A Method to Measure and Predict Rates of Regional Visual Field Decay in Glaucoma

Joseph Caprioli, 1 Dennis Mock, 1 Elena Bitrian, 1 Abdelmonem A. Afifi, 2 Fei Yu, 1, 2 Kouros Nouri-Mahdavi, 1 and Anne L. Coleman 1

PURPOSE. This study was conducted to measure the rate of visual field (VF) decay in glaucoma, to separate faster and slower components of decay, and to predict the rate of VF decay.

METHODS. Patients who had primary glaucoma and 6 or more years of follow-up were included. Thresholds at each VF location were regressed with linear, quadratic, and exponential models. The best model was used to parse the VF into slower and faster rate components. Two independent cohorts (glaucoma [n = 87] and cataract [n = 38]) were used to determine the technique’s ability to distinguish areas of glaucomatous VF changes from those caused by cataract. VF forecasts, derived from the first half of follow-up, were compared with actual VF thresholds at the end of follow-up.

RESULTS. The mean (±SD) years of follow-up and number of VFs for the main cohort (389 eyes of 309 patients) were 8.2 (±1.1) years and 15.7 (±3.0) respectively. The proportions of best fits were linear 2%, quadratic 1%, and exponential 97%. Proportions of eyes with exponential rates of decay ≥10% for the entire visual field (VF), faster components, and slower components were 20%, 56%, and 4%, respectively. The difference in decay rates between the faster and slower components was greater in the independent glaucoma cohort (19% ± 10%) than in the cataract cohort (5% ± 5%; P < 0.001). Test location forecasts significantly correlated with measured values (r² = 0.67; P < 0.001).

CONCLUSIONS. This method isolates faster and slower components of VF decay in glaucoma, can identify patients who are fast progressors, and can predict patterns of future VF loss with appropriate confidence intervals. (ClinicalTrials.gov number, NCT00000148.) (Invest Ophthalmol Vis Sci. 2011; 52:4765– 4773) DOI:10.1167/iovs.10-6414

The measurement of rates of change in glaucoma helps identify those patients whose conditions are deteriorating quickly and can distinguish them from those whose conditions are worsening slowly. 1 Fast progressors may require suitably aggressive treatment, whereas slow progressors might be spared the expense and morbidity of unnecessary treatments. This topic is particularly important for an aging population with limited resources for medical care. Advancing damage in glaucoma can be measured by structural or functional changes, the latter most often estimated with perimetric measurements. In this article, we address the measurement of rates of damage with standard achromatic automated perimetry. Our goals are to develop a method to reliably measure the rate of functional decline in glaucoma, to use it to identify the fast progressors, and to provide clinically useful forecasts of the disease to help guide treatment. To be useful, the method should perform well across the entire range of disease severity.

The many problems with measuring rates with perimetry are well known. Primarily, these include a low signal-to-noise ratio, the requirement of multiple tests to reduce the noise, the requirement of confirmatory tests to validate the signal, and an inherent lack of external validation to evaluate any new method. A method to estimate global rates of VF progression in glaucoma, the visual field index (VFI), has been presented by Bengtsson and Heijl.2 The index is weighted more heavily toward the central VF in proportion to the cortical representation of vision, is normalized to the entire range of VF function, and provides some predictive capability as a linear extrapolation of the index.3 It requires the use of proprietary, stored normative data and assumes a linear rate of worsening. A shortcoming of the global indices in general is the lack of any spatial information with regard to the regions of the VF showing faster progression.

We hypothesize that progression in glaucoma is frequently nonuniform and that it is possible to identify a faster spatial component for VF decay that can be distinguished from the remaining test locations with a slower rate of decay. The latter frequently includes components related to aging and media opacity, although in some cases the slow component may indeed represent true glaucomatous progression.4 To test this hypothesis, we have developed a novel method to measure VF decay with a large cohort of glaucoma patients with long-term follow-up. The method identifies VF locations progressing at the fastest rates, provides a method to spatially separate test locations demonstrating slower progression from those showing faster progression, and predicts future VF measurements with appropriate confidence intervals while preserving spatial information.

PATIENTS AND METHODS

Patient data collected during the conduct of the Advanced Glaucoma Intervention Study (AGIS) were used as our main study sample. The AGIS design and methods are described in detail elsewhere.5,6 In this study, patients who had 6 or more years of follow-up and who underwent 12 or more VF examinations were included. VF data were collected according to the AGIS protocol, which required acceptable

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VF reliability scores.7 VF tests were performed with a visual field analyzer (Humphrey Visual Field Analyzer I; Carl Zeiss Ophthalmic Systems Inc., Dublin, CA) with the 24-2 test pattern, size III white stimulus, and full-threshold strategy. The 24-2 program records sensitivities from 55 locations in the VF, including the physiologic blind spot. All patients gave written informed consent for participation in AGIS, and the study was approved by the individual institutional review boards of the respective clinical centers. The Institutional Review Board of the University of California at Los Angeles approved the present study. All research procedures followed the tenets set forth in the Declaration of Helsinki.

Modeling of Serial Visual Field Threshold Sensitivities
We performed regression analysis of the threshold sensitivity (in dB) against time for each VF location with three models: linear, quadratic, and exponential. Regression coefficients were determined over the entire VF series for each eye. The relationship between the response variable (threshold sensitivity) and the explanatory variable (duration of follow-up) was characterized by the following three mathematical forms:

1. First-order linear: \( y = a + bx \);
2. Second-order linear (quadratic): \( y = a + bx + cx^2 \); and
3. First-order exponential: \( y = e^{ax+bx} \) or, equivalently, \( \ln y = a + bx \).

The rate of change is represented by the coefficient \( b \) in each model. For models 1 and 2, \( b \) represents the average annual rate of change (increase or decrease) in \( y \). For model 3, \( b \) is the average annual rate of change (increase or decrease) in \( \ln y \). Equivalently, for model 3, \( e^b \) represents the ratio of \( y \) in a given year to \( y \) in the year before (on the average). In other words, \( e^b \) is interpreted as the average annual rate of decline of \( y \). The rate of decay is defined as \((1 - e^b)\).

Postregression diagnostics were applied to test the fit for each model. The Akaike information criterion (AIC) was used to choose the best-fitting model.8 The AIC is defined as \( 2k - 2\ln(L) \), where \( k \) is number of parameters and \( L = \) natural log of the maximum likelihood value. From these results, the selected model (exponential) was used to measure the rate of decay of each test location for the entire VF series for each eye.

### Rates of Visual Field Decay
The rates of VF decay measured with the exponential model were plotted as a frequency distribution. The global rate of decay (percentage per year) was determined for the VF series of each eye by taking the mean of individual decay rates for each of the 54 test locations analyzed (the two locations at the blind spot were excluded from all analyses). Positive rates of decay indicate worsening of the VF, whereas negative rates indicate improvement.

### Faster and Slower Rate Components of Visual Field Decay
For each VF series, we defined a separation of the test locations for each eye whereby the decay rate at each location was assigned to 1 of 2 components: a faster VF rate component and a slower VF rate component. The 54 rates were ranked from fastest to the slowest decay and were partitioned into two subgroups (faster and slower) of different sizes. For each partitioning, we computed a \( t \) test statistic, and the corresponding \( P \) values were adjusted for multiple testing. The null hypothesis was that the mean of the fast group equaled the mean of the slow group. Optimal partitioning was determined by finding the fast subgroup that yielded the minimum \( P \) value, with a minimum size of five test locations per cluster. All other locations were assigned to the opposite group. Adjusted \( P \) values were used for this multiple testing procedure with the Benjamini-Hochberg correction.9 Each eye provided its own optimal partitioning. The eyes had components of different sizes, but each component consisted of at least five locations. For each eye, the mean decay rate was calculated for each of the partitioned components. Frequency distributions of the faster and slower component rates and their differences were calculated and displayed.

The percentage rate of decline per year for the average of the slow and fast components was plotted separately against the percentage rate of decline in the mean deviation (MD) value per year. A purely diffuse change would lie along a diagonal line of unity, whereas a localized change would lie nearly on a horizontal line.

### Half-Lives for Fast and Slow Rate Components
VF decay half-lives were calculated from the exponential decay rates of the fast and slow components. Half-life is defined as the time it takes

<table>
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<tr>
<th>Table 1. Characteristics of the Study Samples</th>
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<td><strong>Eyes, n</strong></td>
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<td><strong>Patients, n</strong></td>
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<td><strong>Age, y</strong></td>
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<td><strong>Cataract surgery, n (%)</strong></td>
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<td><strong>Number of visual fields</strong></td>
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<td><strong>Initial MD, dB</strong></td>
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<td><strong>Final MD, dB</strong></td>
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Data are given as mean ± SD unless otherwise noted.

* Visual field MD.
for VF sensitivity to decline to half its baseline value at each location. Fast progressors were described as eyes in which the half-life for the fast component was \( \leq 10 \) years.

**Forecast Models**

VF forecasts were performed by predicting, for each test location, a final threshold value from the first half of the follow-up by exponential extrapolation. The spatial characteristics of the VF are thus maintained. Correlation coefficients of the predicted versus the observed final values (average of the last three thresholds) were calculated for all test locations. Confidence intervals for predictions were computed.

**Separate Cataract and Glaucoma Test Data Sets**

Two smaller, independent clinical samples were assembled from the clinical database at the Jules Stein Eye Institute Glaucoma Division. Patients who were considered glaucoma suspect throughout their course (no change in optic nerve appearance and no glaucomatous VF loss at any time) and who were phakic were included in the first group (CAT). The second group of patients (PGL) had primary open-angle glaucoma with clear or open posterior capsules. The PGL group was used to simulate patients with only glaucoma and no significant media opacity, whereas the CAT group was used to simulate patients with slowly progressive cataract but no significant glaucomatous damage. The CAT and PGL groups were used to compare the relative contributions of the faster and slower components to overall VF decay rates. The hypothesis was that the PGL eyes would have a stronger component of faster progression than would the CAT group. Worsening glaucoma would be represented by relatively faster decay (i.e., large differences in decay rates between the faster and the slower components), and worsening cataract would be represented by a more uniform decay rate and, hence, a smaller difference between the decay rates of the faster and slower components.

**RESULTS**

**Patient Data**

Three hundred eighty-nine eyes of 309 patients with primary open-angle glaucoma were included in the main study group. The mean (±SD) follow up was 8.2 (±1.1) years, and the average number of VFs was 15.7 (±3.0). The characteristics of this group and the demographic data for the independent PGL (87 eyes of 80 patients) and CAT (38 eyes of 31 patients) groups are given in Table 1. Unless otherwise stated, the analyses here pertain to the main study group. Initial and final (at end of follow-up) distributions of the VF MD are shown in Figure 1.

**Model Fitting of Serial VF Threshold Sensitivities**

An example of each of the three model fits for a single test location is shown in Figure 2. Results from the AIC test for the goodness-of-fit for each of the three models (389 eyes each, 54 test locations; total number of regression fits, 21,006) overwhelmingly selected the exponential model as optimal. The total number of best fits for each of the models is linear 2.4%, quadratic 0.8%, and exponential 96.8%.

![Figure 1](iovjournals.org)

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![Figure 2](iovjournals.org)
Rates of Visual Field Decay

Global rates of VF decay (based on the exponential model) for each eye are shown as a frequency distribution in Figure 3. Distribution is skewed to the right, consistent with an overall worsening of VFs over the course of follow-up \( (P < 0.0001) \) with D’Agostino’s test for skewness; skew = 1.1361.10

Faster and Slower Rate Components of Visual Field Decay

An example of separating the rates of decay from a single eye into faster and slower components is given in Figure 4. The frequency distribution for the average decay rates of the faster and slower components and their differences are displayed in Figure 5 for the entire study sample. The proportions of eyes with rates of decay ≥10% for the entire field series (based on MD) and for the faster and slower components were 20%, 56%, and 4%, respectively. The distribution of the differences between the faster and slower components (bottom) is shifted to the right (faster decay) and is proposed to largely represent the glaucomatous component of decay because it is corrected for the decay rate of the slower component. Mean numbers of worsening test locations for each VF in the faster and slower
components were 14.7 ± 8.9 and 39.3 ± 8.9, respectively (P < 0.001).

In Figure 6, the average percentage rate of decay of the fast and slow components is plotted against the linear regression slope of the percentage change in MD in eyes with declining levels of threshold sensitivity. The rate of change (%/year) is determined by an exponential fit of the faster and slower components of each eye. We used a rank-based parametric statistic, with P values adjusted for multiple testing, to partition the progression rates into faster and slower components. Histograms show the distribution of the average rates for the faster and slower components and their difference in each eye.

FIGURE 5. Frequency distributions of the faster and slower components of VF decay in all eyes of the main study sample (n = 389). An algorithm differentiated the fast from the slow components by assigning individual locations to two regions of relatively faster or slower rates of decay. The rate of change (%/year) is determined by an exponential fit of the faster and slower components of each eye. We used a rank-based parametric statistic, with P values adjusted for multiple testing, to partition the progression rates into faster and slower components. Histograms show the distribution of the average rates for the faster and slower components and their difference in each eye.

FIGURE 6. The average rate of decay of the fast and slow VF components is plotted against the rate of change of MD for all eyes (n = 389). As a reference, a line with a slope equal to unity is drawn to represent complete agreement between the rate components and the percentage of MD change. The overall rate of change of the component associated with purely diffuse changes would regress along this diagonal line, with a slope approaching 1. Here the fitted line for regression of the slower rate component against the percentage of MD change has a slope of 0.19 (P < 0.05).

Half-Lives for Faster and Slower Rate Components

Figure 7 shows the half-lives for the slow and fast components for each of the VFs in the main study group (n = 389 for each). A substantial proportion of patients (58%) had a faster VF component, with a half-life of ≤10 years. These patients would be defined by our arbitrary criteria as fast progressors.

Separate Cataract and Glaucoma Test Data Sets

In Figure 8, the pair of histograms shows the distribution of differential rates of decay between the faster and slower rate components (percentage per year) in the PGL and CAT groups. The distribution of mean (±SD) differential rates was significantly different between the PGL (18.7 ± 10.0%) and CAT (5.4 ± 5.0%) cohorts (P < 0.001). The PGL test group, therefore, had a greater average rate for the faster component than did the CAT group, whose average VF decay rate in the faster component was relatively slow.

Forecast Models

The ability of the exponential regression of individual threshold sensitivities to predict future VF appearance was evaluated by comparing the actual versus the predicted thresholds for all declining test locations (n = 389, for a total of 13,905 comparisons). The correlation between actual and predicted final threshold values was strong (r² = 0.67 and P < 0.001; Fig. 9). The 10% and 90% confidence intervals were developed for predictions of threshold sensitivity at individual test locations (Fig. 10) and may be considered suggestions for the appearance of nearly best case and worst case future outcomes.
Clinical Interpretations

An example of how the presented method might be used in practice is shown in Figure 10. The figure is a printout that summarizes the behavior of the VF over time in a typical glaucomatous eye, and it provides predictions of the future behavior of the VF. In this example, the 10-year (final) follow-up predictions were based on the regression slopes estimated from the first 5 years of follow-up.

DISCUSSION

With this novel method, it is possible to describe the longitudinal decay of the VFs of glaucoma patients in terms of fast and slow components and to predict the appearance of future VFs. Previously published work in this area has not been abundant. Chauhan et al.11 published recommendations for measuring rates of VF change in glaucoma. Empirical data were used to provide variability estimates of MD. Models were developed to determine the number of tests required over various periods of time to detect change. For example, three tests are required to detect a change in MD of 4 dB over 2 years in an eye with average long-term measurement variability. Regional changes and focal components of damage, to which MD change is not sensitive, are not addressed.

Bengtsson et al.3 developed a VF index to calculate glaucoma rates of progression and to predict loss by extrapolation of linear trends. The authors proposed that the index is less affected by cataract and cataract surgery than MD and that the technique can be used to make clinically useful predictions. The VFI is weighted more heavily toward the central VF according to cortical projections of the visual pathway and is normalized for the entire range of perimetric vision. Pattern deviation values are used to select the total deviation values used in the calculation of the index, except when there is advanced VF damage (>20-dB loss), when all total deviation values are used. Predictions of future behavior of the VFI are performed by linear extrapolation. As with other global indices such as MD, no regional information about the VF is available with either the rate measurement or the prediction. VFI has been used recently to measure the relationship between intraocular pressure reduction and rates of progressive VF loss in eyes with optic disc hemorrhage.12 This index showed a beneficial effect on the rate of glaucomatous damage from treatment in patients with disc hemorrhage.

Linear regression of summary indices, averages of threshold sensitivities in clusters of test locations, and threshold sensitivities at individual test locations have been performed.

FIGURE 7. Half-lives of the faster and slower components of VF decay, and the identification of fast progressors. Half-life is defined as the time (years) it would take for the VF or its components to lose half their initial sensitivity, here shown for the faster and slower components separately (n = 389). Each VF was assigned a fast and a slow component. Fast progressors are defined here as those eyes with a faster component of ≤10 years (hatched bars).

FIGURE 8. Distribution of the differences between the faster and slower components of VF decay in separate pseudophakic glaucoma (n = 87) and cataract (n = 38) cohorts. The pair of histograms shows the comparison of the distribution of differential rates between the faster from slower components as a rate of change (percentage per year) in both patient groups. The distribution of mean differential rates is statistically different between the glaucoma (18.7% ± 10.0%) and the cataract (5.4% ± 5%) cohorts (P < 0.001).
The estimation of perimetric rates is confounded by the variability of VF data, the requirement for many tests to establish trends beyond the noise of the data, the requirement to confirm the results with repeat tests, and the inherent lack of adequate external validation. In developing this new method, we used a well-described patient database with long-term follow-up and many serial VF tests. The method uses an exponential model to fit the behavior of individual test locations and identifies the test locations deteriorating at the fastest rates. Confirmation (the persistence of the decay signal) is evaluated by the fit of the exponential model. Comparison of the predicted and actual outcomes provides some validation. It separates components of slower, diffuse loss (more commonly caused by media opacities, age, and nonspecific changes) from faster and more localized loss (more likely caused by glaucoma) and provides predictions of VF appearance with appropriate confidence intervals and preservation of spatial information. The method describes the faster and slower components of VF decay in terms of half-lives and presents an opportunity to identify fast progressors.

The exponential fits of the differential light sensitivities at individual test locations was better than either the linear or the quadratic fit in this patient group with moderate to advanced glaucomatous damage. Exponential fits for individual locations seem to work well for advanced damage because values usually approach 0 dB in an asymptotic fashion. The same would not generally be true of summary indices because these are global averages and only approach 0 dB in the most severe cases. The problem of media opacity and nonspecific causes of slow VF decline (including aging given that we used absolute threshold corrections) were addressed by identifying the slower, less clinically relevant component of VF decay and by subtracting this from the faster component of VF decay. Of course, there may be some diffuse loss caused by glaucoma that will remain undetected. However, glaucomatous VF change has proven by spatial processing (regional averaging). Linear examination was a statistically significant linear slope (at the 1% level) of at least $P \leq 0.001$.

Attempts have been made to predict future VF appearance based on an initial set of serial measurements. This technique has sometimes been applied to test the validity of a measurement technique, with the argument that more clinically useful measurement techniques would be better able to predict future outcomes. Nouri-Mahdavi et al. used the coefficient of VF series over the first 4 years of follow-up to predict 8-year outcomes. The sum of the slopes of individual test locations that regressed over time was used to estimate the probability of subsequent VF worsening with clinically useful accuracy. Crabb et al. previously pointed out that predictions of VF progression with pointwise linear regression could be improved by spatial processing (regional averaging). Linear extrapolation of VFI has also been used; predictions based on five initial examinations were found to be a reasonable predictor of future field loss in most patients.

Forecasts were made with exponential fits and extrapolation, on a pointwise basis, to the time of final follow-up. The pointwise predictions allowed for the spatial representation of future VFs, with assigned values for the 10th, 50th (median), and the 90th percentile predictions. These may be considered reasonable representations of the best-case, most likely, and worst-case outcomes.

An advantage of the technique reported here is that it does not depend on the use of proprietary, machine-stored normative data. The method can be applied to other testing strategies, stimulus sizes, or even other machines without the need for establishing confidence intervals for variability through
normative databases. In addition, because this approach is based on the clustering of test locations into slower and faster decay components, it should be resistant to the confounding effect of media opacity in the presence of real progression; this has received preliminary validation in our separate cohorts of patients.

There are some limitations to the technique. We required a minimum of five test locations for the smaller cluster of test locations to avoid detecting falsely worsening fast clusters (false positives). It is not yet clear how this will affect the detection of decay when a smaller number of test locations is actually worsening. It is possible that some less quickly deteriorating locations would then be included in the faster cluster; hence, worsening at very few points may be diluted. The present forecast model was associated with an $r^2$ of 0.67, an encouraging correlation that helps validate the technique. However, because the rates of decay spatially cluster in well-defined nerve fiber layer patterns, it may be possible to improve the forecasting model by using the correlation coefficients between the test locations to weight the contributions of the locations in a smoothing procedure. We should also note that the rates of decay are expressed in percentiles with the proposed technique and that comparison of rates must take into account the starting thresholds.

This approach provides a statistically and clinically reasonable method to develop approximations of rates of worsening of glaucoma and can be entirely automated for rapid retrieval and evaluation of serial VF data. It provides a method with which to isolate the faster and slower components of decay in the VFs of an individual glaucoma patient, to identify those patients who are considered fast progressors for more intensive scrutiny and care, and to predict, with preservation of spatial information and with appropriate confidence intervals, the future outcome of the VF. Additional work to validate the technique includes testing on a separate, larger database of glaucoma patients with
long-term follow-up apart from a clinical trial. We also plan, based on the identification of fast progressors, to explore baseline risk factors for fast VF decay and to test the clinical usefulness of the technique in practice.

References