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## **Visual Field Index Rate and Event-Based Glaucoma Progression Analysis:**

### **Comparison in a Glaucoma Population**

Key words: Glaucoma, Glaucoma progression analysis, visual field index, trend analysis, visual fields.

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**Abstract:**

**Aims:** To compare event-based glaucoma progression analysis (GPA) I with new GPA II software and pattern deviation-based trend analyses (visual field index [VFI]) to detect progression in a glaucoma population.

**Methods:** A retrospective study that included 90 eyes of 90 patients with a minimum of five reliable visual field tests and a follow-up period of at least 2 years.

**Results:** Event-based GPA II detected progression in 16.7% of eyes in which trend analysis VFI failed. GPA detected progression 6.8 months earlier than VFI. GPA I and II showed excellent agreement ( $k=0.94$ ). Agreement between VFI and mean deviation (MD) linear analysis and with GPA criteria was  $k=0.52$  and  $k=0.48$ , respectively. Mean rates of progression of MD and VFI were  $-0.41$  dB and  $-1.30\%$  annually, respectively ( $\rho=0.824$ ;  $P < 0.0001$ ). Using VFI, mean follow-up time was 6.12 and 4.89 years ( $P= 0.004$ ) and mean number of visual field tests was 7.33 and 6.01 ( $P= 0.023$ ) in eyes with and without progression, respectively.

**Conclusions:** Event-based software GPA I and II had an excellent agreement. Event analysis showed earlier and greater sensitivity for detecting progression than VFI analysis and both had only moderate agreement. Trend analysis VFI is likely to detect progression in patients with a greater number of visual field tests and a longer follow-up time. The VFI analysis seems to be more accurate than MD analysis for determining rate of progression.

The ability to detect progression of visual field defects remains one of the most challenging aspects of glaucoma management. Attention has been focused lately on developing methods to detect early glaucoma damage by evaluation of a longitudinal series of visual field tests.[1] Techniques such as the judgment of expert clinicians, defect classification systems, trend analyses, and event-based analyses have been evaluated for determining visual field progression .[2-5]

Event-based analysis has been proposed as an advantageous approach for detecting progression of glaucoma.[2] This method relies on stable glaucoma population-derived variability limits. Glaucoma Progression Analysis (GPA), included in the software of the Humphrey Visual Field Analyzer (VFA) (Carl-Zeiss Meditec, Dublin, CA), is an example of event-based analysis using pattern standard deviation (PSD) values.

Determining the rate of disease progression in every patient is fundamental.[6] Nouri-Mahdavi et al.[7] reported that the faster progression was the strong predictive factor for further progression. Up-to-date mean deviation (MD) trend analysis was the standard index for estimating the glaucoma progression rate. The MD is affected not only by progression of glaucoma but also by cataract. Arnalich-Montiel et al.[8] reported that trend analysis of the MD is poorly correlated with clinical judgment and event-based analysis, is less sensitive, and ignores the detailed spatial information within the computerized field test. Thus, Bengtsson and Heijl [9] described a technique, the visual field index (VFI), to measure the rate of visual field deterioration in glaucoma that is based largely on the Humphrey perimetry PSD analysis. The GPA II software displays the linear regression of the VFI.

The purpose of the current study was to compare the commercially available event-based analysis GPA I with the new GPA II software, including PSD-based trend analyses (VFI) to detect disease progression in a glaucoma population.

## **Patients and Methods**

Analyses were performed using the Humphrey VFA database in the glaucoma unit of our hospital. This retrospective study, approved by the institutional review board of the hospital, included 90 eyes of 90 patients with a definitive diagnosis of primary open-angle glaucoma who had a minimum of five visual field tests that could undergo GPA analysis and a follow-up period of at least 2 years.

The visual field tests were considered reliable if the fixation losses, the false negative results, or the false positive results were 25% or less. The inclusion criteria also included a visual acuity (VA) that exceeded 20/100 and a baseline MD of -15 decibels (dB) or better. When both eyes were eligible, one eye was randomly selected.

We excluded patients with visual field loss from causes other than glaucoma, those who developed visual field loss for reasons other than glaucoma during follow-up, and patients with disorders that affect the visual fields. Patients were included in the study who had no substantial lens opacity as determined by an ophthalmologist at the baseline clinical examination and throughout the study.

Each subject underwent periodic examinations that included measurement of the best-corrected visual acuity, slit-lamp biomicroscopy, gonioscopy, applanation tonometry, dilated funduscopy examination, and visual field testing, the last performed on a Humphrey VFA using the 24-2 program with the Swedish interactive threshold algorithm standard strategy.

As baseline, we used the first two abnormal but reliable visual field tests either displaying a glaucoma hemi-field test outside the normal limits or a corrected PSD of 5% probability or worse.

### **GPA I Definition of Progression**

GPA I printouts were obtained by one author (PC-L) who changed the baseline tests as needed by discarding unreliable visual field test or those affected by the learning curve. Event based GPA I used statistical criteria designed for the Early Manifest Glaucoma Trial [10] that were used to identify incident progression of visual field defects. When significant deterioration ( $P < 0.05$ ) was evident on the PSD probability maps of the GPA I printouts at the same three or more points on two consecutive follow-up tests, the GPA I software interpreted this as possible progression, whereas if deterioration occurred in three consecutive follow-up tests, the software interpreted that as likely progression. The points did not necessarily need to be clustered together to satisfy either criterion. In the GPA I printout, the follow-up probability maps were sometimes marked with Xs at specific locations, indicating that these locations had baseline threshold values that were too low for an effective comparison. Therefore, these locations were not used to assess progression.

GPA I printouts also showed a summary plot of the MD for each test in the analysis plus a MD linear regression analysis. An eye was classified with progressive damage if a negative linear regression slope was significant with a  $P < 0.05$ .

### **GPA II Definition of Progression**

GPA II printouts were obtained by one author (MP-L) who eliminated the last test if it was not included in the GPA I in order to evaluate the same visual fields in both analyses. There are no differences between event based GPA I and II definitions of progression, but in contrast with GPA I, GPA II did not include in its analysis the first visual field if a learning effect was detected automatically. GPA II also did not include patients with a MD worse than -20 dB, because PSD analysis may suggest artifactual visual field improvements despite further visual field deterioration.[9]

GPA II provides the VFI, which is based on the PSD probability maps. For this index, visual field data are age adjusted and expressed as a percentage of a normal visual field and intended to calculate the rate of functional loss. The VFI of a perimetrically normal visual field was set to 100%, and the VFI of a perimetrically blind visual field was set to 0%. Estimates of the cortical representation of the spatial relationships of vision were used to adjust the VFI to be more heavily weighted to central areas of the visual field.[9,11]

Besides event-based analysis, GPA II printouts also showed a trend analysis with summary plot of the VFI index for each test in the analysis plus linear regression analysis of the VFI, i.e., the VFI progression rate. Both event and trend analysis are complementary of each other. An eye was classified with progressive damage if a negative linear regression slope was significant with a  $P < 0.05$ .

### **Statistical Analysis**

Kappa statistics were used to estimate the agreement between the different approaches to assess glaucoma progression. The continuous variable correlation was calculated using Spearman's coefficient. We compared how follow-up time and mean number of visual field tests affected the likelihood of detecting progression by the different methods using the U-Mann-Whitney test. The total level of significance was set to  $P < 0.05$  (two-sided). SPSS 13.0 software for Windows (SPSS Inc, Chicago, IL) was used to provide all of these data and to calculate progression rates and demographic data.

## Results:

### Demographic Data:

Table 1. Demographic Data of the Study Population

Parameter	Mean	Standard Deviation	Range
Age (years)	72.54	7.8	40 to 86
Follow-up (years)	5.06	1.55	2 to 11
VF number	6.19	1.44	5 to 11
Basal MD (dB)	-6.26	3.02	-13.14 to -1.49
Basal PSD (dB)	5.24	3.04	0.87 to 15.40
Basal VFI (%)	87.13	8.9	55 to 99

MD = mean deviation; PSD = pattern standard deviation; dB = decibel; VFI = visual field index.

### Rate of Progression

The rates of progression of visual field loss based on the VFI linear regression, the MD linear regression, and the event based GPA I and II progression are shown in Table 2. Based on the trend analysis VFI and event based GPA II analyses, 63 eyes (70%) were stable and the percentage of eyes classified as the same (either with progressive damage or stable) was 82.2%.

Table 2. Prevalence of Progression

	Event based GPA II	Linear regression VFI	Event based GPA I	Linear Regression MD	P value
%Progression (n)	28.9%(26)	13.3%(12)	31.1%(28)	23.3%(21)	p= 0.000007

GPA = glaucoma progression analysis; VFI = visual field index; MD: mean deviation.

Event based GPA I and II showed similar progression rates (31.1% and 28.9%, respectively). The possible progression rate was slightly higher with GPA I than GPA II (12.2% vs. 10%, respectively).

Table 3. Differences between GPA I and II Progression Criteria

Progression	GPA I (%)	GPA II (%)
Possible	11 (12.2)	9 (10)
Likely	17 (18.9)	17 (18.9)
None	62 (68.9)	62 (68.9)
Wrong basal visual field included	Not applicable	2 (2.2)
MD < -20 dB	Not applicable	2 (2.2)

GPA = glaucoma progression analysis; dB = decibel; MD = mean deviation.

As previously reported [8], we also evaluated the MD linear regression analysis using previous-generation GPA I software, which showed that 76.7% of eyes remained stable, while 23.3% had a significantly worsening slope. There was poor agreement compared with event based GPA II ( $k = 0.22$ ;  $p=0.031$ )

No patients had progressive visual field damage detected by the trend analysis VFI when the event based GPA II analysis indicated stability. The only discrepancy occurred in an eye with a MD worse than -20 dB and as mentioned previously, GPA II does not apply in this case. However, event based GPA II detected progression of damage in 15 of 90 eyes (16.7%) that did not have based on the VFI trend analysis. In 11 patients (12.2%) who had progression using these both criteria, event analysis detected progression 6.8 months earlier than the trend analysis .

### **Rate of Progression**

The mean rate of MD progression was -0.41 dB annually. The mean rate of VFI progression was -1.30% annually. There was a significant correlation between both rates of progression ( $\rho= 0.824$ ;  $P < 0.0001$ )

Figure 1 shows the length of the follow-up related to agreement in the detection of progression by event-based analysis (classified as likely or possible progression) and the VFI.

Using trend analysis VFI, the mean numbers of visual field test in eyes with and without progression were 7.33 and 6.01, respectively ( $P=0.023$ ); the mean follow-up times in eyes with and without progression were 6.12 and 4.89 years, respectively ( $P =0.004$ ). The mean confidence limits in eyes with progression and no progression were  $\pm 2.70\%$  and  $\pm 3.24\%$  ( $P =0.614$ ), respectively. The mean confidence limits were weakly inversely correlated with the follow-up time ( $\rho=-0.32$ ;  $P=0.002$ ). There was no correlation between

the number of visual field tests and the mean confidence limits ( $P=0.23$ ). The mean VFI confidence limits in eyes with and without progression by event-based GPA were  $\pm 4.15\%$  and  $\pm 2.73\%$ , respectively ( $P=0.044$ ). Moreover, the mean confidence limits of the VFI rate were  $\pm 2.72\%$  and  $\pm 5.23\%$  when methods yield identical results and inconsistent results respectively ( $P=0.004$ ).

Fourteen eyes (15.5%) had VFI rate of progression confidence intervals that exceeded 5%; GPA showed progression in seven eyes (50%) of these eyes.

### Agreement between Progression Criteria

Table 4. Kappa Statistics for Pairs of Progression Criteria

	<b>Event based GPA I vs. GPA II</b>	<b>Event based GPA II vs. trend analysis VFI</b>	<b>Event based GPA II vs. trend analysis MD</b>	<b>Trend analysis VFI vs. MD</b>
Kappa value	0.94	0.48	0.22	0.52
Standard error	0.03	0.10	0.11	0.11
<i>P</i> value	0.000	0.000	0.031	0.000

GPA= glaucoma progression analysis; MD = mean deviation; VFI: visual field index.

## **Discussion**

Several methods have been developed to detect visual field progression.[2-5] Event-based GPA was designed primarily to detect whether progression has occurred. However, most patients with glaucoma would eventually show some progression if followed for a sufficiently long time.[6]

The objectives of the current study were to compare previous and actual software event-based PSD analysis (GPA I and II) with PSD-based trend analysis (VFI) of the visual fields to detect glaucoma progression in routine clinical ophthalmic practice.

Not surprisingly, we did not find significant differences in the prevalence of glaucoma progression when comparing GPA I and II event analysis. This prevalence agrees with other published studies.[12,13] The differences are related to the fact that GPA II does not include patients with a MD worse than -20 dB, because PSD analysis may suggest artifactual visual acuity improvements despite further visual field deterioration.[9] However, in the current study, because eyes had to have a MD of -15 dB or better in the basal visual fields to be included, we could not emphasize that difference. In addition, GPA II analysis does not include the first visual field if a learning effect is detected. This difference could have been neutralized because in GPA I printouts, changes were made in the baseline tests as needed by discarding unreliable visual field tests or visual field tests affected by the learning curve. Despite this, in two cases of our sample, GPA II automatically discarded reliable first basal visual field tests as a result of an excessive false positives or fixation losses in the second tests.

In the current study, VFI trend analyses showed moderate agreement ( $k=0.48$ ) with event-based analysis GPA II. Twenty-six eyes (28.9%) were classified by event GPA II as having progressive damage. In fifteen of these twenty-six eyes (57,6%),the worsening slope of the trend VFI was not significant. Therefore, event analysis GPA seems to be more

sensitive for detecting progression than trend analysis VFI. One reason could be that there were few visual fields during follow-up, because if we analyse these eyes, only two of the fifteen (13.3%) had more than eight visual field test. Otherwise, the VFI rate confidence interval was wider in patients with progression detected by event-based GPA and in patients in whom results were inconsistent between methods. Thus, the VFI worsening slope would not be significant when there was great variability while the event GPA analysis is not.

In patients who had progression by both criteria, event-based GPA II detected the progression 6.8 months earlier than trend VFI. Therefore event GPA II showed earlier detection than trend analysis VFI, just as we expected because of event-based methods design.

Regression analysis of any VFI requires a sufficiently large number of tests to detect progression reliably and predictively.[6] Indeed, we found that VFI is likely to detect progression in patients with a greater number of visual field tests and a longer follow-up period. However the follow-up time showed only a weak inverse correlation with the mean confidence limits of the VFI progression rate. Thus, not only follow-up but also variability can affect the estimating of VFI progression rate.

A primary limitation of event-based analysis methods is the detection of very focal progression based on marked worsening of one point within the central 10 degrees,[5,8] since GPA does not consider the location of the point of progression of damage but the presence of progression on at least three different points. In the current study, one patient had this kind of central progression. Neither event GPA nor trend VFI detected progressive damage in this patient.

MD linear regression showed poorer agreement with event-based analysis GPA II ( $k=0.22$ ) than VFI linear regression ( $k=0.50$ ). Therefore, VFI seems to be better than MD

linear regression analysis for determining a patient's rate of progression. Nevertheless, when comparing MD and VFI trend analysis, we found that agreement was moderate (0.52), and there was a strong positive correlation ( $\rho=0.824$ ). This may be explained because only patients without significant lens opacity at the baseline and throughout the study were included.

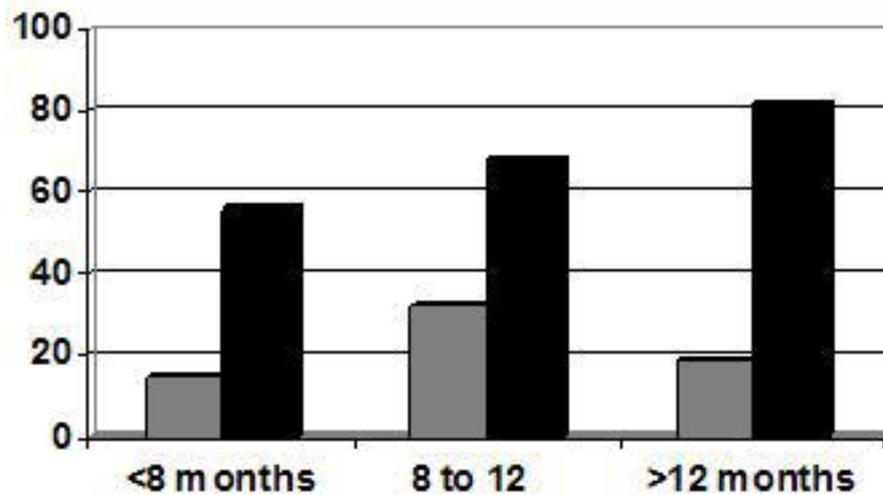
VFI trend analysis has two main limitations: 1) the need for longer follow-up and more visual field tests than event-based methods to detect progression and to estimate the progression rate if high variability is present, and 2) despite the fact that VFI emphasizes the functional importance of central vision,[6,9] it cannot resolve the main GPA limitation [5,8], namely, detection of very focal central progression.

In summary, event-based GPA detected glaucoma progression earlier and was more sensitive for detecting progression than VFI trend analysis, and both had only moderate agreement. The mean VFI rate of progression confidence intervals were wider in patients whom results were inconsistent between GPA and VFI. Trend analysis VFI is likely to detect progression in patients with a greater number of visual field tests and a longer follow-up period. The VFI rate of progression seems to be better than MD linear regression analysis for determining a patient's rate of progression, although both methods had a strong positive correlation. We also found that event-based analysis software GPA I and II identification of progression has a high level of agreement.

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■ GPA/VFI inconsistent results  
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