progression occurred. If IOP in treated eyes exceeded 25 mm Hg at 2 consecutive follow-up visits or 35 mm Hg in control eyes, latanoprost eye drops at a dose of 50 μg/ml were added once daily.

Study Visits

After inclusion, patients were followed every three months for up to 11 years. The study visits included IOP measurements with the Goldmann applanation tonometer, used by technicians masked to study group and to earlier IOP values. Perimetry was performed with the

Humphrey Field Analyzer using the Full Threshold 30-2 program (Carl Zeiss Meditec Inc. Dublin, CA, USA). Patients also had best corrected visual acuity measurements and a comprehensive eye examination, including ophthalmoscopy, with fundus photography every 6 months.

Glaucoma Progression and Unit of Analysis

This report is based on study data up to March 31, 2004**.** Glaucoma progression was defined as worsening of visual fields according to a predetermined criterion, i.e. at least three identical points showing significant deterioration in glaucoma change probability maps, based on change in pattern deviation values, at three consecutive visits.[15] This criterion has been shown to be sensitive to small visual field changes and able to measure deterioration in 12-15 steps from normal to almost blind,[16] while avoiding cataract-induced effects. During the first 9 years of the study, glaucoma progression could also be identified by worsening of the disk, as assessed independently by two certified masked readers at the Optic Disc Reading Center.

EMGT progression is patient-based and occurs when at least one eligible eye meets progression criteria. For patients with one eye eligible, only that eye was considered; for patients with two eligible eyes (n=61; 24%), analyses were based on the first-progressing eye. A similar approach was used in the analyses for this report, which were also patient-based, following methods described and evaluated in a previous EMGT publication.[4] When a patient had two eligible eyes, data from the first progressing eye were used; if neither eye progressed (or both progressed at the same time), data from the worse of the two baseline measurements (e.g., IOP, MD) were included.

Intraocular Pressure

Analyses included all IOP measurements from 3 months (the first study visit after assignment to treatment or no initial treatment) to time of progression or last follow-up visit. All the analyses for this paper are based on the 3-month IOP, rather than the baseline IOP, because of the IOP changes in the treated group after randomization. The main variables of interest were the mean of the IOP at all applicable visits and the IOP fluctuation, defined as the standard deviation of IOP at these visits.

Statistical Analyses

We initially examined the IOP data in univariate analyses. Relationships between two continuous variables, e.g., IOP fluctuation and time to progression, were first evaluated through correlation coefficients. The change in IOP for a patient was measured by the slope, which was obtained from regressing IOP measurements of that patient on time. The IOP slopes represent annual rates of IOP change. Summary statistics were used to describe the distribution of IOP slopes.

For analyses with multiple factors, we considered the mean IOP and IOP fluctuation as time-dependent risk factors for progression. Time-dependent IOP mean (or IOP fluctuation) at time t was calculated as the mean (or standard deviation) of IOP measurements from the 3-month visit to time t. Therefore, the IOP mean (or IOP fluctuation) for a patient at each visit represented that patient's IOP mean (or IOP fluctuation) up to that visit.

Cox regression with time-dependent variables was used to evaluate the association between IOP fluctuation and time to progression, both with and without IOP mean in the models. These analyses also controlled for factors previously found relevant for progression.[4]

The time dependent Cox model is:

$$\log h(t) = \alpha(t) + \beta_1 x_1(t) + \beta_2 x_2(t) + \beta_3 x_3 + \beta_4 x_4 + \ldots,$$

where $h(t)$ is hazard rate at time t; time dependent variable $x_1(t)$ is the standard deviation (SD) of IOP measurements from the 3-month visit to time *t*; the time-dependent variable $x_2(t)$ is the mean of IOP measurements from the 3-month visit to time *t*; and x_3, x_4 etc. are values of other factors, e.g., age group at baseline, exfoliation status. This model indicates that for each patient, the hazard for progression at time *t* depends on the value of the IOP mean and the IOP fluctuation at prior visits, and the values of additional variables previously found to be related to progression, e.g., age, exfoliation status.[4] The Partial Maximum Likelihood method was used to estimate the β_i's, which represent the change in the log hazard ratio resulting from unit change in risk factor $x_i(t)$ or x_i. The Wald χ^2 test was performed to test the association of IOP fluctuation and other factors with progression. The analyses were performed using SAS 9.1 PROC PHREG. [17]

RESULTS

At data closure on March 31, 2004, the median follow-up time was 8 years (ranging from 0.1 to 11.1 years). Data from all 255 patients originally enrolled in EMGT were included in the current analyses. Sixty-eight percent of the patients had progressed, with 59% of treated and 76% of control patients progressing. All patients in the control group remained untreated until reaching the outcome of glaucoma progression. The mean follow-up IOP was 19.5 mmHg for those who progressed and 16.5 mmHg for those who did not. The corresponding values for mean follow-up IOP fluctuation (SD) were 2.02 mmHg vs. 1.78 mmHg, respectively.

IOP was very stable over time. Most patients had a flat IOP slope; 59% (125/254) were within ±0.5 mmHg/year, and 92% (234/254) were within ±3 mmHg/year (results are based on 254 patients because one patient had insufficient follow-up IOP values.)

Table 1. Univariate analyses.
Correlations of mean IOP, IOP fluctuation and time to progression

	R	*P-value*	*No. of patients*
IOP mean vs. IOP fluctuation	0.44	<0.0001	254
IOP mean vs. time to progression	-0.19	0.01	172
IOP fluctuation vs. time to progression	0.12	0.12	172

IOP = intraocular pressure, r = Pearson correlation coefficient

Table 1 presents Pearson correlation coefficients between the mean IOP and IOP fluctuation from 3 months to progression (in those who progressed) or the last visit (in those who did not progress), based on 254 patients. Separate analyses for those who progressed and those who did not progress had the same correlation coefficient, r = 0.42, between the mean IOP and IOP fluctuation. The table also shows the correlation of these variables with time (months) to progression for the 172 patients who progressed. There was a monotonic positive correlation between mean IOP and IOP fluctuation ($p<0.0001$), i.e. patients with the highest level of mean IOP usually had the highest level of IOP fluctuation, while patients with low mean IOP had low IOP fluctuation. Results also show a negative correlation between mean IOP and time to progression ($p<0.01$), indicating that patients with high mean IOP had shorter times to

progression. In contrast, there was a positive and non-significant correlation between IOP fluctuation and time to progression (p=0.12), without a clear relationship between IOP fluctuation and progression in the analyses.

Table 2. Cox regression with time-dependent covariates.
Analyses evaluating association of mean IOP and IOP fluctuation with progression

Variable	*Hazard ratio (95% CI)*	*P-value**
Mean IOP (mmHg)†	1.11 (1.06 – 1.17)	<0.0001
IOP fluctuation (mmHg)†	1.00 (0.81 – 1.24)	0.999
Age, ≥68 years††	1.37 (1.00 – 1.88)	0.047
IOP ≥21 mmHg††	1.06 (0.73 – 1.52)	0.771
Exfoliation (yes) ††	1.89 (1.12 – 3.19)	0.016
Both eyes eligible (yes) ††	1.77 (1.25 – 2.50)	0.001
MD ≤ -4 dB††	1.47 (1.05 – 2.05)	0.025

IOP=intraocular pressure, CI=confidence interval, dB=decibel
* χ^2 test
†Follow-up data
†† Baseline data

Table 2 presents analyses based on time-dependent variables. When jointly considering IOP mean and IOP fluctuation in the same model, results indicate that IOP mean was a significant risk factor for progression, with an 11% increase in the hazard ratio for every mmHg higher. The IOP fluctuation, on the other hand, was not significantly related to progression; the hazard ratio was 1.00 per mmHg, with 95% confidence limits ranging from 0.8 to 1.2. When parallel analyses were performed for the treatment and control groups separately, similar results were found, as shown in Table 3A+B. Thus, IOP fluctuation had little influence on the hazard ratio in the presence of IOP mean. In contrast, the effects of mean IOP on progression were significant and consistent in both study groups (HR ~1.11 in both groups, $p<0.05$), regardless of the presence of IOP fluctuation.

Table 3A. Cox regression with time-dependent covariates.
Analyses evaluating association of mean IOP and IOP fluctuation with progression
Control Group

Variable	*Hazard ratio (95% CI)*	*P-value**
Mean IOP (mmHg)†	1.10 (1.01 – 1.19)	0.0245
IOP fluctuation (mmHg)†	0.94 (0.73 – 1.21)	0.6378
Age, ≥68 years††	1.62 (1.05 – 2.50)	0.0294
IOP ≥21 mmHg††	1.18 (0.63 – 2.20)	0.6002
Exfoliation (yes) ††	1.90 (0.94 – 3.82)	0.0727
Both eyes eligible (yes) ††	1.34 (0.79 – 2.28)	0.2781
MD ≤ -4 dB††	1.35 (0.84 – 2.17)	0.2194

Table 3B. Cox regression with time-dependent covariates.
Analyses evaluating association of mean IOP and IOP fluctuation with progression
Treated Group

Variable	*Hazard ratio (95% CI)*	*P-value**
Mean IOP (mmHg)†	1.12 (1.01 – 1.24)	0.0406
IOP fluctuation (mmHg)†	1.16 (0.75 – 1.80)	0.5151
Age, ≥68 years††	1.16(0.73 – 1.86)	0.5305
IOP ≥21 mmHg††	0.95 (0.53 – 1.71)	0.8567
Exfoliation (yes) ††	2.05 (0.91 – 4.61)	0.0817
Both eyes eligible (yes) ††	2.25 (1.37 – 3.70)	0.0014
MD ≤ -4 dB††	1.54 (0.92 – 2.58)	0.1030

IOP=intraocular pressure, CI=confidence interval, dB=decibel
* χ^2 test
†Follow-up data
†† Baseline data

DISCUSSION

Our results continue to support our earlier conclusion regarding the effect of the magnitude of IOP on glaucoma progression,[4,14] and we were unable to demonstrate any effect of increased IOP fluctuation on glaucoma progression. In fact, our results yielded no significant relationship between higher IOP fluctuation and glaucoma progression.

Just as in the AGIS report,[13] we used the standard deviation of follow-up IOP measurements as a surrogate for IOP fluctuation, as no diurnal tension curves were obtained. Just as in the AGIS report, we used the same database for calculating mean IOP level and IOP fluctuation, unlike some previous studies where IOP fluctuation was measured at baseline and mean IOP level at follow-up visits, or before or after a possible intervention.[8,9] Thus both AGIS and EMGT studied the concurrent independent effects of IOP fluctuation and mean IOP on progression, but revealed opposite results. AGIS indicated that IOP fluctuation was an independent and stronger factor for glaucoma progression than mean IOP level, which was in contrast to the conclusion previously reported by the AGIS investigators.[5] In EMGT, however, mean IOP level remained as the strongest risk factor for glaucoma progression, even when including IOP fluctuation as a risk factor.

At first glance, this contradictory result appears difficult to interpret. However, the different types of patient selection, intervention and approach to analyses might provide, at least a partial explanation of some of the difference. In AGIS, only patients with uncontrolled maximum acceptable therapy were included. Patients with IOP lower than 18 mmHg were not eligible, 95% of all included had IOP higher than 20 mmHg, and 74% had 23 mmHg or higher.[12] The main evaluation of IOP fluctuation was based only on 68% of these AGIS participants (64% of AGIS eyes), as patients had to meet specific criteria related to visual field scores, reliability and length of follow-up. The results based on this subset may not have been consistent in each AGIS intervention arm, which was a significant or near-significant variable in some models. The EMGT results presented here are based on all study patients, with comparable results in each study group.

In EMGT, only untreated patients with newly detected glaucoma were eligible, who were mostly recruited via a population-based screening among specific age groups. There was no

lower IOP limit for inclusion, but patients with any IOP greater than 35 mmHg or a mean IOP greater than 30 mmHg were excluded. At baseline, untreated IOP was lower than 20 mmHg in 45% of the patients.[15] Therefore, most EMGT patients were newly identified from the general population, while those included in AGIS were highly selected, i.e. patients with more advanced glaucoma and uncontrolled IOP at maximum therapy. Also, while most AGIS patients had high IOP at baseline and all were treated, EMGT had lower IOP at baseline and included a treatment and a control arm.

At follow-up, patients included in the AGIS analysis had lower mean IOP, and higher IOP fluctuations, than EMGT patients. This difference is likely due to the more aggressive treatment applied in AGIS. The mean follow-up IOP in AGIS was 15.4mmHg among the patients who progressed and 14.5mmHg among those who did not; the mean IOP fluctuation was 4.0 and 3.4 mmHg respectively. In EMGT, mean follow-up IOP was 19.5mmHg and 16.5mmHg among the progressing and non-progressing patients, respectively, and IOP was very stable over time. The mean IOP fluctuation among those progressing was 2.0 mmHg, and 1.8 mmHg among the not progressing patients. Only 10.0% had inter-visit fluctuations larger than 3 mmHg, with a maximum of 5.0 mmHg. This IOP stability could limit evaluations of the independent role of IOP fluctuation on glaucoma progression, as it does not provide a wide range of individual fluctuations.

An important strength of EMGT is that treatment remained unchanged during the period analyzed, i.e., as long as progression did not occur. Therefore, progression or suspicion of progression did not lead to biases caused, e.g., by more intense IOP-lowering treatment in progressing eyes. Our time-dependent analyses considered factors only up to the time of progression. As such, they did not include post-progression IOP values, which would be affected by treatment and thus unavoidably result in higher IOP fluctuation. In AGIS, eyes were randomly assigned to one of two surgical intervention sequences. If the first intervention was a failure, a second intervention was offered, and a third when the second failed. Failure was defined by amount of visual field loss, by deterioration of disk rim, and also by magnitude and duration of IOP elevation. Although the number of surgical glaucoma interventions was included in the multivariate analysis to attempt correcting this bias, one cannot eliminate the possibility that treatment-induced IOP changes affected the results by increasing IOP fluctuation. It seems likely that progressing patients were more likely to receive newer, more potent topical medication, and such changes of therapy would not be corrected by the statistical analyses. Therefore, the inclusion of post-progression IOP values in the analyses could result in a spurious association between IOP fluctuation and progression. To evaluate this possibility, we conducted Cox regression analyses that included post-progression IOP values, rather than IOP up to the time to progression. The inclusion of post-progression IOP led to an increase in IOP fluctuation values. In contrast to the time-dependent results in Table 2, IOP fluctuation was significantly related to progression in these new analyses (HR=1.66 (1.44-1.93), p=<0.0001), while IOP mean was not (HR= 0.97 (0.92-1.02), p=0.2614). These results suggest that the results of the AGIS analysis may have been affected by the inclusion of post-progression IOPs, which would cause higher IOP fluctuation because of increased treatment.

We also considered the possible effects of other differences between the studies, e.g., the use of different progression criteria. AGIS applied pointwise linear regression analyses of threshold sensitivities, which are more sensitive to increasing media opacities than the EMGT progression criterion.[18] Filtering surgery often leads to progressive cataract, which in turn, leads to a slow and monotonic worsening of threshold values. Therefore, it is reasonable to

assume that the authors' visual field analysis resulted in more false positive progression in filtered than in non-filtered eyes, thus leading to an apparent link between IOP change and progression. Also, since the patients included in EMGT were newly diagnosed and with mostly mild to moderate glaucomatous visual field loss, our findings may not be applicable to patients with advanced glaucoma, as in AGIS. By using Cox time-dependent analyses, we took time to progression into account. Time to progression was not considered in the AGIS analysis, which possibly also might explain some of the difference.

In summary, we were unable to confirm earlier reports stating that IOP fluctuation is an independent risk for glaucoma progression. Instead, the current findings confirm our earlier results, i.e., that elevated IOP level is a strong risk factor for glaucoma progression. Our conclusion is based on data from previously undiagnosed and untreated glaucoma patients, found by a population screening. Therefore, we believe that our conclusion would be more applicable to a general glaucoma population, and not to highly selected sub groups.

References

1. Sommer A. Risk factors observed in the Baltimore Eye Survey. Curr Opin Ophthalmol. 1996; 7:93-8.
2. Leske MC, Wu SY, Nemesure B, Hennis A. Incident open-angle glaucoma and blood pressure. Arch Ophthalmol 2002;120:954-9.
3. Gordon MO, Beiser JA, Brandt JD et al. The ocular hypertension treatment study: baseline factors that predict the onset of primary open-angle glaucoma. Arch Ophthalmol 2002; 120:714-20.
4. Leske MC, Heijl A, Hussein M et al Factors for progression and the effects of treatment: the early manifest glaucoma trial. Arch Ophthalmol 2003; 121:48-56.
5. Langely D, Swanljung H. Ocular tension in glaucoma simplex. Br J Ophthalmol 1951; 35:445-58.
6. Saccá SC, Rolando M, Marletta A, Cerqueti P, Ciurlo G. Fluctuations of intraocular pressure during day in open-angle glaucoma, normal-tension glaucoma and normal subjects. Ophthalmologica 1998; 212:115-9.
7. Gonzalez I, Pablo IE, Pueyo M, Ferrer B, Melcon E, Abecia E, Honrubia FM. Assessment of diurnal tension curve in early glaucoma damage. Int Ophthalmol 1997; 20: 113-15.
8. Bergeå B, Bodin L, Svedbergh B. Impact of intraocular pressure regulation on visual fields in open-angle glaucoma. Ophthalmology 1999; 106:997-1005
9. Asrani S, Zeimer R, Wilensky J, Gieser D, Vitale S, Lindenmuth K. Large diurnal fluctuations in intraocular pressure are an independent risk factor in patients with glaucoma. J Glaucoma 2000; 9: 134-42.
10. Bengtsson B, Heijl A. Diurnal IOP fluctuation: not an independent risk factor for glaucomatous visual filed loss in high-risk ocular hypertension. Graefes Arch Clin Exp Ophthalmol 2005; 243: 513-8.
11. Daugeline L, Yamamoto T, Kitazawa Y. Risk factors for visual field damage progression in normal-tension glaucoma eyes. Graefes Arch Clin Exp Ophthalmol 1999; 237:105-8.
12. The AGIS Investigators. The Advanced Glaucoma Intervention Study (AGIS): 1. Study design and methods and baseline characteristics of study patients. Controlled Clinical Trials 1994; 15:299-325.
13. 2004 Nouri-Mahdavi K, Hoffman D, Coleman AL, Liu G, Li G, Gaasterland D, Caprioli J. Advanced Glaucoma Intervention Study. Predictive factors for glaucomatous visual field progression in the advanced glaucoma intervention study. Ophthalmology 2004; 111; 1627-35.
14. Heijl A, Leske MC, Bengtsson B et al. Reduction of intraocular pressure and glaucoma progression. Results from the early manifest glaucoma trial. Arch Ophthalmol 2002; 120:1268-79.
15. Leske MC, Heijl A, Hyman L, Bengtsson B. Early manifest glaucoma trial: design and baseline data. Ophthalmology 2000; 107:2144-53.
16. Heijl A, Leske MC, Bengtsson B et al. Measuring visual field progression in the Early manifest glaucoma trial. Acta Ophthalmol Scand 2003; 81:286-93.
17. SAS Manual: SAS/STAT 9.1.
18. Bengtsson B, Lindgren A, Heijl A, Lindgren G, Åsman P, Patella M. Perimetric probability maps to separate change caused by glaucoma from that caused by cataract. Acta Ophthalmol Scand 1997; 75: 184-8.