Visual Field Progression in Glaucoma: Total Versus Pattern Deviation Analyses

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PURPOSE. To compare visual field progression with total and pattern deviation analyses in a prospective longitudinal study of patients with glaucoma and healthy control subjects.

METHODS. A group of 101 patients with glaucoma (168 eyes) with early to moderately advanced visual field loss at baseline (average mean deviation [MD], −3.9 dB) and no clinical evidence of media opacity were selected from a prospective longitudinal study on visual field progression in glaucoma. Patients were examined with static automated perimetry at 6-month intervals for a median follow-up of 9 years. At each test location, change was established with event and trend analyses of total and pattern deviation. The event analyses compared each follow-up test to a baseline obtained from averaging the first two tests, and visual field progression was defined as deterioration beyond the 5th percentile of test-retest variability at three test locations, observed on three consecutive tests. The trend analyses were based on point-wise linear regression, and visual field progression was defined as statistically significant deterioration (P < 5%) worse than −1 dB/year at three locations, confirmed by independently omitting the last and the penultimate observation. The incidence and the time-to-progression were compared between total and pattern deviation analyses. To estimate the specificity of the progression analyses, identical criteria were applied to visual fields obtained in 102 healthy control subjects, and the rate of visual field improvement was established in the patients with glaucoma and the healthy control subjects.

RESULTS. With both event and trend methods, pattern deviation analyses classified approximately 15% fewer eyes as having progressed than did the total deviation analyses. In eyes classified as progressing by both the total and pattern deviation methods, total deviation analyses tended to detect progression earlier than the pattern deviation analyses. A comparison of the changes observed in MD and the visual fields' general height (estimated by the 85th percentile of the total deviation values) confirmed that change in the glaucomatous eyes almost always comprised a diffuse component. Pattern deviation analyses of progression may therefore underestimate the true amount of glaucomatous visual field progression.

CONCLUSIONS. Pattern deviation analyses of visual field progression may underestimate visual field progression in glaucoma, particularly when there is no clinical evidence of increasing media opacity. Clinicians should have access to both total and pattern deviation analyses to make informed decisions on visual field progression in glaucoma. (Invest Ophthalmol Vis Sci. 2005;46:4600-4606) DOI:10.1167/iovs.05-0827

Determining visual field progression remains one of the most important but challenging aspects of glaucoma management. In addition to influencing the clinical care of patients, visual field progression is used as an end-point in many clinical trials in glaucoma and ocular hypertension.1-8 Visual fields vary from one examination to the next, even if no real change has taken place. This variability can both mask and mimic glaucomatous change, and several statistical methods have been devised to distinguish it from true progression.

One method of identifying visual field change is to derive statistical limits of test-retest variability in a group of patients with glaucoma tested frequently in close succession (e.g., over a few weeks) so that any differences between the test results can more likely be attributed to variability rather than to true change.9 10 These limits are then applied to visual fields of patients who are observed over time. If, at any given test location, the difference between the current test and a previously established baseline is beyond the lower limit of test-retest variability, the location has likely worsened. This event analysis, incorporated into software (the older Statpac program of the Humphrey Field Analyzer [HFA]; Carl Zeiss Meditec, Dublin, CA) as glaucoma change probability (GCP) analysis, is based on total deviation (i.e., the difference between the observed threshold and the age-corrected normal value).

Because glaucoma is an age-related disease, glaucomatous visual field changes must be distinguished from those caused by other age-related diseases, principally cataract. The glaucoma progression analysis (GPA) was devised for this purpose. It is based on pattern deviation, defined as the deviation from age-corrected values adjusted for the general height (GH) of the visual field. The GH is estimated from the relative depression of the 15th percentile of the total deviation values. By adjusting for any diffuse changes in visual field sensitivity, pattern deviation analyses seek to separate glaucomatous changes from those due to cataract, on the assumption that cataract causes a diffuse reduction of visual field sensitivity, whereas glaucoma leads to focal visual field changes.10 The hypothesis that glaucomatous visual field loss is exclusively focal, however, has often been challenged. Several studies have shown that focal visual field loss in glaucoma is usually associated with a diffuse component,11-12 whereas others have demonstrated that a minority of patients with glaucoma may present with exclusively diffuse visual field losses.13

Trend analyses of visual field change (available in the Progressor14 and the PeriData15 software packages), are based on a statistical approach different from that of the event analyses. Using regression analysis, they establish the statistical significance of change over the entire series of examinations. Unlike event analyses of visual field change, trend analyses relate the magnitude of change to the variability observed within the
individual data series and therefore do not rely on population-derived variability limits that can be inappropriate in individual patients.

The objective of this study was to compare total and pattern deviation change analyses of visual field progression in patients with glaucoma with a long prospective follow-up and no clinical evidence of increasing media opacity. To estimate the specificity of the progression criteria, we applied the same analyses to a group of healthy control eyes followed up identically, as well as estimating the rate of visual field improvement in the patients with glaucoma.

**METHODS**

**Study Design and Material**

Analyses were performed on visual field data collected for a prospective longitudinal study of patients with glaucoma and healthy control subjects. Patients with glaucoma were recruited consecutively from the clinics at the QEII Health Sciences Centre in Halifax, Nova Scotia. Patients were included if they had a clinical diagnosis of open-angle glaucoma based on optic disc and/or visual field changes, a visual field examination at baseline, and a clinical diagnosis of open-angle glaucoma less than 2 months after surgery were included in the analysis. Also, if patients had undergone cataract surgery during the course of the study, only those visual fields obtained later than 2 months after surgery were included in the analysis. Also, if during two or more examinations of the study a participant’s VA was reduced below 0.4 logMAR (20/50) or was reduced by >0.2 logMAR below baseline, they were excluded from the analysis. To reduce the influence of learning effects, we excluded the first visual field examination.

Patients and control subjects were examined in 6-month intervals with standard automated perimetry (Humphrey Field Analyzer 30-2 test, full-threshold strategy). For the present analyses, only the 52 test locations of the 24-2 test were used (excluding the two blind-spot locations). We intended to compare the differences between total and pattern deviation analyses in eyes without clinical evidence of increasing media opacity. Therefore, if participants had undergone cataract surgery during the course of the study, only those visual fields obtained later than 2 months after surgery were included in the analysis. Also, if during two or more examinations of the study a participant’s VA was reduced below 0.4 logMAR (20/50) or was reduced by >0.2 logMAR below baseline, they were excluded from the analysis. To reduce the influence of learning effects, we excluded the first visual field examination of each subject from the analyses.

In the patients with glaucoma, both eyes were examined, whereas in healthy control subjects, only the randomly selected study eye was examined. We used both eyes of the patients with glaucoma in the descriptive analyses if they met the inclusion criteria. For statistical significance testing, however, data were analyzed from only one randomly selected eye of each patient.

**Analyses of Visual Field Progression**

**Event Analyses of Total and Pattern Deviation.** The limits of test-retest variability of total and pattern deviation were determined in 64 patients with glaucoma who had been examined five times within 4 weeks for an earlier study.8 Treating the five tests as interchangeable, we examined all 30 permutations of two baseline tests and one follow-up test. For each level of baseline deviation (in steps of 1 dB), we derived the empiric 5th and 95th percentiles of the distribution of follow-up data. The 5% and 95% change probability limits were derived by smoothing the empiric percentiles using fourth-order polynomials.

Event analyses of visual field progression and improvement were performed by a point-by-point comparison between the baseline deviation, calculated as the mean value at the first two examinations, with all subsequent examinations. Test locations at which the deviation was more negative than the lower test-retest limit of the baseline value were classified as having deteriorated and those with deviations more positive than the upper limit were classified as having improved. The criteria for visual field progression and improvement were defined in terms of locations with changes from baseline on three consecutive follow-up examinations (Fig. 1), so that progression or improvement could be ascertained only after five or more examinations (two baseline and three follow-up tests).

**Trend Analyses of Total and Pattern Deviation.** Trend analyses were performed by point-wise linear regression of the deviation values with follow-up time, using the two-omitting method to increase specificity.16 This method establishes two regression lines: one while omitting the last test, and the other while omitting the penultimate test. Locations were flagged as progressing if the slopes of the deviation value were more negative than −1 dB/y and different from zero at a significance level of $P < 0.05$ on both occasions (Fig. 2). Improvements were flagged using the same approach, with slopes greater than +1 dB/y. Similar to the event analyses described for total and pattern deviation, trend analyses were performed when at least five visual field examinations were available for analysis.

![Figure 1](image1.png) **Illustration of event analysis at one test location. Solid horizontal line:** the mean of the two baseline test results. If the deviation at a subsequent follow-up examination is more negative than the lower 5% limit of test-retest variability (dotted line), deterioration is flagged with a filled triangle. In this example, the progression criterion has been met after the last observation (3 years).

![Figure 2](image2.png) **Illustration of trend analysis with point-wise linear regression using the two-omitting method. A test location was classified as having progressed if the slope of the linear regression line was more negative than −1 dB/y and significantly different from zero at $P < 0.05$. These criteria must be met when the last examination is included (a) and also when the penultimate examination is excluded (b). Solid lines: regression obtained by omitting the last or penultimate observation (open circles). Dotted line: regression including all observations. In this example, the location was not classified as having progressed because the slope was not significant when the last observation was excluded (a).**
Comparison between Analyses

Progression rates were established by Kaplan-Meier analysis to account for censoring that occurs when subjects are lost to follow-up.17,18 For a comparison between the total and pattern deviation analyses, we established which eyes had been classified as having progressed after 10 years of follow-up. This information was used to plot area-proportional Venn diagrams19 to illustrate the agreement between the methods. Differences in time-to-progression were investigated only in those eyes that had been classified as having progressed with both total and pattern deviation analyses. To explain the differences between the total and pattern deviation analyses of visual field progression, the slope of GH over time was plotted against the slope of MD over time. In eyes with purely focal progression, the slope of the MD index would be negative, whereas that of GH would be zero. In eyes with entirely diffuse change, both MD and GH would show similar, negative slopes. For this analysis, eyes were stratified into three equal groups, according to baseline MD.

To judge the likely specificity of the criteria for visual field progression, we derived the rate of progression in the healthy control eyes, as well as the rate of visual field improvement in the glaucomatous eyes, using the same criteria as had been used for detecting progression.

RESULTS

Subject Groups

Data from 101 patients with open-angle glaucoma and 102 healthy control subjects were included in the analysis. Details for both groups of subjects are shown in Table 1.

Comparison between Total and Pattern Deviation Analyses

Both event and trend analyses of total deviation detected progression in a larger number of glaucomatous eyes than the corresponding pattern deviation analyses. With the total deviation event analysis, 50 (30%) glaucomatous eyes were classified as having progressed after 10 years of follow-up, but only 35 (21%) met the criteria with the pattern deviation analysis (Figs. 3a–c). Similar findings were obtained with the trend analyses.
time-to-progression differences, pointwise

**FIGURE 4.** Point-by-point differences in time-to-progression with event (a) and trend (b) analyses of total and pattern deviation. On average, the total deviation–based analyses detected progression approximately 6 months (1 examination) earlier than the pattern deviation analyses. Numbers on top of each histogram bar give percentages.

analyses; after a 10-year follow-up, the total deviation trend analysis had classified progression in 61 (36%) eyes of which only 41 (24%) were classified with pattern deviation analyses (Figs. 3d, 3h). The differences between the progression rates obtained with total and pattern deviation analyses were statistically significant in both event and trend analyses (P < 0.01; McNemar test). In eyes that were classified as progressing, with both the total and pattern deviation analyses, the time-to-progression differences between both analyses followed a skewed distribution that suggested earlier detection with the total deviation analyses (Figs. 3d, 3h).

The systematic differences in time-to-progression were confirmed in a point-by-point analysis (Fig. 4). Although most test locations were classified as having progressed at the same time, the distributions of the differences showed a long tail (earlier detection with the total deviation analyses). In most, but not all, eyes, the total deviation analyses classified more test locations as having progressed than did the pattern deviation analyses. These findings applied equally to both event and trend analyses (Fig. 5).

To interpret the observed differences between the total and pattern deviation analyses of progression, we compared the change in GH to the change in the MD index in both groups of subjects (Fig. 6). Eyes with purely focal change would be associated with data points that lie on a horizontal line (slope of GH = 0), whereas those with purely diffuse changes would lie along the dotted diagonal line (slope of GH = slope of MD). Most glaucomatous eyes showed negative GH slopes as well as negative MD slopes, indicating that purely focal changes occurred rarely. In the healthy control eyes, almost all changes were diffuse.

To obtain an indication of how specific (i.e., robust to random variability) the evaluated progression criteria were likely to be, we derived the progression rate in the healthy control eyes, as well as the improvement rate in the glaucoma eyes. Visual field progression in the healthy control eyes was rare with both event and trend criteria. After 10 years of follow-up, the cumulative progression rates in the healthy control eyes were between 2% and 6% in all analyses (Fig. 3, dotted curves), and differences between the analyses were not statistically significant (P > 0.18, paired comparison of proportions). The rate of visual field improvement in the glaucomatous eyes was also low (Table 2). After 10 years of follow-up, the improvement rates were between 1% and 7% in all four analyses. Together, these findings imply that the analyses and criteria evaluated in this study possess high specificity.

**Case Examples**

The following examples illustrate some of the findings of our study. The patient in the first example (Fig. 7), showed widespread deterioration in both the inferior and superior hemifields, and changes appeared larger with the total deviation than with the pattern deviation analyses. In the second example (Fig. 8), the grayscale plots revealed a large degree of progression that was underestimated by all four analyses, owing to large variability within the visual field series. In this example, the total-deviation analyses identified more test locations as having changed than the pattern deviation analyses.

**DISCUSSION**

Visual field progression is often the only clinical sign that a change in the patient’s vision has taken place. It is therefore usually regarded as a strong indication that the treatment regimen should be intensified. Many recent clinical trials in glaucoma have yielded important scientific information and jointly have the potential of dictating strong practice guidelines throughout the spectrum of the disease, from suspected to advanced glaucoma. However, one impediment of translating
the results of these trials into clinical practice is the large difference in visual field endpoints that had been specified. This lack of standardization is understandable, given the extent of knowledge about the longitudinal behavior of visual fields and their variability when the trials were designed and executed. Newer and potentially better methods of analyzing visual field progression may, however, allow standardization of progression criteria, such that information from different studies can be compared and translated to clinical practice.

One of these new tools is the glaucoma progression analysis (GPA) which is based on pattern deviation values which compensate for changes in the GH of the visual field, thought to be caused primarily by cataract. Important glaucoma-related clinical trials, such as the Early Manifest Glaucoma Trial, have used similar analyses for defining endpoints. To date, however, the performance of the GPA has been evaluated in surprisingly few studies and a comparison with the GCP analysis, based on total deviation, has been reported in only one published study. The specificity of the GPA has not been published. Therefore, our objectives in this study were to investigate the differences between total and pattern deviation analyses of visual field progression in subjects without clinical evidence of increasing media opacity, as well as to estimate the specificity of the progression analyses over time.

Our results indicate that between 10% and 15% of glaucomatous eyes show evidence of progression with the total deviation but not the pattern deviation analyses. In individual eyes, on average, total deviation analyses also classified more test locations as having progressed. Both these findings were similar with event and trend analyses. They agree with those of Katz which showed a lower incidence of progression with the pattern deviation event analysis (GPA) compared with total deviation (GCP). One possible explanation for these findings is the confounding factor of concurrently progressing cataract, which would have been reduced with pattern deviation analyses. However, we feel that progressing cataract is unlikely to be the sole explanation for the differences between the total and pattern deviation analyses. We excluded patients whose visual acuity had deteriorated by more than 2 lines over the course of the study, as well as those who had undergone cataract surgery. Moreover, recent evidence established in the same population suggests that cataract surgery, despite a mean improvement of 2 lines of visual acuity, results in only a very small and statistically insignificant improvement in total devia-

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<th>Trend Analyses</th>
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<tr>
<td></td>
<td>Total Deviation</td>
<td>Pattern Deviation</td>
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<tr>
<td>Control eyes (n = 102)</td>
<td>2 (2%)</td>
<td>0 (0%)</td>
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<td>Glaucomatous eyes (n = 168)</td>
<td>3 (2%)</td>
<td>1 (1%)</td>
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**Table 2.** Number of Improvement Events in Eyes of Healthy Control Subjects and Patients with Glaucoma with Event and Trend Analyses of Total and Pattern Deviation

**Figure 7.** Case example 1. Grayscale plots of first (a) and last (b) visual field test results in a patient with extensive progression. (c, d) Locations with significant deterioration beyond the 5th percentile of test–retest variability on the last three consecutive examinations. (e, f) Test locations meeting the two-omitting criterion on the last examination.

**Figure 8.** Case example 2. Grayscale plots of first (a) and last (b) visual field test results in a patient with extensive progression. (c, d) Locations with significant deterioration beyond the 5th percentile of test–retest variability on the last three consecutive examinations. (e, f) Test locations meeting the two-omitting criterion on the last examination.
affected GH24 and therefore would have led to a systematic un-
dents. Moreover, in patients with moderately advanced dam-
field progression comprises both focal and diffuse compo-
ments. In patients with advanced damage, the pattern deviation cal-
ulations often produce obviously misleading results.25

Although, in most glaucomatous eyes, the total deviation
alyses revealed a larger number of locations as progressing
than did the pattern deviation analyses (Fig. 4), the opposite
was true in a small number of eyes. This finding can be
explained by the fact that pattern deviation analyses may com-
ensurate a significant positive slopes of MD and GH with time occurred in a significant number of patients as well as healthy control subjects (Fig. 5). In these subjects, pattern deviation analyses may have advantages over those based on total deviation.

Although computer simulations have been used to investi-
gate and compare the performance of different criteria to
determine progression,16 –20 such simulations depend largely
on comprehensive models for glaucomatous visual field change
that are difficult to validate. We were interested primarily in
the specificity of the progression analyses (i.e., the likelihood
that a given visual field was classified as having progressed
although no real change had taken place). To obtain estimates of
specificity from real clinical data, we derived two indepen-
dent proxy measures of specificity. First, visual field progres-
sion was analyzed in a group of healthy control subjects. The
rationale for using the rate of progression in the normal control
eyes as a proxy index of specificity in patients with glaucoma
is based on the assumptions that: (1) normal ageing effects are
accounted for by both total and pattern deviation analyses, (2)
visual field progression is specific to glaucoma, and (3) both
analyses compensate for the different levels of variability ob-
erved in patients with glaucoma and control subjects. Any
deterioration observed in the healthy control subjects should
therefore be due only to random variability. With any of the
analyses performed, the progression rate in healthy eyes was
low; after 10 years of follow-up, only between 2% and 6% of
control eyes had met the criteria for progression. Second, the
rate of visual field improvement was determined in the glau-
comatous eyes, based on the rationale that genuine visual field
improvement in glaucoma is rare. Although learning effects,
which manifest as visual field improvement, occur to varying
degrees and over various time periods,26 –28,30,31 they would
lead us to underestimate, rather than overestimate, the speci-
ficity of the progression analyses. With both event and trend
analyses, the improvement rates were below 10% after 10 years
of follow-up, suggesting that the true specificity of the progres-
sion analyses was high. Although the differences between
the ratio indices of specificity (rates of progression in control
eyes, rates of improvement in both groups of subjects) with
the event and trend analyses were not statistically significant,
we cannot be confident that the specificities of the criteria are
truly similar. To obtain sufficient statistical power to detect a
real difference between two low rates, very large sample sizes
are necessary. For example, a sample size of approximately 500
would be necessary to obtain 80% power to confirm the 5% differ-
cence between specificities of 90% and 95%. Because these
rather small absolute differences in specificity can be clinically
important, the lack of statistical power for comparisons of
diagnostic tests is an important, though not easily addressed,
problem.

In summary, the pattern deviation analyses generally
yielded a smaller number of progressing eyes than did the total
deviation analyses. Although the average differences in time-
to-progression were small (earlier detection with total devia-
tion by approximately 6 months, or one examination), the
spread of differences in individual patients was sufficiently
wide to be of clinical importance. If the clinical evidence is not
suggestive of increasing media opacity, pattern deviation anal-
yses may significantly underestimate visual field progression
in glaucoma. Because, in individual eyes, either total or pattern
deviation analyses can have distinct advantages, we argue that
clinicians should have access to both methods for clinical
decision-making in glaucoma.

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