Behavior of Visual Field Index in Advanced Glaucoma

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Purpose. To evaluate the magnitude of Visual Field Index (VFI) change attributable to change in the estimation algorithm from the pattern deviation probability plot (PDPP) to the total deviation probability plot (TDPP) when the mean deviation (MD) crosses −20 decibels (dB).

Methods. In a retrospective study, 37 stable glaucoma eyes in which MD of the VFs crossed −20 dB were identified. For each eye, a pair of VFs was selected so that one VF of the pair had a MD better than but close to −20 dB and the other had a MD worse than but again close to −20 dB. The change in VFI in the VF pairs and its associations with the number of points in probability plots with normal threshold sensitivities were evaluated. Similar pairs of VFs from 28 stable glaucoma eyes where the MD crossed −10 dB were chosen as controls.

Results. The change in VFI in VF pairs when the MD crossed −20 dB ranged from 3% to 33% (median: 15%), while the change when MD crossed −10 dB ranged from 1% to 8% (median: 4%). Difference in the number of points with normal threshold sensitivities in PDPP when MD was better than −20 dB compared to those in TDPP when MD crossed −20 dB significantly influenced the VFI change ($R^2 = 0.65$). Considering the eccentricity of these points further explained the VFI change ($R^2 = 0.81$).

Conclusions. The decrease in VFI when MD crosses −20 dB can be highly variable. This has to be considered with the use of VFI in clinical and research settings. (*Invest Ophthalmol Vis Sci.* 2013;54:307–312) DOI:10.1167/iovs.12-10836

The recently introduced Guided Progression Analysis (GPA) by the Humphrey Visual Field (HVF) Analyzer (Carl Zeiss Meditec, Inc., Dublin, CA) provides a new global index of the visual function of the eye called Visual Field Index (VFI). Details of the calculation of the VFI have been described elsewhere.[1] In brief, VFI is the aggregate percentage of visual function for a given field at each point where the visual thresholds are estimated. VFI is calculated from the pattern deviation probability plot (PDPP) in eyes with a mean deviation (MD) better than −20 decibels (dB) and from the total deviation probability plot (TDPP) in eyes with a MD worse than −20 dB. The central points have more weight than the peripheral points. The VFI can range from 100% (normal visual field) to 0% (perimetrically blind field).[1] The VFI has been shown to be less susceptible than the MD to the effects of cataract or diffuse media opacities.[1,2] VFI is intended for use in calculating rates of progression and staging glaucomatous functional damage.

Since its introduction, numerous studies have used VFI to quantify the amount of visual function remaining in an eye.[3–13] However, little is known about the behavior of VFI when the estimation of VFI changes from PDPP to TDPP as the MD crosses the −20 dB threshold. Bengtsson and Heijl in their original article on VFI mentioned that "shifting from pattern deviation probabilities to total deviation probabilities for identification of depressed points is likely to result in a slight stepwise worsening of VFI near MD values of −20 dB."[1] The purpose of the present study was to evaluate the magnitude of change in VFI that can occur when the MD crosses −20 dB and the factors that accounted for this change.

Methods

Patients for the study were selected from the database of all primary glaucoma patients with five or more VFs between September 1989 and March 2011, who were treated by a single physician at our institute. Characteristics of the patients in the database were described earlier.[8] The collection of data was approved by the ethics committee of L V Prasad Eye Institute, and written informed consent obtained from all subjects. All methods adhered to the tenets of the Declaration of Helsinki for research involving human subjects. From the database, eyes of patients in whom the MD of the VFs crossed the −20 dB mark were identified. For each eye, a pair of VFs was selected so that one VF of the pair had a MD better than but very close to −20 dB and the other had a MD worse than but again very close to −20 dB. Both VFs of the pair had to be performed with the 24-2 standard strategy of the Swedish interactive threshold algorithm. If multiple VFs were eligible to be included in the pair, then the two VFs that performed closest to each other in time were selected. As a control cohort, we selected similar pairs of VFs from eyes of patients in whom the MD crossed −10 dB. The clinical impression noted in the medical records of all these eyes by the treating physician was that the glaucoma was stable, and the change in VFs was judged as fluctuations. The GPA classification in the control eyes, in addition, was "no progression detected."

As PDPP is considered for the estimation of VFI in VFs with MD better than −20 dB and TDPP in VFs with MD worse than −20 dB, we concentrated on these plots to evaluate the factors affecting the VFI estimation in the pairs of VFs. We calculated the number of points having threshold sensitivities within the normal limits ($P > 0.05$) in the PDPP of the VF with MD better than −20 dB and in the TDPP of the VF with MD worse than −20 dB (hereafter called normal points). As the estimation of VFI is also dependent on the eccentricity of the points in the VF, we also separately calculated the number of normal points in each of the five zones of the PDPP and TDPP of the VF pairs (Fig. 1), with zone 1 being the innermost and zone 5 the outermost.

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Submitted for publication August 24, 2012; revised October 22 and November 17, 2012; accepted December 1, 2012.

Disclosure: **H.L. Rao**, Allergan (C); **S. Senthil**, None; **N.S. Choudhari**, None; **A.K. Mandal**, None; **C.S. Garudadri**, Allergan (C), Merck (C), Alcon (C)

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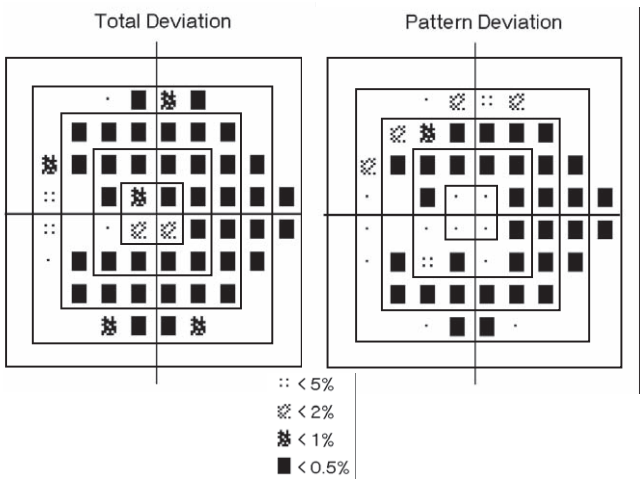

Figure 1. Total and pattern deviation probability plots showing the points flagged off as within normal limits and abnormal at different probabilities. The figure also shows the plots divided by squares into zones depending on the eccentricity of the points, with zone 1 being the innermost and zone 5 the outermost. Note that although a seemingly normal point on the pattern deviation plot can be significantly depressed on the total deviation plot, it is assigned a value of 100% for estimation of Visual Field Index.

Statistical Analysis

Descriptive statistics included mean and standard deviation for normally distributed variables and median and interquartile range (IQR) for non-normally distributed variables. Shapiro-Wilk test was used to test the distribution of the variables. Linear regression models were used to evaluate the factors responsible for the change in VFI in the VF pairs. As both eyes of a few subjects were included for the analysis, a cluster of data for the study subject was considered the primary sampling unit during the estimation of standard errors.[14] Statistical analyses were performed using Stata (version 11.2; StataCorp, College Station, TX). A P value of ≤ 0.05 was considered statistically significant.

Results

Thirty-seven eyes of 34 patients in whom the MD of the VFs crossed −20 dB fulfilled the inclusion criteria. Mean age (± standard deviation) of the patients was 65 ± 11 years. Twenty-three patients (67.7%) were male. MD, pattern standard deviation (PSD), and VFI of the included VFs are shown in Table 1. The change in MD in the VF pairs ranged from 0.24 dB to 3.7 dB (median: 1.49 dB; IQR: 1.02 to 2.64) while the decrease in VFI when the MD crossed −20 dB showed a wide variability ranging from 3% to 33% (median: 15%; IQR: 10 to 18, Fig. 2a). Median duration between the VFs of the pair was 1.5 years (IQR: 0.9 to 2.2 years). Twenty-eight stable glaucoma eyes from 26 patients in whom the MD crossed −10 dB were

Table 1. Characteristics of the Visual Fields (VF) of the Pair

	VF with MD Better Than −20 dB	VF with MD Worse Than −20 dB
Fixation losses (%)	0 (0, 6)	0 (0, 6)
False-positive responses (%)	1 (0, 2)	1 (0, 2)
False-negative responses (%)	0 (0, 6)	0 (0, 0)
MD (dB)	−19.56 (−19.76, −19.08)	−20.82 (−21.31, −20.32)
PSD (dB)	10.80 (9.87, 12.26)	10.41 (9.08, 11.34)
VFI (%)	51 (47, 54)	35 (33, 39)

Numbers indicate median with interquartile range in brackets.

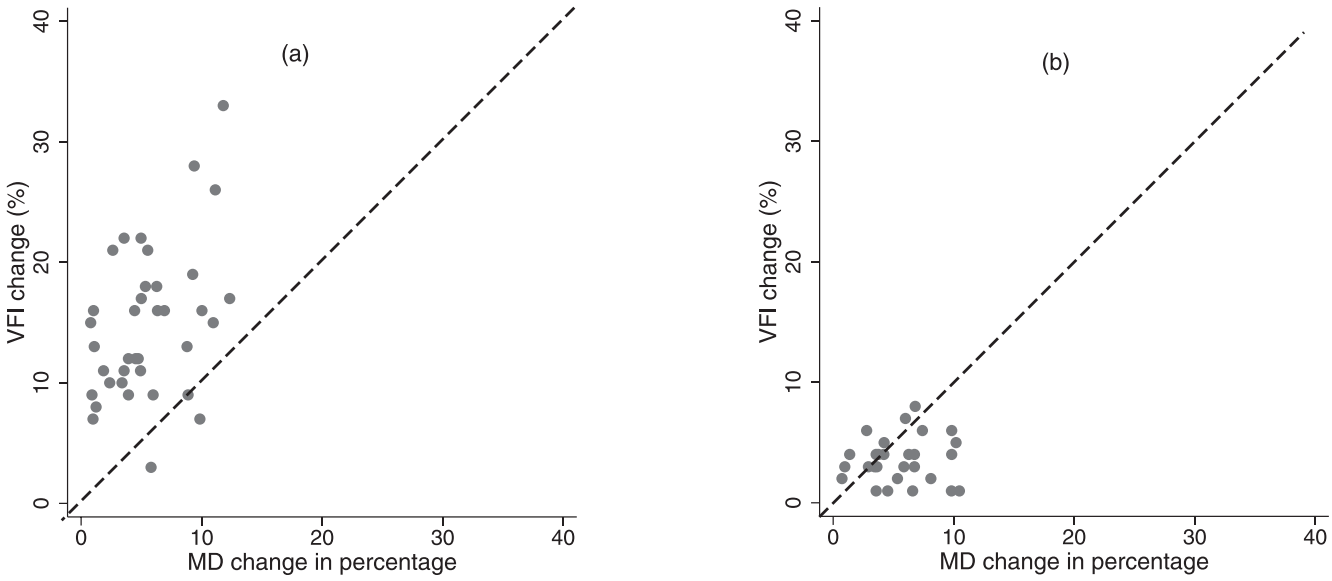

Figure 2. Relationship between the change in Visual Field Index (VFI) and change in mean deviation (MD) in the group of eyes where the MD crossed −20 dB (**a**) and in the control eyes where the MD crossed −10 dB (**b**). To make the comparison meaningful, the change in MD has been scaled in percentage, considering 0 and −30 dB loss as 0% and 100% loss, respectively.

Table 2. Median (with Interquartile Range) and Range of the Number of Points with Threshold Sensitivities within Normal Limits in the PDPP of the VF with MD Better Than −20 dB and TDPP of the VF with MD Worse Than −20 dB

	Number of Normal Points in PDPP of VF with MD Better Than −20 dB		Number of Normal Points in TDPP of VF with MD Worse Than −20 dB		Difference in the Number of Normal Points between PDPP of VF with MD Better Than −20 dB and TDPP of VF with MD Worse Than −20 dB	
	Median	**Range**	**Median**	**Range**	**Median**	**Range**
Zone 1	2 (2, 3)	0–4	0 (0, 0)	0–1	2 (2, 3)	0–4
Zone 2	4 (3, 6)	0–8	0 (0, 0)	0–2	4 (3, 5)	0–8
Zone 3	4 (3, 6)	0–10	0 (0, 0)	0–2	4 (3, 6)	0–10
Zone 4	6 (4, 7)	0–8	0 (0, 0)	0–4	5 (3, 7)	0–8
Zone 5	0 (0, 0)	0–2	0 (0, 0)	0–0	0 (0, 0)	0–2
Entire plot	16 (13, 19)	8–26	0 (0, 1)	0–6	16 (12, 19)	7–26

Zones 1 to 5 represent the five zones of the probability plots, with zone 1 being the innermost and zone 5 being the outermost (refer to Fig. 1).

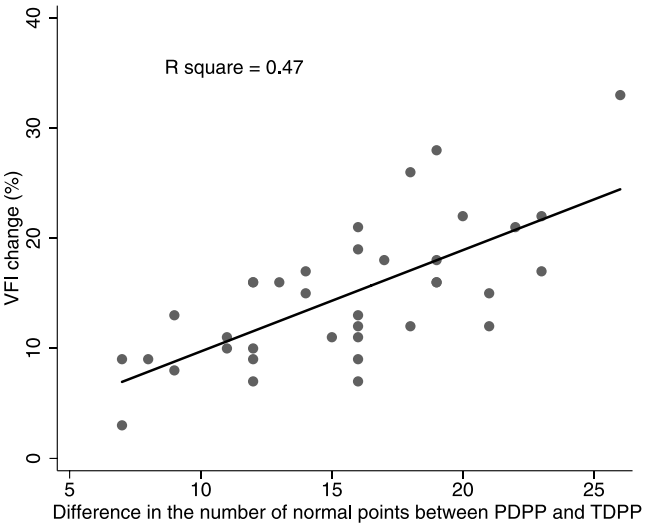

Figure 3. Relationship between the change in Visual Field Index (VFI) and difference in the number of points with threshold sensitivities within normal limits (referred to as normal points) between the pattern deviation probability plot of visual field (VF) with mean deviation (MD) better than −20 dB (PDPP) and the total deviation probability plot of VF with MD worse than −20 dB (TDPP).

chosen as control eyes. Mean age (± standard deviation) of the control patients was 58 ± 11 years. Seventeen patients (65.4%) were male. The MD and VFI change in the VF pairs of control eyes ranged from 0.22 to 3.14 dB (median: 1.68 dB; IQR: 1.07 to 2.13) and 1% to 8% (median: 4%; IQR: 2–5), respectively (Fig. 2b). Median duration between the VFs of the pair was 1 year (IQR: 0.6 to 1.3 years). The variability in VFI was significantly less around a MD of −10 dB compared to that around −20 dB ($P < 0.001$, Wilcoxon rank-sum test).

We first evaluated if the change in VFI in the VF pairs where the MD crossed −20 dB was explained by the change in MD. For every dB change in MD, VFI changed by 2.6% ($P = 0.01$). However, change in MD explained only 16% of the variability of the VFI change (coefficient of determination, $R^2 = 0.16$).

We then investigated if the VFI change when the MD crossed −20 dB was explained by the difference in the number of normal points between the PDPP of the VF with MD better than −20 dB and the TDPP of the VF with MD worse than −20 dB. Table 2 shows the number of normal points in the PDPP of the VF with MD better than −20 dB and the TDPP of the VF with MD worse than −20 dB. For every one normal point less in the TDPP of the VF with MD worse than −20 dB compared to the PDPP of the VF with MD better than −20 dB, the VFI decreased by 0.9% (Fig. 3). Difference in the number of normal points between PDPP and TDPP of the VF pairs explained 47% of the variability in VFI change, and together with the change in MD, it explained 65% of the variability in VFI change. Change in MD was not associated ($P = 0.93$) with the difference in the number of normal points between PDPP and TDPP of the VF pairs.

Knowing that the difference in the number of normal points between PDPP and TDPP influenced the VFI change, we went on to investigate how the eccentricity of these normal points influenced the VFI change. Table 3 shows the multivariate model evaluating this. Evaluating the difference in the number of normal points zone-wise between the PDPP of VF with MD better than −20 dB and the TDPP of VF with MD worse than −20 dB, along with the MD change, explained 81% of the variability of VFI change. Change in MD was not associated with the difference in the number of normal points

Table 3. Multivariate Regression Model Showing the Effect of Eccentricity of Normal Points on Visual Field Index Estimation

	Coefficient	**95% Confidence Interval**	***P* Value**
MD change	2.67	1.65 to 3.68	<0.001
Difference in the number of normal points in zone 1	1.97	1.25 to 2.69	<0.001
Difference in the number of normal points in zone 2	1.49	0.94 to 2.04	<0.001
Difference in the number of normal points in zone 3	0.78	0.30 to 1.26	0.002
Difference in the number of normal points in zone 4	0.66	0.14 to 1.19	0.02
Difference in the number of normal points in zone 5	0.45	−1.97 to 2.87	0.71
Intercept	−6.49	−11.31 to −1.66	0.01

Difference in the number of normal points in zones represents the difference in the number of points with threshold sensitivities within normal limits between the pattern deviation probability plot of the visual field (VF) with mean deviation (MD) better than −20 dB and total deviation probability plot of the VF with MD worse than −20 dB.

Zones 1 to 5 represent the five zones of the probability plots, with zone 1 being the innermost and zone 5 being the outermost (refer to Fig. 1).

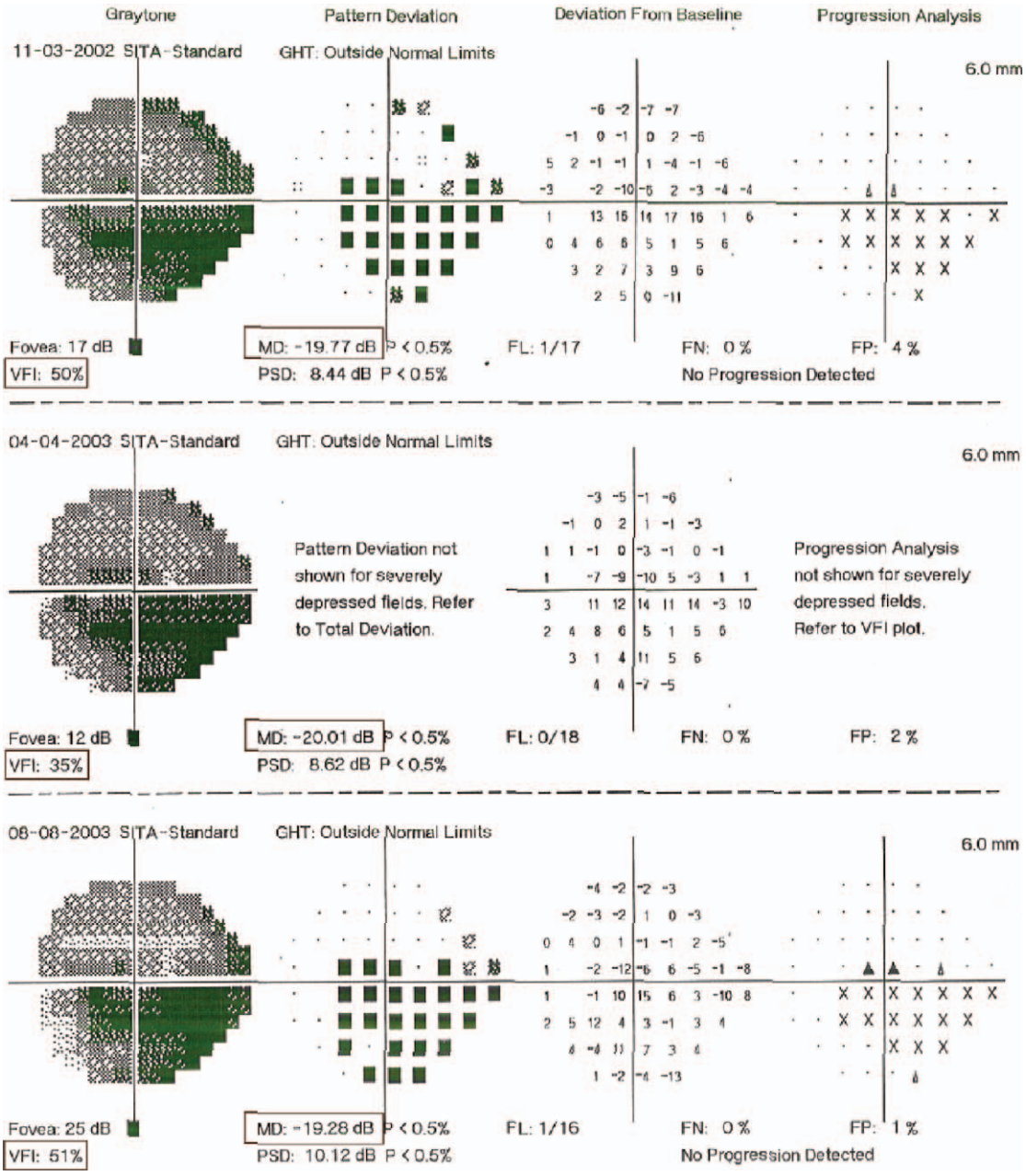

Figure 4. Stable visual fields of an eye showing little fluctuation in mean deviation (MD) and a significant change in Visual Field Index (VFI).

between the PDPP and TDPP in any zone ($P > 0.2$ for all comparisons). The regression formula derived from Table 3 to account for the change in VFI could be thus written as –6.49 + 2.67* MD change + 1.97* difference in the number of normal points in zone 1 + 1.49* difference in the number of normal points in zone 2 + 0.78* difference in the number of normal points in zone 3 + 0.66* difference in the number of normal points in zone 4.

Figure 4 shows an example of the MD of a stable glaucoma patient crossing –20 dB during the follow-up visits. While the MD changed very little from –19.77 dB to –20.01 dB, the VFI showed a drastic change from 50% to 35%. When the MD subsequently got better than –20 dB, the VFI again got back to 51%. Figure 5 shows the PDPP of the VF with MD better than –20 dB and the TDPP of the VF with MD worse than –20 dB of the eye seen in Figure 4. The MD change between these two VFs is 0.24 dB, and the difference in the number of normal points between the PDPP and TDPP in zones 1, 2, 3, and 4 are 0, 4, 10, and 7, respectively. Applying the regression equation in Table 3, the VFI change explained by the change in MD and the change in the VFI estimation strategy (from PDPP to TDPP) comes up to 13% (–6.49 + 2.67*0.24 + 1.97*0 + 1.49*4 + 0.78*10 + 0.66*7) and the corrected VFI to 48% instead of the estimated VFI of 35%.

Discussion

In this study, we evaluated the magnitude of change in VFI that occurred when the VFI calculation strategy changed from PDPP to TDPP as the MD crossed –20 dB. We found that the change in VFI was highly variable compared to the change in VFI that occurred around a MD of –10 dB.

Global indices of VFs have always played an important role in summarizing the VF loss in glaucoma. MD and PSD are the two most popular global indices used in clinical practice. However, both of them have limitations. MD is affected by media opacities and by other causes of generalized depression of visual function in addition to glaucoma.[15–18] PSD is less affected by media opacities, but has the disadvantage that it falsely improves as the severity of VF loss increases.[1] VFI was meant to address some of the limitations of MD and PSD; and since its introduction, VFI has been used extensively to quantify the amount of VF loss in clinical studies.[3–13] The results of our study show that a significantly steep step in the VFI scale can occur when MD crosses the −20 dB mark and the VFI estimation strategy changes from PDPP to TDPP.

We also found that the number of points flagged off as within normal limits on the probability plots from which the VFI was estimated had a significant influence on the VFI estimation. The extent of decrease in VFI that occurred when MD crossed the −20 dB mark was decided to a large extent by the difference in the number of points flagged off as within normal limits on the TDPP of the VF with MD worse than −20 dB as compared to the PDPP of the VF with MD better than −20 dB. If the number of normal points on the TDPP of the VF with MD worse than −20 dB was significantly less than that on the PDPP of the VF with MD better than −20 dB, then the change in VFI that occurred due to the change in the VFI estimation strategy was substantial. In addition to this, we found that the eccentricity of the normal points on the probability plots had a significant effect on the extent of change in VFI that occurred when the VFI estimation strategy changed from PDPP to TDPP. To summarize, the fewer the number of normal points on the TDPP of the VF with MD worse than −20 dB compared to the PDPP of the VF with MD better than −20 dB, and the greater this difference in the inner-zone points, the greater the artifactual decrease in VFI because of the change in VFI estimation strategy.

The clinical implications of the behavior of VFI beyond a MD of −20 dB can be significant. In case of a steep step in VFI, the rate of progression calculated using the VFI values would show a steeper downward slope and could lead to a false diagnosis of glaucoma progression. The simple correction formula demonstrated in this study can be a quick and handy tool to calculate the change in VFI due to the change in the VFI estimation strategy from PDPP to TDPP when the MD crosses the −20 dB threshold. However, the validity of the formula needs to be tested further in a separate cohort. Recognition of this behavior of VFI when MD crosses −20 dB can prevent a false call of progression and the accompanying sequence of events like enhancement of therapy or surgery.

Our study has a few limitations. For the study, we chose VFs from eyes in which the MD over the follow-up crossed the −20 dB mark. The clinical impression noted in the medical records of all these eyes by the treating physician was that the glaucoma was stable, and the change in VFs was judged as fluctuations. However, the differences in the MD between the VFs of the VF pair ranged from 0.24 dB to 3.7 dB. Though fluctuations are shown to be significantly larger in eyes with severe glaucoma,[19] the possibility that this change in MD was true progression was difficult to rule out with certainty because of the retrospective nature of the study. Therefore in models investigating the factors responsible for the change in VFI, we also included the MD change as a variable to account for the change in VFI that occurred because of a possible true progression. Though statistically significant, the association between MD change and VFI change in the VF pairs was weak, with the change in MD explaining only 16% of the variability of VFI change. The other possible limitation is that we evaluated only the points

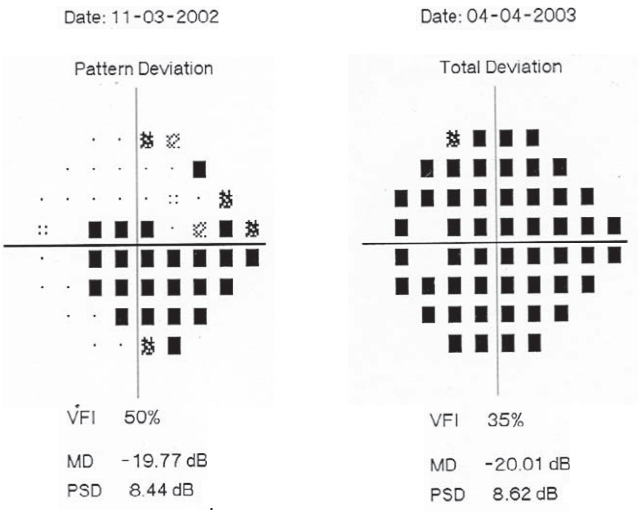

Figure 5. Pattern and total deviation probability plots of two different visual fields of a stable glaucoma patient showing the mean deviation (MD), pattern standard deviation (PSD), and Visual Field Index (VFI). Note that the number of points with threshold sensitivities within normal limits is significantly more in the pattern deviation plot compared to the total deviation plot and therefore the change in VFI (15%) is significant.

that had threshold sensitivities within the normal limits on the probability plots. The reason was that VFI values at these points are considered 100%, so the influence of these points on the VFI estimation is supposed to be significant. Considering the actual threshold sensitivities at the remaining points (points depressed at probability values of less than 5% on the probability plots) would have increased the ability to explain the VFI change. However, we did not evaluate this because it would have been too complicated for use in clinical practice.

In a recent study, Artes et al.[19] demonstrated that VFI, because of its dependence on PDPP, had a ceiling effect that reduced its sensitivity to change in early glaucoma. This, along with our results, which show a significant variability in VFI scale at a MD of −20 dB, indicates that the utility of VFI may be limited at either end of the spectrum of glaucoma severity.

In conclusion, in this study we demonstrated that a significant step can occur in VFI when the VFI estimation strategy changes from PDPP to TDPP as the MD goes beyond the −20 dB mark. We also demonstrated that the major factors responsible for this were the difference in the number of normal points between TDPP of VF with MD worse than −20 dB and PDPP of VF with MD better than −20 dB, as well as the eccentricity of these points. These results have to be considered with the use of VFI in clinical and research settings.

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