Article

Modifying the Conventional Visual Field Test Pattern to Improve the Detection of Early Glaucomatous Defects in the Central 10°

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Purpose: To simulate modified versions of the 24-2 (6° grid) visual field (VF) test pattern by adding points from the 10-2 (2° grid) test pattern, and to assess their ability to detect early glaucomatous defects in the central 10°.

Methods: One hundred forty-four eyes of 144 glaucoma patients and suspects with 24-2 mean deviations better than −6 dB were tested with 10-2 and 24-2 VFs. Based upon both 10-2 VF and optical coherence tomography probability plots, 63 hemifields were defined as abnormal, while 121 hemifields were defined as normal. Three modified 24-2 VF test patterns, called 24-2 +4, 24-2 +16 (Even), and 24-2 +16 (Empirical), were simulated by adding 4 or 16 test points from the 10-2 VF.

Results: Based upon the number of abnormal points ($P \leq 5\%$), the area under the ROC curves (AROC scores) of the three modified 24-2 VFs were significantly greater than that of the 24-2 VF for both the upper and lower VF. For a specificity of 85%, the number of true positives was 25 (24-2), 30 (24-2 +4), 31 (24-2 +16, even), and 32 (24-2 +16, empirical) of 34 total true positives for the upper VF and 23, 26, 27, and 28 of 29 for the lower VF.

Conclusions: Adding points from the 10-2 test pattern to the 24-2 test pattern significantly improved its ability to detect macular defects without employing more test points than a single 10-2 test.

Translational Relevance: Additional central points should be added to the 24-2 pattern to improve the detection of macular damage.

Introduction

Early glaucomatous damage often includes the macula and impacts central vision, and this damage can be among the first signs of glaucoma (see Ref. 1 for a review). Yet the test most commonly used to assess glaucomatous visual field (VF) loss, the central 24-2 threshold test, underestimates damage to the macula,^{1–5} the most essential region of the retina for everyday visual functions,^{6,7} such as reading, driving, and face recognition.⁶ The 6° stimulus spacing of the 24-2 VF can completely miss defects within the central 10° of vision. For example, in a prospective study of

100 eyes from glaucoma suspects and patients, Traynis et al.⁵ found that 16% of the eyes classified as normal on the 24-2 VF were abnormal on the 10-2 VF. Although this macular damage is seen on the 10-2 VF, a 10-2 VF test alone will miss defects picked up by the 24-2 VF.⁵ Simply performing both a 10-2 and 24-2 VF test is not a practical solution to this problem, especially if both eyes need to be tested, as many patients find multiple tests too taxing and results can become less reliable with each additional VF test.

While alternative VF test patterns that more heavily sample the central retina have been proposed, these patterns have not been widely accepted, largely

because clinicians are reluctant to give up the 24-2 test pattern. There are at least three reasons for this reluctance. First, clinicians often have years of 24-2 VF data on a patient. Second, they have learned how to interpret the 24-2 VF report. Finally, the 24-2 VF allows for the detection of classic arcuate damage, which can be missed with the 10-2 test pattern.

We recently proposed modifying the 24-2 VF test by adding test point locations from the 10-2 pattern.⁸ There are three reasons why we suggested adding points from the 10-2 test pattern rather than devising an entirely new pattern. First, with a 24-2 VF modified in this way, a traditional 24-2 report could still be produced, allowing a comparison to earlier 24-2 VF data for the purpose of monitoring progression. Second, the normative sensitivity data already exist for the current 10-2 test point locations. Finally, the results for the added 10-2 test points can be compared with 10-2 VFs.

In particular, we suggested that adding two additional test points from the 10-2 test pattern, located at $(-1^\circ, 5^\circ)$ and $(1^\circ, 5^\circ)$, to the upper hemifield of the 24-2 VF would allow detection of relatively common and very serious arcuate defects close to fixation in the upper VF.⁸ Here we tested this hypothesis by adding four test points, two in each hemifield, to create a 24-2 +4 test pattern.

We also tested the hypothesis that adding eight test points to both the upper and lower VF hemifields will further improve the detection of glaucomatous macular damage. The 10-2 VF has 68 test point locations (not including fixation), while the 24-2 VF tests 52 locations, not counting fixation or the blind spot. Therefore, by adding 16 test point locations to the 24-2 test pattern (i.e., creating a 24-2 +16 pattern), the time needed to perform the modified VF test should not be considerably greater than that of the 10-2 VF. In particular, we assessed the diagnostic performance of two different 24-2 +16 patterns, one (even) with evenly spaced test points and a second (empirical) based on a post hoc analysis of the VF data.

Because all test patterns detect extensive damage, we focused on the detection of early or mild glaucomatous defects. Eyes were included based on suspicious or abnormal disc exams and a 24-2 VF mean deviation (MD) of -6 dB or better. Both macular frequency domain optical coherence tomography (fdOCT) scans and 10-2 VFs were used to identify two subsets of hemifields, those with (abnormal) and those without (normal) macular damage.

Methods

Patients

One hundred forty-four eyes of 144 glaucoma patients and suspects (aged 57.1 ± 13.8 years) were included. Data from 58 of the 144 eyes were part of a previous study.⁹ All eyes had gonioscopically open angles and an abnormal appearing disc on fundus examination. All subjects had MDs of -6 dB or better on the 24-2 VF (Humphrey 750i Visual Field Analyzer [HFA]; Carl Zeiss Meditec, Inc., Dublin, CA). Eyes with cataracts worse than “early cataracts” on slit-lamp examination were excluded. Early cataracts were defined as those with scores on the Lens Opacities Classification System III (LOCS) better than NO02, NC02, C2, and P2. Eyes with other conditions likely to impact VF testing, such as corneal opacity, neurophthalmic, or retinal disease, were also excluded. Additionally, eyes needed a best-corrected visual acuity of 20/40 or better. All subjects were prospectively tested with 10-2 VFs and fdOCT macular volumetric (cube) scans. On average, the 10-2 VF, 24-2 VF, and fdOCT macular cube scan for an individual were obtained within 2.7 months of each other. The median of the maximum time between tests was 1.6 months (interquartile range of 0.6–4.3 months, with 6 between 9 and 11.6 months).

Written informed consent was obtained from all participants. The study protocol followed the tenets of the Declaration of Helsinki and was approved by the institutional review boards of Columbia University (New York, NY) and New York Eye and Ear Infirmary (New York, NY).

Standard Automated Perimetry

Patients were tested with standard automated perimetry (SAP) using the 10-2 and 24-2 SITA Standard protocols (Humphrey 750i Visual Field Analyzer [HFA]; Carl Zeiss Meditec, Inc., Dublin, CA). The 10-2 and 24-2 VFs were required to have fixation losses, false-positives, and false-negatives all less than or equal to 33%. The upper and lower hemifields of the 10-2 VF were classified separately. In the first round of classifications, in which structural and functional tests were assessed separately, a hemifield was considered abnormal if the total deviation (TD) probability plot contained a set of three or more contiguous points (cluster) respecting the horizontal midline that were abnormal (at 5%, 5%, 1%, or 5%, 2%, 2%).

Frequency Domain OCT

Volumetric (cube) scans of the macula (6×6 mm, 128 horizontal B-scans with 512 A-scans each) were obtained for all subjects using fdOCT (3D-OCT 1000/2000; Topcon Medical Systems, Inc., Oakland, NJ). The macular cube scans were centered on the fovea, as marked on an OCT B-scan slice. The combined thickness of the retinal ganglion cell (RGC) plus inner plexiform layers (RGC+) was measured using a previously validated¹⁰ automated segmentation algorithm that was hand-corrected as needed.¹¹ The segmented fdOCT macular cube scans were used to produce RGC+ thickness maps for each eye. To create RGC+ probability plots similar to the VF TD probability plots, the RGC+ thickness maps were down-sampled into an 8×8 grid and compared with the control data from 54 healthy eyes of 54 individuals to code for probability at each of the 64 locations.⁹ (See Fig. 2 of Ref. 9 for a schematic description of this procedure.) A hemifield of the macular RGC+ probability plot was considered abnormal if it contained a cluster of three or more test points that were abnormal (at 2%, 2%, 1% or worse) and respected the horizontal midline. Applying this classification criterion to the control eyes yielded a false positive rate of 4.6% (5 of 108 control hemifields).⁹

Hemifield Classifications

To be reasonably certain of the presence or absence of a glaucomatous defect in the central 10° in either hemifield of a particular eye, only hemifields that were classified as normal (or abnormal) on both the structural and functional tests were analyzed further. Accordingly, a hemifield was only considered abnormal (i.e., considered to have a central defect) if both the 10-2 VF and the fdOCT RGC+ probability plots were initially classified as abnormal according to the cluster criteria. Similarly, a hemifield was considered normal (i.e., considered to lack a central defect) only if both the VF and RGC+ thickness were normal. Table 1 shows that 63 hemifields (of 46 eyes) were abnormal on both tests, and thus were classified as abnormal, while 121 hemifields (of 78 eyes) were normal on both tests and classified as normal. Of the 63 abnormal hemifields, 34 were in the upper VF (inferior retina) and 29 were in the lower VF (superior retina). For the 121 normal hemifields, 61 were in the upper VF (inferior retina) and 60 were in the lower VF (superior retina).

Table 1. Number of Upper and Lower VF Hemifields Classified as Normal or Abnormal

10-2 VF Hemifield	Abnormal	Normal	Total Number
Upper	34	61	95
Lower	29	60	89
Total number	63	121	184

Modified VF Test Patterns

A custom MATLAB (version R2013a; MathWorks, Inc., Natick, MA) program was written to simulate modified versions of the 24-2 VF test pattern (6° stimulus grid) by selecting particular subsets of points from the 10-2 VF (2° grid) and adding these points to the 24-2 VF for each eye. For the stimulus locations that the 24-2 VF shares with the 10-2 VF, the TD values and probabilities from the 24-2 VF were used in the simulated VFs. Three modified 24-2 VF test patterns were simulated.

24-2 +4 VF

In an independent dataset, we previously identified two test points from the 10-2 VF, at (1° , 5°) and (-1° , 5°), as empirically optimal for detecting arcuate defects close to fixation in the upper VF. Here, we simulated a 24-2 +4 VF test pattern, which included these two points added to both the upper and lower hemifields for a total of four additional test points. Figure 1A shows the test point locations in the superior central 10° for the 24-2 VF (blue) with the two test points (red) of the 10-2 VF added to form the 24-2 +4 VF pattern.

24-2 +16 (Even) VF

With the aim of further improving the ability of the 24-2 VF to detect central defects, we tested the effect of adding 16 test points selected from the 10-2 VF. We chose to add 16 test points (8 per hemifield) so that the resulting 24-2 +16 (even) VF test pattern would have the same number of test points as the 10-2 VF (68 test points). As shown for the upper VF in Figure 1B, to create the 24-2 +16 (even) VF pattern, we added points from the 10-2 VF in an even and symmetric pattern so as to minimize the amount of unsampled space in the central 10° .

24-2 +16 (Empirical) VF

To assess the importance of the particular locations of the 16 added test points, we also simulated an empirical 24-2 +16 VF. The 16 additional points of

Figure 1. (A) The 24-2 +4 test pattern for the upper VF. It includes two 10-2 test point locations (*smaller red squares*), which were empirically selected in an independent dataset of upper VF arcuate defects, added to the 24-2 test pattern. (B) The test point locations of the 24-2 +16 (even) VF for the upper hemifield. Eight 10-2 points per hemifield (*smaller red squares*) were added to the 24-2 pattern in order to evenly sample the central 10°. In both (A) and (B), the *black semicircles* mark the superior central 10°, while the *larger blue squares* are the original test point locations of the 24-2 VF. For both test patterns, the same test point locations (reflected across the horizontal midline) were used for the lower VF.

the 24-2 +16 (empirical) VF were selected based on the test points that were most frequently abnormal across the group with macular defects. The right panels of [Figure 2](#) show the percentage of points, across the abnormal upper (A) and lower (B) VF hemifields that had TD P values less than or equal to 5%. These percentages are color-coded according to their magnitude (red: $\geq 67\%$; orange: $\geq 33\%$, $< 67\%$; green: $< 33\%$). In each hemifield, we added the eight test points that had the highest percentage of

abnormal points. The resulting 24-2 +16 (empirical) VF test patterns for the upper (A) and lower (B) hemifields are shown in the left panels of [Figure 2](#).

Results

[Figure 3](#) shows the receiver operating characteristic (ROC) curve for the upper (A) and lower (B) hemifields using the number of test points with $P \leq 5\%$; [Table 2](#) has the associated area under the ROC curves (AROC scores). As expected, the diagnostic performance of the modified 24-2 VFs improved as the number of additional test points increased. For the upper VF, adding just two test points per hemifield resulted in a greater AROC score for the 24-2 +4 VF (0.954) than for the 24-2 VF (0.924), and this difference was borderline significant ($P = 0.047$ based on the method of Hanley and McNeil¹²). The AROC scores for both the 24-2 +16 (even) VF (0.969) and 24-2 +16 (empirical) VF (0.980) were significantly greater than that of the 24-2 VF (for both, $P < 0.02$) and greater than that of the 24-2 +4 VF. As the test point locations of the 24-2 +16 (empirical) VF were selected empirically, it is not surprising that its AROC score (0.980) was greater than that (0.969) for the 24-2 +16 (even) VF, although these scores were not significantly different ($P = 0.186$).

[Table 2](#) also shows the sensitivities at an arbitrary specificity of 85% or higher (third column), along with the number of true positives detected (last column). Out of a maximum of 34 abnormal upper VFs, the 24-2 +4 identified 30 as compared with 25 by the 24-2 VF. The 24-2 +16 (even) VF and the 24-2 +16 (empirical) VF detected 31 and 32, respectively.

The same trends were seen for the lower VF results. The AROC score of the 24-2 +4 VF (0.948) was significantly ($P = 0.016$) greater than that of the 24-2 VF (0.902), as were the AROC scores of the 24-2 +16 (even) VF (0.960; $P = 0.022$) and the 24-2 +16 (empirical) VF (0.980; $P = 0.008$). Just as for the upper VF, although the 24-2 +16 (empirical) VF was slightly more sensitive at a specificity of 85% (97%) than the 24-2 +16 (even) VF (93%), the difference in their AROC scores was not statistically significant ($P = 0.127$). The number of true positives at an arbitrary specificity of 85% or higher also showed the same trend. Out of a maximum of 29 abnormal lower VFs, the 24-2 +4 identified 26 as compared with 23 by the 24-2 VF, while the 24-2 +16 (even) VF and the 24-2 +16 (empirical) VF detected 27 and 28, respectively.

A.

Empirical 24-2 +16 (Upper VF)

B.

Empirical 24-2 +16 (Lower VF)

Figure 2. The left panels show the test pattern of the 24-2 +16 (empirical) VF for the upper (A) and lower (B) VF. Of the 10-2 test point locations that are not shared with the 24-2 VF, the eight (smaller red squares) with the highest percentage of abnormal points were added to the 24-2 pattern. In the right panels, the percentages of points across the abnormal upper (A) and lower (B) VF hemifields that were abnormal (TD $P \leq 5\%$) at each test point location are shown. Percentages were color-coded as follows: red: $\geq 67\%$; orange: $\geq 33\%$, $< 67\%$; green: $< 33\%$. In all panels, the larger blue squares represent the 24-2 VF test point locations.

Discussion

Because the conventional 24-2 VF inadequately samples the macula,¹ central defects can be missed.¹⁻⁵ By adding 10-2 test point locations to the 24-2 test pattern, we improved its sensitivity for detecting central defects. For example, by adding eight test points per hemifield in an evenly distributed pattern, the number of true positives (for a fixed specificity of 85%) increased 24% from 25 (24-2 VF) to 31 (24-2 +16 [even] VF) hemifields in the upper VF, and by 17.4% from 23 (24-2 VF) to 27 (24-2 +16 [even] VF) hemifields for the lower VF. Interestingly, the 24-2 +4 VF did only slightly worse than the 24-2 +16 (even)

VF. A total of five abnormal hemifields were missed by the 24-2 +16 (even) VF, while seven were missed by the 24-2 +4 VF.

The question of how many points to add is a question of a trade-off between sensitivity/specificity on the one hand, and the duration of the test on the other. Because adding four points significantly improved the sensitivity/specificity of the 24-2 VF, we suggest adding at least four points. However, adding 16 points should improve sensitivity/specificity further, while also testing the same number of test points as the 10-2 VF. Thus, at present we recommend adding 16 test point locations (8 per hemifield) to the 24-2 VF test pattern in order to improve the detection of macular damage. Although the 24-2 +16

A. **B.**

Figure 3. The ROC curves for the upper (A) and lower (B) VF. The curves are a function of the number of abnormal test points ($TD P \leq 5\%$) in the superior (A) and inferior (B) central 10° of the VF.

TABLE 2. AROC Analysis for Number of Abnormal Test Points (TD $P \leq 5\%$) in the Central 10°

Hemifield and VF Test Pattern	AROC $\pm$ SE	SN at SP $\geq 85\%$	TP at SP $\geq 85\%$
Upper VF			
24-2	0.924 $\pm$ 0.033	73.50%	25
24-2 +4	0.954 $\pm$ 0.026	88.20%	30
24-2 +16 (even)	0.969 $\pm$ 0.021	91.20%	31
24-2 +16 (empirical)	0.980 $\pm$ 0.017	94.10%	32
Lower VF			
24-2	0.902 $\pm$ 0.040	79.30%	23
24-2 +4	0.948 $\pm$ 0.030	89.70%	26
24-2 +16 (even)	0.960 $\pm$ 0.026	93.10%	27
24-2 +16 (empirical)	0.980 $\pm$ 0.019	96.60%	28

SN, sensitivity; SP, specificity; TP, true positives.

* Standard error (SE) calculated using the method of Hanley and McNeil.¹³

(empirical) pattern detected two more true positives than did the 24-2 +16 (even), future work is needed to determine if this marginal advantage will generalize to a different population of patients.

Limitations and Future Directions

In order to generate individual 24-2 +4 and 24-2 +16 VFs using pre-existing 24-2 and 10-2 VFs, we assumed that the threshold measured at a particular test point would remain the same, regardless of the test pattern used. However, retrospectively simulating VFs in this way may not produce the same results as would testing patients with the actual 24-2 +4 and 24-2 +16 stimulus arrangements. For example, the SITA-standard algorithm employs estimates of neighboring points and this theoretically could affect the sensitivity measured. In any case, a study is needed in which patients with early damage are prospectively tested with a modified 24-2 VF test pattern, along with the traditional 10-2 and 24-2 VFs, to assess the value-added of using additional test stimuli locations in practice.

Furthermore, we classified VF hemifields with stringent criteria in order to ensure that we were dealing only with hemifields that were either clearly abnormal (had a central defect), or clearly normal (lacked a central defect). The use of these well-defined groups with stringent criteria for hemifield abnormality had the potential to artificially inflate AROC scores. The ability of the 24-2 +16 test patterns to discriminate between less strictly defined groups, for example in which the classification of the fdOCT macular RGC+ probability plots is not part of the inclusion criteria, may be different.

Translation to the Clinical Setting

Commonly used automated perimeters allow the user to define custom VF test protocols for patient testing. Once a custom test pattern is created, it can subsequently be used to test future patients without additional set-up time. By using a custom protocol with added central stimuli locations, such as the 24-2 +16 (even) pattern, clinicians could gain more information regarding the likelihood of macular damage and the necessity of running additional 10-2 VF tests. However, defining each test point location via custom protocol is by no means as user-friendly as selecting a pre-existing, standard VF test pattern. Further, presently the custom protocol on the HFA uses the Full Threshold protocol; it does not allow the faster SITA protocol to be used. Thus, we suggest that manufacturers supply a streamlined feature, in which a subset of 10-2 test point locations can be easily selected and added to the 24-2 test pattern, along with the SITA algorithm. In addition, the software should allow the generation of standard reports with and without these additional points. Finally, although the focus here was on the 24-2 VF of the HFA, the same VF patterns used here can be created with other instruments such as the Octopus perimeter (Haag-Streit, Inc., Köniz, Switzerland).

Conclusions

In order to improve the detection of macular damage, the 24-2 test pattern should be modified to include additional test point locations within the central 10° . Although one approach, adding 16 test points from the 10-2 test pattern in the evenly

distributed or empirical pattern, shows promise and should be prospectively tested, it is too early to definitively choose a particular number of added test points, or their specific locations. As the optimal modified 24-2 test pattern has yet to be defined, and may vary across different populations, perimeter manufacturers should grant clinicians the option to easily add 10-2 test point locations to the 24-2 test pattern. Such a feature would allow for a single VF test with better detection of central defects, as well as provide clinicians and researchers with the flexibility to continue to learn the best procedures for detecting macular damage in different populations.

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