Glaucoma With Early Visual Field Loss Affecting Both Hemifields and the Risk of Disease Progression

Carlos Gustavo V. De Moraes, MD; Tiago S. Prata, MD; Celso Tello, MD; Robert Ritch, MD; Jeffrey M. Liebmann, MD

**Objective:** To evaluate whether damage to both hemifields in glaucomatous eyes predicts more rapid disease progression than does single-hemifield involvement.

**Methods:** We reviewed the medical records of 43,660 consecutive patients. Eyes with glaucomatous optic neuropathy, 10 or more Swedish Interactive Threshold Algorithm standard 24-2 visual fields in at least 5 years, and mean deviation (MD) smaller than −6.0 dB were included. Pointwise linear regression was used to determine progression. Cox proportional hazards analysis was used to calculate risk of progression based on different baseline covariates.

**Results:** We enrolled 205 eyes (205 patients; mean [SD] age, 64.2 [11.0] years; follow-up, 6.5 [1.8] years; number of visual fields, 12.3 [2.9]). Patients were divided into 3 groups: initial superior defect (group A; n=79; MD, −3.4 [1.9] dB), initial inferior defect (group B; n=61; MD, −3.4 [1.8] dB), and both hemifields affected (group C; n=65; MD, −4.2 [1.5] dB). Group C progressed faster than did groups A and B (P < .02). Multivariate analysis showed significant effect of higher baseline intraocular pressure, thinner central corneal thickness, and initial damage to both hemifields.

**Conclusions:** Initial damage to both hemifields increases the risk of glaucoma progression. More aggressive therapy should be considered for these eyes.

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Identification of ocular or systemic risk factors associated with a faster rate of visual field (VF) loss remains an important goal of glaucoma research. A combination of variables, such as the extent of baseline optic nerve and VF damage, life expectancy, and the presence of additional risk factors, has been used to estimate the risk of loss of visual function and to determine future management. Although a variety of structural and functional tests are used to diagnose and follow glaucoma, standard achromatic perimetry remains the most widely used method for assessing visual function.

Several studies have investigated whether baseline VF characteristics are associated with increased risk of future disease progression and have typically focused on VF global indexes (ie, mean deviation [MD] and pattern deviation). These are well-established indexes that summarize measures of the entire VF but provide scarce spatial information.

Although patterns of VF injury vary in patients, glaucomatous field loss often begins with localized injury that respects the horizontal meridian and subsequently spreads in an archetypal pattern consistent with the orientation of the retinal nerve fiber bundles. In more advanced disease, these scotomata, particularly when present in both hemifields, may threaten fixation. We hypothesize that eyes with VF defects in both hemifields early in the disease course are more likely to experience progressive functional injury. To investigate this hypothesis, we evaluated eyes with similar baseline global VF damage to determine whether VF loss affecting both hemifields could be a harbinger of a worse prognosis than those with a similar degree of total damage limited to one hemifield.

**METHODS**

This retrospective study was part of a larger cohort initiated to investigate whether the findings of the major prospective multicenter clinical trials are applicable to the heterogeneous populations that confront physicians in daily practice. The different arms of this study originated from the medical records of 43,660 consecutive patients (132,512 VF tests) evaluated in the glaucoma referral practice of some of us (C.T., R.R., and J.M.L.). The study was approved by the New York Eye and Ear Infirmary institutional review board and followed the tenets of the Declaration of Helsinki.

The medical records of all patients examined between January 1, 1999, and June 30, 2008, were reviewed. Only patients with 10 or more Swedish Interactive Threshold Algorithm standard 24-2 fields (SITA-SAP; HFA II; Carl Zeiss Meditec Inc, Dublin, California) in either eye were included. A glaucomatous VF
Glaucoma is a multifactorial disease that results in different patterns and rates of progression for different individuals. An improved understanding of risk factors at all stages of disease is critical to estimating the risk of future disease progression for a specific affected individual. The results of the present study confirm that initial damage to both visual hemifields connotes a worse prognosis than does more localized damage limited to one hemifield, even when there is early VF loss (MD smaller than −6.0 dB). This involvement of both hemifields is an independent predictor of more rapid future VF injury in eyes with early functional damage and greatly increases the risk of progression.

In agreement with other studies, we found a significant role for higher baseline IOP and thinner CCT as risk factors for progression. The continued importance of these risk factors in treated patients with glaucoma is particularly important for physicians who must make clini-
cal decisions for patients who may not precisely resemble the individuals who were enrolled in masked, prospective, longitudinal clinical trials. Despite an initial mean baseline IOP of 17 mm Hg in eyes with early VF loss, the risk of progression increased 7% for each additional 1 mm Hg. A thinner CCT was also a risk factor for progression, in-

![Pattern Deviation](image1)

![Pattern Deviation](image2)

![Pattern Deviation](image3)

![Pattern Deviation](image4)

Table 1. Baseline Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group A (n=79)</th>
<th>Group B (n=61)</th>
<th>Group C (n=65)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>63.0 (10.3)</td>
<td>63.6 (11.1)</td>
<td>66.4 (11.4)</td>
<td>.13</td>
</tr>
<tr>
<td>European ancestry, No. (%)</td>
<td>69 (87.3)</td>
<td>49 (80.3)</td>
<td>59 (90.8)</td>
<td>.22</td>
</tr>
<tr>
<td>Diagnosis, No. (%)</td>
<td>43 (54.4)</td>
<td>25 (41.0)</td>
<td>33 (50.8)</td>
<td>.27</td>
</tr>
<tr>
<td>XFG</td>
<td>20 (25.3)</td>
<td>9 (14.8)</td>
<td>4 (6.2)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Other</td>
<td>16 (20.3)</td>
<td>27 (44.3)</td>
<td>28 (43.1)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>MD (SD), dB</td>
<td>-3.4 (1.9)</td>
<td>-3.4 (1.8)</td>
<td>-4.2 (1.5)</td>
<td>&lt;.02</td>
</tr>
<tr>
<td>No. of points with P&lt;1%, mean (SD)</td>
<td>6.5 (4.2)</td>
<td>7.2 (4.4)</td>
<td>9.5 (4.2)</td>
<td>&lt;.02</td>
</tr>
<tr>
<td>CCT, mean (SD), µm</td>
<td>540.5 (41.0)</td>
<td>533.8 (41.5)</td>
<td>542.9 (41.5)</td>
<td>.55</td>
</tr>
<tr>
<td>Baseline IOP, mean (SD), mm Hg</td>
<td>17.5 (4.3)</td>
<td>17.7 (3.5)</td>
<td>18.8 (4.6)</td>
<td>.12</td>
</tr>
<tr>
<td>Topical medications, mean (SD), No.</td>
<td>1.8 (1.2)</td>
<td>1.7 (1.2)</td>
<td>1.6 (1.1)</td>
<td>.66</td>
</tr>
</tbody>
</table>

Abbreviations: CCT, central corneal thickness; IOP, intraocular pressure; MD, mean deviation; POAG, primary open-angle glaucoma; XFG, exfoliation glaucoma.

a Analysis of variance with Bonferroni post hoc analysis showed significant differences between group C and the other groups.

b By χ² test.
Exfoliation syndrome was not a significant risk factor in the final multivariate model, suggesting that other factors, such as distance normal pressures.

clear the increased risk associated with VF loss in both hemifields. Glaucomatous functional damage usually respects the horizontal meridian and the anatomy of the retinal nerve fiber layer. In 1984, Mikelberg and Drance reviewed the pattern of VF progression using static and kinetic perimetry and found that 70% of eyes had initial damage limited to a single hemifield; at the completion of follow-up, 57% still had only single-hemifield involvement, whereas 13% had involvement of both hemifields. The most common pattern of field loss was deepening of an existing scotoma, which was later confirmed using static perimetry. Boden et al found that early glaucomatous field loss rarely crosses the horizontal midline. In a cross-sectional analysis that included patients with mild to severe glaucoma, they found a prevalence of 30% of VF defects across the horizontal meridian, 90% of which could be explained by changes at the optic nerve head (ONH) as assessed using stereophotography. The definition used in their study implied that the superior and inferior affected sectors should be adjacent to the horizontal midline (Figure, C). The present study did not require VF defects to be adjacent to the midline and contiguous, a clinical characteristic that may be found more commonly in practice (Figure, D). Although it has been suggested that worse functional damage (MD) is associated with an increased risk of progression, the present findings suggest that it is also possible to determine different levels of risk based on the extent and location(s) of the defect, even when the VF damage is mild. Despite initially having similar global field damage, damage to both hemifields suggests that more widespread structural and functional abnormality is present, which increases the susceptibility to progression.

Experimental models have been developed to try to clarify the pathogenesis of glaucomatous damage and progression. There is strong evidence that damage to the retinal ganglion cell axons, which ultimately converge to the ONH, is the key cause of vision loss in glaucoma. Burgoine and Downs reviewed this issue and proposed that alterations in ONH biomechanics underlie the clinical behavior and likely increased susceptibility of the ONH. That is, a more damaged optic nerve would be more susceptible to future damage. Quigley et al suggested that the structure of the lamina cribrosa is an important determinant of the degree of susceptibility to damage by elevated IOP. Jonas et al showed a correlation between the progression of VF defects and the morphologic features of the lamina cribrosa and suggested that a larger single pore area increased glaucoma susceptibility in the inferior and superior disc regions.

We hypothesized that the presence of damage to both hemifields may reflect greater overall optic nerve susceptibility to glaucoma (in both the superior and inferior poles rather than localized to one location), which resulted in the accelerated rate of progression found in this study. Because we did not address this issue directly, further studies to assess structural characteristics of the ONH and lamina cribrosa in eyes with faster progression rates are necessary to confirm this hypothesis.

To support this hypothesis, Demirel et al recently assessed the role of baseline perimetry data in predicting future progression. They found that depressed VF

### Table 3. Cox Proportional Hazards Including Each Variable Independently (Univariate Model)

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.01 (0.99-1.03)</td>
<td>.10</td>
</tr>
<tr>
<td>MD</td>
<td>1.05 (0.94-1.17)</td>
<td>.27</td>
</tr>
<tr>
<td>No. of points with P&lt;1%</td>
<td>1.01 (0.97-1.05)</td>
<td>.54</td>
</tr>
<tr>
<td>CCT, per 40-µm decrease</td>
<td>1.32 (1.08-1.61)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Baseline IOP</td>
<td>1.08 (1.03-1.13)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Exfoliation syndrome</td>
<td>1.11 (0.63-1.96)</td>
<td>.70</td>
</tr>
<tr>
<td>Baseline damage to both hemifields</td>
<td>1.58 (1.07-2.32)</td>
<td>.02</td>
</tr>
</tbody>
</table>

Abbreviations: CCT, central corneal thickness; CI, confidence interval; HR, hazard ratio; IOP, intraocular pressure; MD, mean deviation.

### Table 4. Cox Proportional Hazards (Multivariate Model)

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCT, per 40-µm decrease</td>
<td>1.27 (1.04-1.54)</td>
<td>.02</td>
</tr>
<tr>
<td>Baseline IOP</td>
<td>1.07 (1.02-1.12)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Baseline damage to both hemifields</td>
<td>1.62 (1.09-2.39)</td>
<td>.01</td>
</tr>
</tbody>
</table>

Abbreviations: CCT, central corneal thickness; CI, confidence interval; HR, hazard ratio; IOP, intraocular pressure.

The χ² test showed significant differences between groups (P<.01).


determine the role of IOP even in a treated population with statistically normal pressures.

Age was not a significant risk factor in the final multivariate model, suggesting that other factors, such as disease stage, treatment, and other covariates, may play stronger roles in predicting progression in this treated population. In its first report, the EMTG also found a 7% increased risk of progression for each additional 1 mm Hg of IOP and a 23% increased risk per 40-µm decrease in CCT. The Diagnostic Innovations in Glaucoma Study also found a 7% increased risk of progression for each additional 1 mm Hg of IOP and a 62% increase for each 40-µm decrease in CCT in a group of patients with early glaucoma damage. The present study reemphasizes the role of IOP even in a treated population with statistically normal pressures.

The nature of glaucoma pathogenesis and functional and structural associations in glaucoma may help explain the increased risk associated with VF loss in both hemifields. Glaucomatous functional damage usually respects the horizontal meridian and the anatomy of the retinal nerve fiber layer. In 1984, Mikelberg and Drance reviewed the pattern of VF progression using static and kinetic perimetry and found that 70% of eyes had initial damage limited to a single hemifield; at the completion of follow-up, 57% still had only single-hemifield involvement, whereas 13% had involvement of both hemifields. The most common pattern of field loss was deepening of an existing scotoma, which was later confirmed using static perimetry. Boden et al found that early glaucomatous field loss rarely crosses the horizontal midline. In a cross-sectional analysis that included patients with mild to severe glaucoma, they found a prevalence of 30% of VF defects across the horizontal meridian, 90% of which could be explained by changes at the optic nerve head (ONH) as assessed using stereophotography. The definition used in their study implied that the superior and inferior affected sectors should be adjacent to the horizontal midline (Figure, C). The present study did not require VF defects to be adjacent to the midline and contiguous, a clinical characteristic that may be found more commonly in practice (Figure, D). Although it has been suggested that worse functional damage (MD) is associated with an increased risk of progression, the present findings suggest that it is also possible to determine different levels of risk based on the extent and location(s) of the defect, even when the VF damage is mild. Despite initially having similar global field damage, damage to both hemifields suggests that more widespread structural and functional abnormality is present, which increases the susceptibility to progression.

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### Table 2. Distribution of Eyes Based on Rates of Visual Field Progression

<table>
<thead>
<tr>
<th>Rate of Progression</th>
<th>Group A (n=79)</th>
<th>Group B (n=61)</th>
<th>Group C (n=65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fast (&gt;1.5 dB/y)</td>
<td>5 (6.3)</td>
<td>2 (3.3)</td>
<td>13 (20.0)</td>
</tr>
<tr>
<td>Moderate (0.5-1.5 dB/y)</td>
<td>27 (34.2)</td>
<td>17 (27.9)</td>
<td>28 (43.1)</td>
</tr>
<tr>
<td>Slow (&lt;0.5 dB/y)</td>
<td>47 (59.5)</td>
<td>42 (68.8)</td>
<td>24 (36.9)</td>
</tr>
</tbody>
</table>

Abbreviations: CCT, central corneal thickness; CI, confidence interval; HR, hazard ratio; IOP, intraocular pressure.
locations close to the midline, mostly in the superior and inferior nasal sectors, are most predictive of future progression. If this is the case, eyes with abnormal points in both hemifields would have a summed effect of susceptibilities from different VF sectors. Similarly, Pascual et al28 showed a spatial relationship between initially defective locations found at baseline and those found on subsequent testing. The authors described superior defects related to progression in the superior field, resembling the nerve fiber bundle patterns, whereas the inferior defects did not show clearly specific patterns of progression. These studies may help explain why fewer eyes with baseline damage limited to the inferior hemifield reached a progression end point in the present study.

We chose to use PLR rather than event analysis in this study for several reasons. First, the commercially available software provides automated values that can be easily determined and reproduced at different medical centers. Second, in contrast to other methods that have been proposed for major clinical trials, PLR can determine the rate of VF loss globally, by sector, or at individual points with decreased subjectivity.30 Finally, the larger number of VFVs required for PLR enhances specificity.30

This study has several limitations. Enrolling eyes with mild functional damage limits the conclusions to this specific population. However, eyes with moderate or severe VF damage often have damage to both hemifields, making identification of a comparable group with damage to one hemifield more difficult. The use of PLR may have provided a more sensitive method of progression than is typically used in clinical practice. As in most clinical studies, we analyzed the predictive value of baseline characteristics (level of damage, CCT, age, IOP, and exfoliation glaucoma).6-10 However, reassessment and reevaluation of risk factors during treatment (intercurrent risk factors) might provide more important information than the initial baseline risk factor assessment. In clinical practice, physicians constantly adjust risk profiles as information becomes available (eg, advancing age and a major cardiovascular event), and the use of a continuous and dynamic measure of progression (expressed as rates) may be particularly helpful in these circumstances. Last, the retrospective nature of this study design and the tertiary care setting create certain biases in patient selection. The long-term follow-up and the similar characteristics among the study groups (age, IOP, CCT, and treatment) serve to mitigate potential bias and suggest that such bias likely did not significantly affect the results. Despite the retrospective nature of this study, the consonance of these results with the major prospective clinical trials serves to confirm the validity of the data set.

In a treated glaucoma population, assessing other variables that could be associated with faster rates of disease progression may help direct future management and aggressiveness of treatment. In these patients with early and similar baseline VF damage, eyes with defects involving both hemifields progressed more quickly and were more likely to reach a predefined end point than were those with a single affected hemifield. For the practicing physician, these findings suggest that a lower target IOP may be warranted for patients with initial, reproducible damage extending to both hemifields.

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Correspondence: Jeffrey M. Liebmann, MD, 310 E 14th St, New York, NY 10003 (jml18@earthlink.net).

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REFERENCES


Cavernous Hemangioma of the Retina
Stephen Jae Kim, MD

Figure 1. Composite color fundus photograph of the left eye of a 13-year-old healthy white girl who presented with vitreous hemorrhage. The photograph shows the characteristic appearance of a cavernous hemangioma of the retina with thin-walled, saccular aneurysms partly covered by a fine glial membrane.

Figure 2. Composite fluorescein angiogram demonstrating grapelike clusters of aneurysms, some with sedimented blood in the lower half and clear serum in the upper half (arrow), indicating low perfusion. There was a corresponding ipsilateral cavernous malformation in the corpus callosum.