A Method to Measure Visual Field Sensitivity at the Edges of Glaucomatous Scotomata

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Purpose. To develop and evaluate a method to map glaucomatous visual field (VF) damage by allocating additional test points to the standard 6° interval VF test pattern, considering the distribution of VF scotomata.

Methods. Subjects comprised 22 glaucomatous patients. Gradients of sensitivity were calculated for "squares" of test points in a patient's 24-2/30-2 VF results, so that the edges of scotomata could be identified where gradients were steep. Next, 10 new VF points were placed in these locations for each patient. Each patient's VF was then measured using this novel test grid (52 standard 24-2 test points and 10 additional points examined concurrently) on two separate occasions. The absolute difference between the measured sensitivity at each new additional test point and the average of the sensitivities of its surrounding four test points was calculated (Δ_{ave}). The intra- and intervisit reproducibility of the additional test points' thresholds was calculated. Finally, fluctuation of overall VF damage was estimated using the intraclass correlation coefficient (ICC) and the coefficient of variation (CV).

Results. The average of the sensitivities (Δ_{ave}) increased as the gradient of the plane steepened, whereas the reproducibility of the additional test points' thresholds remained stable. ICC was significantly higher and CV was significantly lower for the novel test grid compared with the standard 24-2 test pattern.

Conclusions. It may be advantageous to increase the density of VF test points where there are large local differences in VF sensitivity. These additional measurements may result in more reproducible and well-defined estimates of scotomata.

Keywords: glaucoma, visual field, test grid

Glaucoma damages a sufferer's visual field (VF) and is one of the major causes of blindness worldwide.[1,2] It is essential to accurately detect VF progression as early as possible to prevent visual impairment, because damage is irreversible. The Humphrey Field Analyzer (HFA; Carl Zeiss Meditec, Dublin, CA, USA) is commonly used to monitor VF damage in glaucoma patients throughout the world. In the HFA 24-2 and 30-2 test patterns, each VF location is regularly distributed in 6° intervals. However, these test patterns with 6° intervals merely measure the "tip of the iceberg." In fact, more than 13 × 13 (n = 169) Goldmann size III targets could be located between a "square" of four VF test points in the 24-2 and 30-2 VF test grids (see Figs. 1A, 1B). Thus, the HFA gray scale printout of VF sensitivity fills huge gaps by interpolating between adjacent test points. Considering this fact, one may argue that the HFA 24-2/30-2 test patterns could be improved, in terms of monitoring glaucoma and VF damage, by increasing the number of test points. Indeed, the popular G1/G2 programs in Octopus perimeters (Haag-Streit AG, Switzerland) were created to consider the stream of retinal nerve fiber layers,[3] placing more test points around the fixation point. Maddess reported that there is no guarantee that glaucomatous VF damage will be properly reflected when testing in six-degree intervals, due to spatial undersampling.[4] In addition, Weber et al.[5] tested 68 glaucomatous eyes using both HFA 30-2 and 30-1 VF test grids and observed clear differences in the appearance of scotomata in 29 eyes out of 68.

Since the inception of automated perimetry, several attempts have been made to improve the VF test grid in order to better estimate scotomata.[6,7] However, the regular six-degree VF test grid remains the most popular pattern used in the clinical setting, except for the G1 program in Octopus perimetry. This is probably because tests patterns developed for individual patients are often time-consuming to set up as additional points need to be manually added based on the opinion of a trained ophthalmologist. In clinical settings, the 30-2 and 24-2 VF test grids are frequently used. The 30-2 VF test grid is composed of 74 points (not including the two points adjacent to the blind spot), and comprises an additional 22 test points compared with the 24-2 VF test grid. It may be clinically more useful, in terms of measurement time, to not use the 30-2 VF and instead allocate additional test points to the standard 24-2 VF test grid which are designed to capture more information about an individual patient's VF damage. These novel test grids could be implemented in perimetry software, such as the Open Perimetry Interface,[8] without the need for clinicians to manually select test locations.

It has been reported that test-retest reproducibility is poor near a scotoma and where differences in neighboring VF sensitivities are large.[9] Other reports have also suggested that

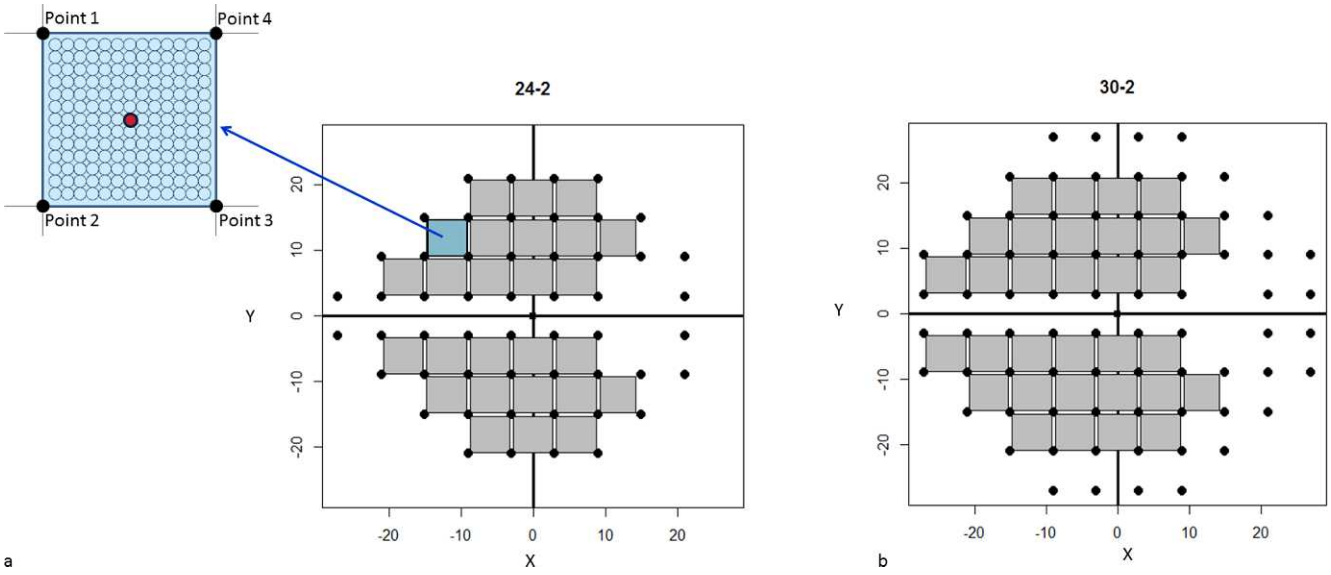

FIGURE 1. The planes analyzed for placement of an additional ten test points with the Humphrey Field Analyzer 24-2 (**a**) and 30-2 (**b**) test grids. For this calculation, points crossing the horizontal meridian and those touching the blind spot were excluded. Also, some outer planes in the 30-2 test grid were not used. As a result, the gradients were calculated for 26 planes with the 24-2 test grid (**a**) and for 32 planes with the 30-2 test grid (**b**). Figures are shown for a right eye. The *top-left* subplot in (**a**) illustrates that more than 13×13 Goldman size III targets can be located in any given plane. The *red circle* represents the location of an additional test point in the center of a plane.

variability increases near the edges of scotomata[10,11] and that variability is correlated with the "steepness" of the edge of the scotoma,[12] which may be a result of eye and head movements. The reproducibility of VF measurements is clinically very important, because detection of VF progression is delayed when there is large fluctuation of VF thresholds; for example, identifying progression using trend analyses of VF summary indices or point-wise sensitivity is hindered.[13,14]

Another criticism of the standard 24-2 VF grid is that it is not ideal for understanding the relationship between structural and functional measurements[15]; indeed, studies have shown that adding test points to the 24-2 test pattern, following inspection of patients' fundus images, resulted in better estimates of VF defects.[16,17] However, this subjective and time-consuming approach could rarely be used, if at all, in the clinical setting. On the other hand, the merit of adding test points to the standard VF grid is diminished where there are no local differences in VF sensitivity (i.e., the local gradient of VF sensitivity approaches a plateau). Thus, we set out to develop a VF grid in which additional test points are allocated automatically based on local gradients of VF sensitivity, and without the need for additional measurements such as fundus imaging. In this study, first, a method to identify the edges of VF damage was established by calculating the plane (gradient) of sensitivity between each square of adjacent test points in the standard 24-2 and 30-2 VF test grids (see Figs. 1A, 1B). Then a strategy to measure glaucomatous VF damage at these edges was developed by allocating additional test points (as illustrated by the red circle in Figs. 1A, 2) where gradients were steep. Finally, we investigated whether these additional test points improved the accuracy and reproducibility of VF measurements.

METHODS

Subjects

Twenty-two eyes of 22 glaucomatous patients were included in this investigation (primary open angle glaucoma: five; normal tension glaucoma: 14; exfoliation glaucoma: one, congenital glaucoma: one; and primary angle closure glaucoma: one). All the patients were being treated in the University of Tokyo Hospital, Tokyo, Japan, and informed consent was provided prior to VF testing. Criteria for inclusion were visual acuity better than 6/12, no previous ocular surgery including trabeculectomy and refractive surgery (except for cataract extraction, intraocular lens implantation and trabeculotomy), and no other posterior segment eye disease. The study was approved by the Institutional Ethics Committee and adhered to the tenets of the Declaration of Helsinki.

VF Testing

In an effort to identify the edges of VF scotomata, the gradient of sensitivity between each square of four adjacent test points was calculated using a patient's most recent VF (Humphrey Field Analyzer 24-2/30-2 SITA-Standard). For example, for the VF sensitivities of the four test points (points 1–4) shown in Figure 2, the magnitude of the gradient along the *x*-axis is calculated as

$$\frac{\text{Point } 4 + \text{Point } 3 - \text{Point } 1 - \text{Point } 2}{2 \times 6\ (\textit{test point interval})},$$

where the numerator consists of the sensitivity of each test point. The magnitude of the gradient along the *y*-axis is then equal to

$$\frac{\text{Point } 1 + \text{Point } 4 - \text{Point } 2 - \text{Point } 3}{2 \times 6\ (\textit{test point interval})}.$$

Then the gradient of the plane is calculated as $\sqrt{(x\text{-axis gradient})^2 + (y\text{-axis gradient})^2}$. Only four neighboring test points were used to calculate the gradient of the plane as it has been reported that further spaced test points in the 24-2 VF have little predictive value.[18] Locations in the blind spot or opposite hemifield were excluded from the calculation. In addition, upper, lower, and temporal-upper and temporal inferior areas in the 30-2 test grid were excluded to avoid

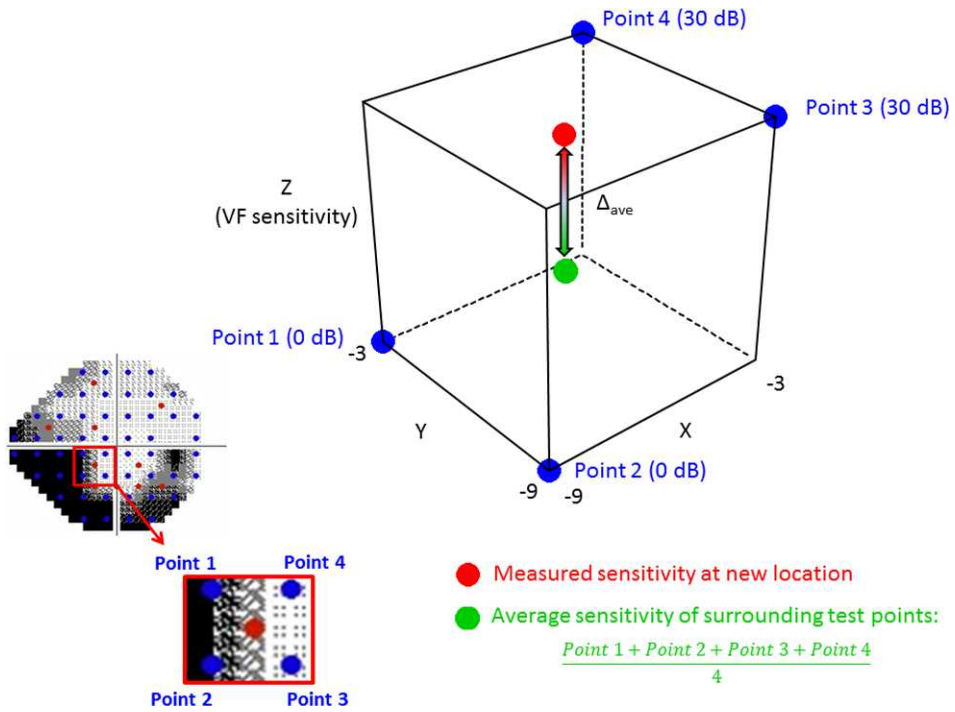

Figure 2. The absolute difference between the measured sensitivity at each additional test point and the average of the sensitivities of its surrounding four test points. *X* and *Y* represents *x*- and *y*-axis coordinates, respectively, while the *Z* axis represents visual field sensitivity. In this example, the sensitivities of points 1 and 2 were equal to 0 dB, whereas points 3 and 4 were equal to 30 dB. The *bottom-left* plot shows the gray scale image of these four points (72 years old, male, right eye). Δ_{ave}, absolute difference between the measured sensitivity at each additional test point and the average of the sensitivities of its surrounding four test points.

artifacts caused by drooping upper eyelids; consequently, 32 planes were calculated for the 30-2 test pattern and 26 planes for the 24-2 test grid (see Figs. 1A, 1B). The 10 steepest planes were recorded and an additional VF test point was placed at the center of each of these 10 planes using the "Custom mode" of the HFA (full threshold algorithm); these 10 test points are subsequently referred to as "10E" to indicate their locations at the edges of scotomata. Figure 3 illustrates the test pattern for a sample patient; the additional 10 test points (10E) are colored in dark red while the standard test points of the 24-2 test pattern ($n = 52$) are colored in blue. Within 6 months of their last visit, each patient underwent a VF test, using the novel "24-2E" test pattern (Custom mode), whereby all 52 test points from the standard 24-2 grid plus the additional 10E points were tested, in random order (Custom mode). This VF measurement was then repeated. Patients had at least 15 minutes rest between each VF test. Three months later, each patient underwent the same procedure again. The HFA Custom mode

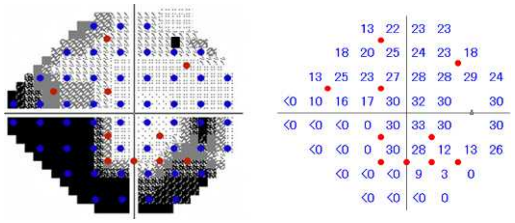

Figure 3. The novel test grid in a sample case; points are superimposed on a gray scale image (72 years old, male, right eye). *Red circles* represent 10 new additional test points placed where the gradient of a plane is steep, whereas *blue circles* represent the standard ($n = 52$) 24-2 VF test points, which are distributed in regular 6° intervals.

does not measure fixation losses, false positives, or false negatives; hence, fixation was monitored by the examiners (YA, MT, RA) throughout the examination and was acceptable for all tests.

Statistical Analysis

The absolute difference between the measured sensitivity at each new additional test point and the average of the sensitivities of its surrounding four test points was calculated (Δ_{ave}; see Fig. 2) to investigate where differences were large, therefore, the utility of adding test locations is greater. Then, the relationship between this difference (Δ_{ave}) and the gradient of its plane was investigated using multilevel modeling (MLM),[19] in which patients were treated as a random effect. MLM is equivalent to ordinary multiple linear regression in that a model describing the relationship between several predictor variables and a single outcome variable may be developed and estimated. Ordinary linear regression analysis makes the assumption that all observations are independent of each other. However, in the data presented, measurements are nested within subjects and thus not independent. An analysis ignoring this grouping of the measurements will result in the underestimation of the standard errors of regression coefficients. MLM adjusts for the hierarchical structure of the data, explicitly modeling the way in which measurements are grouped within subjects. The significance associated with MLM was evaluated using the Markov chain Monte Carlo (MCMC) method which is appropriate to be used in a relatively small sample.[19]

In addition, Strouthidis et al.[20] have investigated the relationship between an anatomic map of the retinal nerve fiber layer (RNFL) distribution and distance to the optic nerve head against a functional map derived from the interpoint correlation of raw sensitivities in the 24-2 VF. In this study, it

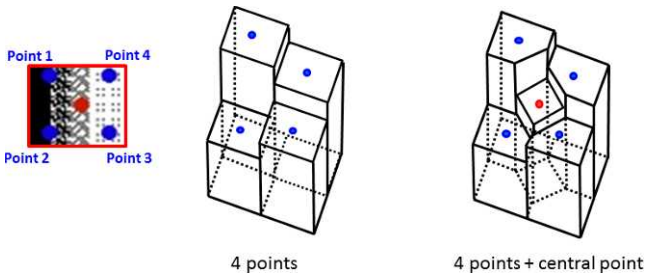

FIGURE 4. Schematic illustrating the calculation of the VF's cubic volume; cubic volume = total deviation values ("height") × area a test point occupies ("base"). For this calculation, four or five test points were used in each plane. As total deviation values are usually negative, figures are drawn "upside-down" to aid comprehensibility.

was suggested that the inter-point correlation can be calculated as:

$$0.9325 - (0.0029 \times ONHd) - (0.0077 \times RETd) + (0.0001 \times ONHd \times RETd), \quad (1)$$

where *ONHd* represents the angular distance (in degrees) between test points at the optic nerve head and *RETd* represents angular distances between each test point. Following their approach, the VF sensitivity values of the additional 10E test points were predicted. Then the differences between the predicted values and the measured sensitivity values (Δ_{SFmap}) were investigated, in relation to the calculated gradient.

As the distribution of additional test points varies from subject to subject, conventional global indices, such as mean deviation (MD) or the visual field index (VFI), which are weighted according to the location of test points, were not compared. Instead, the cubic volume of VF damage was calculated; "height" was calculated using total deviation values and "base" was calculated using the area that the VF test points exclusively occupy (e.g., a square of four adjacent VF points occupies an area of 36° squared); cubic volume = total deviation values (height) × occupying area (base; Fig. 4). Then the fluctuation of this cubic volume derived from the four repeated VF measurements, with and without the additional ten test points (24-2 and 24-2E VF grids), was estimated using the intraclass correlation coefficient (ICC), which can cope with repeated measurements. The ICCs associated with the cubic volumes from the 24-2 and 24-2E VF grids were compared by carrying out a "bootstrap percentile test" with 10,000 iterations.[21] In addition, the coefficient of variation (CV) was calculated by comparing these cubic volume measurements with and without the ten additional test points; this was then compared using the Wilcoxon signed-rank test.

All analyses were performed using the statistical programming language (R version 2.15.1; The Foundation for Statistical Computing, Vienna, Austria). MLM was carried out using the statistical package (R package "lme4"; The Foundation for Statistical Computing) and significance was evaluated by MCMC sampling (10,000 times) using a statistical package (R package "languageR"; The Foundation for Statistical Computing).

RESULTS

Characteristics of subjects are given in Table 1.

The average ± standard deviation (range) of the minimum, median, and maximum gradient was 5.5 ± 3.0 (2.9–14.3); 10.0 ± 4.0 (4.0–17.1); and 21.2 ± 5.3 (7.8–20.0) dB/deg interval, respectively. On average, the measurement duration of the 24-2E test was 14 minutes and 29 seconds, whereas it was 12 minutes and 5 seconds with the 24-2 grid. Figures 5A and 5B illustrate a linear interpolation of VF sensitivities in two patients. The distributions of calculated VF gradients for each patient are depicted in Figure 6. The boxplot in Figure 7 shows the intra- and intervisit reproducibility of the thresholds of the added 10 test points. The reproducibility tended to be worse where gradients were steeper. The boxplots in Figure 7 illustrate the relationship between the gradient of the plane and Δ_{ave}. As shown in these boxplots, Δ_{ave} increases as the gradient of the plane becomes steeper. These boxplots are in agreement with the results of MLM where there was a significant positive relationship between the gradient of sensitivity and Δ_{ave} in each of the four VF test results ($P < 0.001$); $\Delta_{ave} = 0.20 \times$ gradient + 2.7 (day 1, measurement 1); $\Delta_{ave} = 0.20 \times$ gradient + 3.2 (day 1, measurement 2); $\Delta_{ave} = 0.17 \times$ gradient + 3.8 (day 2, measurement 1); $\Delta_{ave} = 0.29 \times$ gradient + 2.6 (day 2, measurement 2). As shown in Figure 8, Δ_{SFmap} increases as the gradient of the plane becomes steeper. Thus, a large discrepancy is still observed even when the anatomical and functional relationship in Equation 1 was incorporated.

Table 2 shows ICCs and CVs of the cubic volume associated with the 24-2 VF grid and the 24-2E VF grid. ICCs were high with both patterns; however, bootstrapping suggested that the ICC associated with the 24-2E VF grid was significantly greater than that associated with the 24-2 VF grid (percentile bootstrap test, $P = 0.02$). The median of CVs associated with the 24-2E VF grid was 11.2%, which was significantly lower than that observed with the 24-2 VF grid (13.1%, $P = 0.0057$, Wilcoxon signed-rank test).

TABLE 1. Subject Demographics

Subtypes of glaucoma	Primary open angle glaucoma (5 eyes) Normal tension glaucoma (14 eyes) Exfoliation glaucoma (one eye) Congenital glaucoma (one eye) Primary angle closure glaucoma (one eye)
Age, y (range)	56.5 ± 11.4 (37–76)
Male/female ratio	10:12
Mean deviation (range)	−6.1 ± 4.1 (−15.4 to −1.2) dB

DISCUSSION

In the current study, a method to identify the edges of VF scotomata is introduced and additional ten test points were allocated where VF sensitivity changes most markedly between adjacent test points in the standard 24-2 pattern. Our results suggested that it is very difficult to predict VF sensitivity at the edge of a scotoma. Nevertheless, the reproducibility of VF damage, as measured by the cubic volume index, was improved by adding ten test points at the edges of scotomata. Improving the reproducibility of VF measurements is clinically very important because this allows earlier detection of progression.[22]

Wyatt et al.[9] investigated the relationship between the reproducibility of measured VF sensitivity and the gradient of VF sensitivities in 10-2 and 24-2 VFs. In their study, the variability of measured sensitivity increased with an increase in gradient.[9] It is worth noting that the HFA used in the present study was set to "Custom mode" whereas the previous study employed SITA standard and full threshold methods. In these algorithms, four primary test points are measured first and the results from these points dictate initial stimulus values for

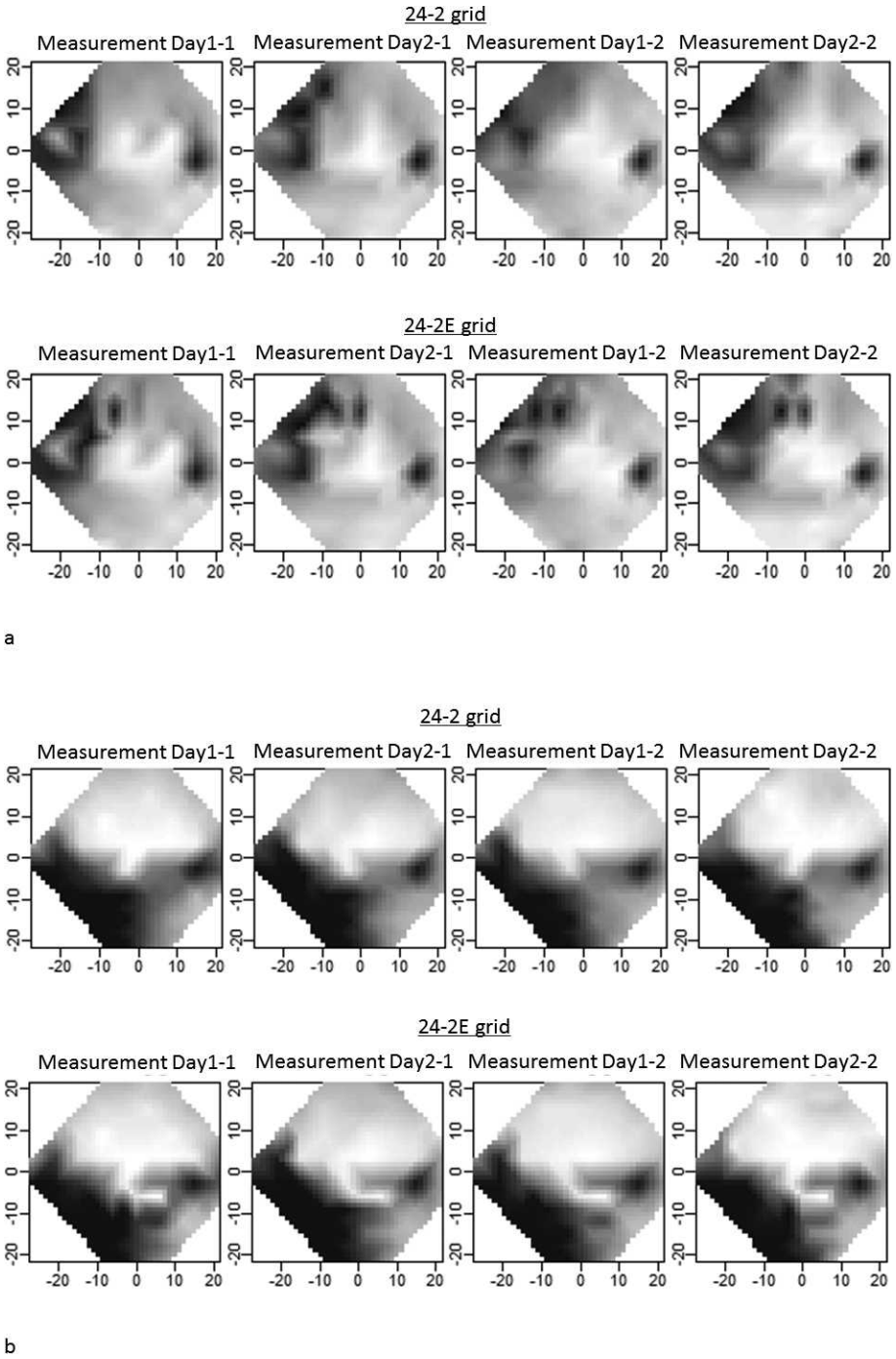

Figure 5. VF gray scales of two samples cases: four images in the *upper row* represent the gray scales associated with the 24-2 grid, while the four images in the *bottom row* represent the gray scales associated with the 24-2E grid. VF sensitivity was linearly interpolated. (**a**) A 57-year-old female with primary open angle glaucoma. The coefficient of variation of the VF cubic volume was 4.3% with the 24-2 grid and 3.6% with the 24-2E grid; the Bjerrum scotoma in the superior hemifield is better defined with the 24-2E grid compared with the 24-2 grid. (**b**) A 61-year-old male with primary open angle glaucoma. The coefficient of variation was 16.5% with the 24-2 grid and 11.4% with the 24-2E grid; a preserved region in the inferior paracentral area is clearly shown with the 24-2E grid but is less obvious in the 24-2 pattern.

neighboring locations (growth pattern).[23] As test-retest variability is related to the difference between initial stimulus value and final value,[13,14,24,25] this difference of the measuring algorithms may have an influence on the test-retest reproducibility. Another factor to be considered is the influence of eccentricity (spatial distance from fixation) since test-to-test reproducibility decreases with increasing eccentricity.[26] Nevertheless, the influence of eccentricity in the previous report is much smaller when compared with the importance of the gradient on Δ_{ave} observed in the current study. Importantly, our results suggest that the discrepancy between measured sensitivity at a new location and the average sensitivity of its encompassing points is much greater where the gradient is steep. Furthermore, a large discrepancy was still observed when the anatomical and functional relationship in Equation 1 was incorporated, as shown in Figure 8.

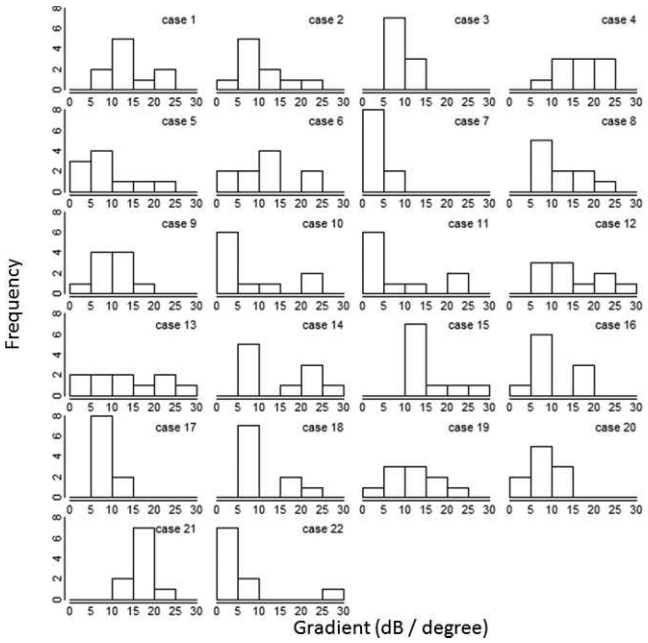

FIGURE 6. The distribution of calculated sensitivity gradients for each patient.

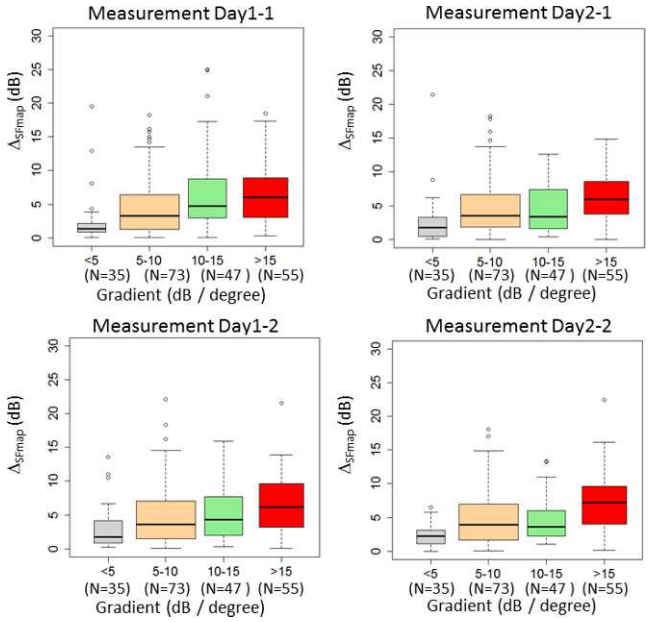

FIGURE 8. *Boxplots* illustrating the relationship between the gradient of the plane and the difference between measured sensitivity and predicted sensitivity at the VF test point following the relationship proposed by Strouthdis et al.[20] The width of each *boxplot* illustrates the number of test points. No benefit in accuracy was observed by predicting the sensitivity at the additional test points after incorporating this relationship.

There has been a recent renewed interest in the question "What is the best VF test grid in glaucoma?" Schiefer et al.[16] have suggested that adding test points in-between standard HFA grid locations, decided according to an individual's fundus image, significantly increases the detection rate of glaucomatous VF damage. Similar findings were also reported by Nevalainen et al.[17] In addition, Asaoka et al.[15] proposed a new test grid to increase the structure-function correlation between RNFL thickness and VF sensitivity measurements. In the current study, we have proposed an objective and automated method to improve the standard 24-2 VF test grid in the HFA. Our results suggest that the approach is clinically useful to better understand and replicate the status of VF scotomata. Furthermore, the locations of additional test points can be decided without the need for an extra measurement, such as fundus images, and moreover, locations can be automatically inferred from just a single VF.

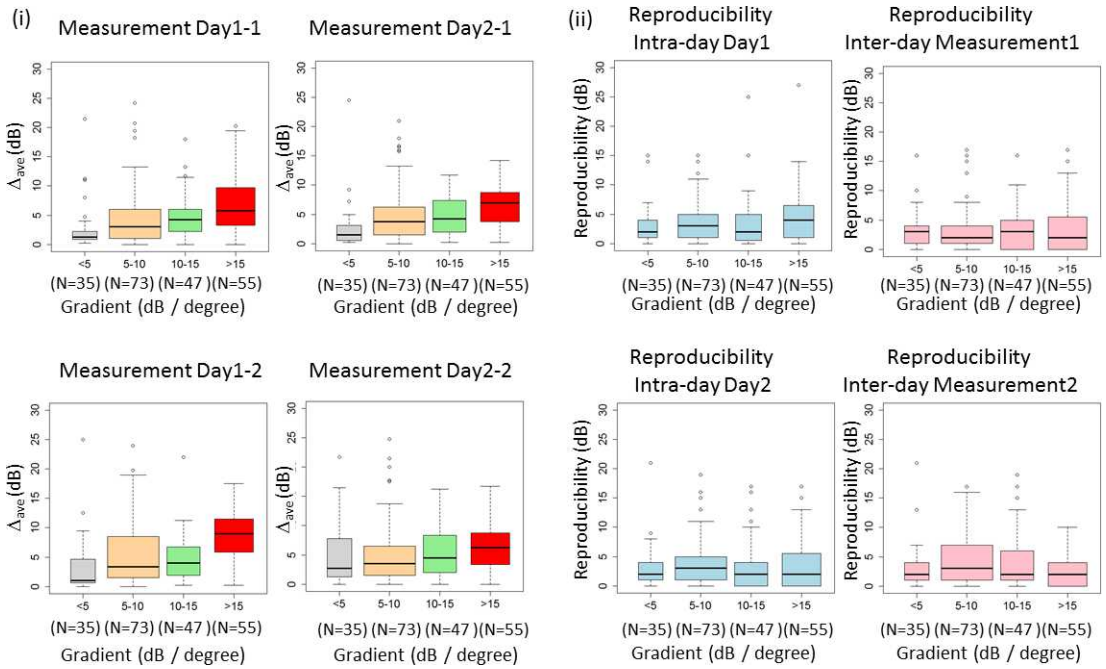

FIGURE 7. *Boxplots* illustrating the relationship between the gradient of the plane and Δ_{ave}; and the gradient of the plane and the intra- and interday reproducibility. The width of each *boxplot* illustrates the number of test points.

Table 2. ICC and CV of Cubic Volume Calculated With 24-2E and 24-2 VF Grids

CV	24-2E, 62 Points	24-2, 52 Points
Median, %	11.2	13.1
Range, %	2.1–53.1	2.0–54.2
ICC, %	0.89	0.87

24-2E: 24-2 VF grid and 10 additional test points.

There is clearly a downside to having a longer VF test: although this may increase the resolution of the measurements, it could also lead to fatigue. In the current study, an extra two minutes testing was required on average, by including the ten additional test points in the 24-2E pattern. However, the current study was carried out using the Custom mode, which is considerably less efficient than more modern algorithms, such as SITA. Furthermore, in the near future, it may even be possible to include additional test points without increasing overall VF test time, by using information from previous VF test results.[27]

It is recommended to use the same VF test grid pattern when measuring VF change.[28] A merit of the current approach is that the "core" 52 test points of the 24-2 grid are not removed. Interestingly, we carried out further experiments where the additional 10E test locations were measured separately to the 24-2 VF and very similar results were obtained (data not shown). This suggests that the advantages associated with adding test points to the 24-2 grid can be obtained even if the additional measurement is carried out after the standard VF test; this makes the extra measurement easier to implement using software such as the Open Perimetry Interface.[8]

The current study also suggests that adding test locations to the 24-2 grid where local threshold differences are small (the gradient is flat) is unlikely to be beneficial; in these regions sensitivity can already be accurately predicted. Thus, carrying out extra measurements would merely increase the overall test duration, which, in turn, generally results in less accurate VF measurements.[24,29,30] In the current study, the number of added test points ($n = 10$) was large enough to cover steep gradients in an individual's VF, such as >15 dB/6° interval. However, it is worth noting that the current study population consists only of relatively early to moderate stage glaucoma patients; thus, future research should investigate whether adding 10 test points is sufficient in more advanced glaucoma cases.

Wall et al.[31] reported that test-retest variability increases with a decrease in sensitivity, and at some point (approximately 15–20 dB) variability decreases again due to a floor effect. It is reasonable to assume that many test points at the steep edge of VF scotoma have midrange (≃15 dB) VF sensitivity. This would lead us to believe that test-retest reproducibility is worse at the edge of a scotoma; indeed a previous study suggested this to be the case.[11] Nevertheless, the improved reproducibility of VF damage (measured by cubic volume) shown in this study suggests it is clinically useful to measure VF damage at the edges of scotomata when measuring VF progression.

In the current study, the number of additional test points was decided arbitrarily, although we considered that more than 10 test points would extend testing time excessively. As shown in Figure 6, the gradient of the 10th steepest plane was <10 dB/deg in most patients and Δ_{ave} was not very large (see Fig. 7) so 10 test points appears sufficient in this sample of glaucoma subjects. It is possible that less than 10 test points would be adequate in some patients (such as case 7 in Fig. 6); the most suitable number of test points for a given patients should be investigated in a future study.

In conclusion, we have demonstrated an automated way to increase the coverage of VF test locations and thereby map the edges of VF scotomata. The results from this novel "individualized" test grid may be beneficial for clinicians monitoring a patient's VF damage over time.

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