Improvement of the visual field index in clinical glaucoma care

Shawn L. Cohen, MDCM,* Aaron I. Rosen, MDCM,* Xianming Tan, PhD,†
Frederick A.A. Kingdom, PhD‡

ABSTRACT

Objective: This article investigates the prevalence and attributes of patients with open-angle glaucoma who exhibit improvement of visual field loss in a clinical setting.

Design: We conducted a retrospective chart review of patients in a clinical glaucoma practice.

Participants: We identified 719 glaucoma patients with at least 5 SITA strategy visual field tests and a minimum continuous follow-up period of 5 years.

Methods: The change in the slope of the visual field index (VFI) over time was illustrated using histogram analysis for the study eye with the worst VFI at baseline. Multiple variables were analyzed to determine their impact on rates of visual field progression, including sex, age, disease staging, intraocular pressure (IOP), and incisional surgeries. Eyes with severe nonophthalmic and ophthalmic comorbidities were excluded.

Results: Considering 582 eligible eyes, 232 (39.9%) showed significantly positive slopes of the VFI as a function of time, 76 (13.1%) showed nonsignificant slopes, and 276 (47.4%) showed significantly negative slopes. In all, 10 eyes (1.7%) demonstrated VFI slope improvement of ≥2% per year, whereas 21 (3.6%) demonstrated VFI slope reduction ≥2% per year. More advanced disease stage was significantly associated with a negative VFI slope (p < 0.0001). Trabeculectomy and poor compliance were not associated with a negative VFI slope, whereas cataract surgery correlated with higher odds of a negative VFI slope (p = 0.048).

Conclusions: In a clinical setting, a significant VFI improvement over time was observed over an interval of greater than 5 years.

Much of the clinical practice in open-angle glaucoma (OAG) focuses on the reduction of intraocular pressure (IOP) to stabilize optic nerve and visual field (VF) deterioration. Unfortunately, reversal of optic nerve cupping and improvement of VF loss do not constitute current therapeutic endpoints. Although data on optic nerve cupping reversal are sparse,1–3 the improvement of the VF over a time span of 5 years or more was noted in prominent clinical trials and longitudinal studies and appears independent of any learning effect.4–5 With the introduction of the visual field index (VFI), the entire visual field is represented by a new global measurement that weighs central points more strongly than peripheral points to correlate with structural representation and to allow the user to plot VFI changes as a function of age.6 Use of the VFI parameter is advantageous over the mean deviation because the VFI is less sensitive to the influence of cataracts and cataract surgery.6–7 To date, the impact of IOP reduction, disease stage, and surgical intervention on the long-term VFI progression rate remains uncertain.

We hypothesize that VF improvement in a clinical population, defined as a positive slope of the VFI, occurs with a clinically relevant prevalence that may be sustained over a long-term period. We set out to determine the rate
of change of VF using the slope of the VFI as a function of age, spanning a time period of greater than 5 years, to identify associations with demographic variables, disease stage, IOP, surgical intervention, and adherence to established Canadian guidelines for OAG.8

Methods
This study was conducted after approval was obtained from the Institutional Review Board and Ethics Committee of the Research Institute of the McGill University Health Center. All study procedures conformed to the tenets of the Declaration of Helsinki for research involving human subjects.

A retrospective chart review and visual field analysis of all OAG subjects in a clinical practice of approximately 77,000 subjects meeting the visual field criteria included a review of glaucoma type, demographic data, IOP at each visit, the presence of ophthalmic and/or nonophthalmic comorbidities, surgical and/or laser intervention, and clear indications of noncompliance to therapy. Using regularly calibrated (at least every 3 months) Goldmann tonometry, 1 author (S.L.C.) obtained all IOP measurements over time and each IOP measurement was recorded at each visit and for each eye. For each eye, mean IOP was calculated after removing the first 3 IOP measurements of that eye in order to obtain a lower variability of the mean follow-up IOP. The same author (S.L.C.) performed the selective laser trabeculoplasty (SLT) in all cases, using the Coherent laser (Selecta 7000; Coherent Medical Group, Santa Clara, CA). The same author (S.L.C.) performed the cataract surgery, trabeculectomy (limbal-based in all cases), and combined phacotrabeculectomy (1 site, in all cases).

For each study eye, primary outcomes were the VFI slope (expressed as %/year) and its associated standard deviation, together with the baseline mean deviation value (expressed in dB) that was obtained with the FORUM software (Version 3.1.1; Carl Zeiss Meditec Inc). A VFI slope was claimed as significantly different from 0 if the reported 95% confidence interval for the VFI slope did not include 0.

Descriptive analysis was conducted on all demographic data. Homogeneity of demographical variables between subgroups (e.g., disease severity groups) was examined by Wilcoxon Rank Sum test for numerical variables or by Fisher’s exact test for categorical variables. Comparisons between subgroups were carried out using a 2-sided test at an alpha level of 5%. Using a multiple linear regression analysis, we also assessed the impact of age, sex, and mean IOP on VFI reversal, stratified according to disease severity as per the Canadian guidelines.8 We conducted a multinomial logistic regression analysis in which slope trend (positive/zero/negative) was the multinomial outcome, and IOP on VFI reversal, stratified according to disease severity as per Canadian guidelines.8 All statistical analysis was performed using SAS Version 9.3 (SAS Institute, Cary, NC).

Results
We identified 719 subject files with 1 or 2 eyes that met the inclusion criteria for this study. Of these, 104 subjects demonstrated macular, media, vascular, or retinal detachment comorbidities and were excluded from the study. An additional 33 eyes with comorbidities in 1 eye had insufficient data in the unaffected eye. As per Canadian guidelines for staging in OAG,8 all remaining 582 eligible eyes (without comorbidities) were categorized by disease stage. There were no sex differences between subject groups (p = 0.22) or age of subjects at the latest visit (p = 0.61). Disease stage was significantly associated with lower achieved mean IOP for more advanced glaucoma stages (p < 0.001) (Table 1).

A total of 582 study eyes were identified, of which 289 were right eyes and 293 were left eyes. A total of 232 (39.9%) study eyes showed significantly positive slopes of

### Table 1—Demographics

<table>
<thead>
<tr>
<th></th>
<th>Suspect (n = 40)</th>
<th>Mild (n = 128)</th>
<th>Moderate (n = 152)</th>
<th>Severe (n = 262)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>VFI slope</td>
<td>−0.02 (1.71)</td>
<td>0.09 (0.71)</td>
<td>−0.19 (1.09)</td>
<td>−0.45 (1.48)</td>
<td>0.00</td>
</tr>
<tr>
<td>Follow-up time in days</td>
<td>2771 (792)</td>
<td>2641 (708)</td>
<td>2576 (717)</td>
<td>2621 (709)</td>
<td>0.57</td>
</tr>
<tr>
<td>Mean IOP</td>
<td>17.2 (2.90)</td>
<td>14.5 (2.16)</td>
<td>13.9 (2.12)</td>
<td>13.96 (2.65)</td>
<td>0.00</td>
</tr>
<tr>
<td>Age at last visit, years</td>
<td>72.48 (9.2)</td>
<td>71.73 (11.0)</td>
<td>70.75 (11.3)</td>
<td>72.03 (12.6)</td>
<td>0.61</td>
</tr>
</tbody>
</table>

*The values are mean ± SD. Study eye visual field index (VFI) slope (% change/year), follow-up time (days), mean intraocular pressure (IOP; mm Hg), and age at last visit as a function of Canadian guideline stages for open-angle glaucoma.8*
the VFI as a function of time, 76 (13.1%) showed nonsignificant slopes, and 276 (47.4%) showed significantly negative slopes (Fig. 1). There was no significant difference between study eye and control eye in terms of VFI slope ($p = 0.158$). In all, 29 study eyes (5.0%) demonstrated a VFI improvement of $\geq 1\%$ per year and 10 (1.7%) $\geq 2\%$ per year. A total of 21 study eyes (3.6%) demonstrated VFI slope deterioration of $\geq 2\%$ per year. In the severe glaucoma group, 12 study eyes (4.6%) demonstrated $\geq 1\%$ per year VFI improvement. An example of a study eye with positive VFI slope is shown in Figure 2.

The study eyes had a mean IOP of $14.0 \pm 2.6$ mm Hg (median = 13.6 mm Hg), and mean VFI of $85.6 \pm 19.9$ (median = 94.5). An average of $7.9 \pm 2.5$ (median = 7.0) VFI measurements were done for each study eye. This corresponded to $1.24 \pm 0.76$ (median = 1.1) VFI measurements per year. Study eyes with positive slopes had lower total number of VFI tests ($p = 0.0137$) and a lower mean number of VF per year ($p < 0.0001$) compared with subjects in the nonsignificant and negative slope groups. The positive VFI group experienced a mean of $7.5 \pm 2.2$ (median = 7) VF over the study period, compared with $8.2 \pm 2.4$ (median = 8) and $8.2 \pm 2.7$ (median = 8) in the nonsignificant and negative slope groups, respectively.

Multivariate analysis demonstrated significantly higher odds of having negative VFI slopes in subjects who underwent cataract surgery ($n = 286$ eyes; $p = 0.048$). No study eye received multifocal intraocular lens implants. Disease stage was significantly associated with VFI slope, with severe stage associated with a negative VFI slope, in comparison to mild stages ($p < 0.0001$) (Fig. 3). We did not find statistically significant associations between VFI slope and trabeculectomy surgery ($n = 268$ eyes; $p = 0.77$), SLT ($n = 23$ eyes; $p = 0.14$), subjects with documented poor glaucoma eye drop compliance ($n = 25$ eyes; $p = 0.74$), and mean deviation $< 20$ dB in this multivariate analysis ($n = 23$; $p = 0.70$).

**DISCUSSION**

Much of the clinical practice in glaucoma focuses on the reduction of IOP in order to stabilize optic nerve and VF deterioration, with very few studies specifically attempting to address the prevalence of VFI improvement over an interval of greater than 5 years that was most prominent in advanced glaucoma. The significant VFI improvement over time in 39.9% of eyes greatly exceeds the 13.9% improvement noted at 5 years and 19.6% at 7 years in the Collaborative Initial Glaucoma Treatment Study (CIGTS). The magnitude of the VFI improvement of 5.0% of advanced glaucoma subjects with a VFI improvement of $\geq 1\%$ per year suggests an important clinical impact of this observation. In a longitudinal quality of life study, each 1 dB in binocular mean sensitivity loss was significantly associated with a change of 2.9 units in the NEI VFQ-25 scores during the follow-up period of $3.5 \pm 0.7$ years. In a cross-sectional study, the VFI correlated better than mean deviation with quality of life assessment.

Visual field parameters and testing factors can impact the results of longitudinal studies. The SITA Fast strategy may be slightly less sensitive than the SITA Standard, yet the relative changes in VFI over time would be expected to be either suppressed or unaffected by the testing method if conducted over a longer time period and a sufficient number of VFs are performed to account for such imprecisions and variabilities. Although a possible influence of the testing strategy used might result in variability that could explain a higher prevalence of positive slopes, our incorporation of the standard deviation analysis to determine significance should account for this variability over time, as higher variability contributes to slope non-significance. VFI improvement over time, independent of learning, was observed in a similar study by Heijl et al. that only included subjects with VF defects.

Considering the retrospective nature of the study, several biases may occur. Subjects with improvement of the VFI over time are less likely to undergo repeated VFI measurements when compared with less stable subjects in whom frequent treatment effects on VF slopes are evaluated. Yet, this effect was small as all subjects shared greater than 5 VF examinations (median of 7 in positive VFI group vs 8 in the remaining study eyes). Although repeated VF testing might alter the standard deviation, it is
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Fig. 2—Visual field index (VFI) improvement sample. An improvement of the VFI slope of $+2.5\% \pm 1.6\%$/year is noted over a time span of 10 years and 8 visual fields, including the 2 baseline visual field examinations.

more likely that repeated confirmation of a defect would result in greater odds of slope significance, which would favour the negative slope subjects, although an impact on the significance of positive slope subjects cannot be ruled out. Although a single individual obtained all measurements and performed all procedures, a team of experienced technicians masked to the VFI slope and trends performed the VF examinations.

The retrospective design of the study also precludes causation analysis and introduces selection bias and time-dependent covariance problems for interventions. Although the VFI is less sensitive to the effect of cataract surgery than mean deviation,\textsuperscript{6,7} we observed a significant negative effect on the VFI slope in our study, likely due to an increased prevalence of cataract surgery in the advanced-stage subjects with negative VFI scores who also sustained simultaneous trabeculectomy surgery. The impact of SLT or trabeculectomy on the VFI would vary depending on how long after the intervention the measurements were made, though no correlation with VFI slope was observed in the present study. Pre- versus postintervention analysis was not feasible as, in most cases, insufficient data were available. The selection bias of waiting to perform glaucoma surgery only after a significant loss of IOP control with medical therapy or a perceived true trend in VFI reduction might act to reduce the impact of trabeculectomy on the reversal of the VFI. Any improvement of the VFI after trabeculectomy might
contribute to an increase in the standard deviation of VFI slope and thus nonsignificance, a complete reversal of a downward trend of VFI slope, or a slowed but still significant deterioration of the VFI over time. A prospective and randomized design would be better suited to analyze the impact of trabeculectomy of the VFI slope over time. In a retrospective study by Caprioli et al., patients who underwent trabeculectomy demonstrated a long-term improvement of 44% of locations in the visual field over a mean follow-up period of 5.1 ± 2.1 years.¹²

It is of interest to note that, in 1 case, the performance of a trabeculectomy in the left eye resulted in a visually striking improvement in the optic nerve head configuration in the operated eye, noted over a time interval of 10 years (Fig. 4). The mean IOP was 14.4 mm Hg in the right eye and 16.5 mm Hg left eye pretrabeculectomy versus 7.3 mm Hg posttrabeculectomy. The VFI was unchanged in either eye (−0.3% ± 1.0% per year in the right eye and −0.2% ± 1.2% per year in the left eye) and the VFI remained stable in a range of 89%–96% in the operated left eye (Fig. 5). Future studies aimed at correlating visual field improvement from baseline or reversal of a downtrend should incorporate optic nerve head analysis to corroborate these findings.

The question remains whether the low mean IOP in this study might explain the higher prevalence of VFI improvement. Because the treatment strategy in the study population was designed to keep the target IOP at or below Canadian guidelines, the low mean IOP of study...
subjects and the high prevalence of near-zero VFI slopes, despite the 47.4% prevalence of negative slopes, might reflect an impact of such guidelines on VF outcomes. In fact, the effect of IOP on VF progression was noted in another large Canadian population study. In this study by Balwantray et al., there was a mean follow-up IOP of 17.1 mm Hg that was associated with less reduction of the mean deviation, although this was calculated to account for only 0.1–0.2 dB/year of the observed 0.5 dB/year difference in the mean deviation rate. The high percentage of positive VFI slopes from our current study results might be explained by the much lower mean IOP of 14.0 ± 2.0 mm Hg, which was intentionally targeted, compared to the 18.1 mm Hg in the Heijl et al. or 17.1 mm Hg in the Balwantray et al. studies. A dose-dependent effect was noted in CIGTS with the lowest maximum IOP (< 13 mm Hg), an effect that was associated with an average of 18.7% of visits showing a substantial gain in mean deviation, compared with 13.4%, 10.6%, and 8.0% in subjects with maximum IOP of 14–17, 18–21, and ≥ 22 mm Hg, respectively.

In summary, VFI improvement occurs with a clinically relevant prevalence and is sustainable over a period of greater than 5 years. With the lower mean IOP observed in our study versus historical data, the effect of IOP reduction on VFI improvement deserves further study to establish a causal link. Specific revision of the target IOP ranges might allow for the prospective study of IOP therapeutic impact of medical and/or surgical intervention through the use of visual field improvement as a therapeutic endpoint.

REFERENCES


Fig. 5—Unchanged visual field index (VFI) slope in either eye of study subject M.M. despite optic nerve head reversal of cupping in the left eye.
Footnotes and Disclosure:

The authors have no proprietary or commercial interest in any materials discussed in this article.

From the *McGill University, Montreal, Que; †University of North Carolina, Chapel Hill, North Carolina.

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Correspondence to Shawn L. Cohen, MDCM, McGill University, 1414 Drummond, Suite 322, Montreal, Que. H3G 1W1; shawn.cohen@mcgill.ca