

Detection of Glaucomatous Visual Field Defect by Nonconventional Perimetry

MICHELE IESTER, MD, MICHELE ALTIERI, MD, PAOLO VITTONI, MD,
GIOVANNI CALABRIA, MD, MARIO ZINGIRIAN, MD, AND CARLO E. TRAVERSO, MD

- **PURPOSE:** To report the correlations among Humphrey Field Analyzer 750 (HFA), high-pass resolution perimetry (HRP), and frequency-doubling technology (FDT) perimetry in glaucoma patients and ocular hypertensive patients.

- **DESIGN:** Cross-sectional study.

- **METHODS:** Eighty-two eyes of 82 consecutive patients with primary open-angle glaucoma (POAG) or ocular hypertension were included in this study. One eye of each patient was randomly selected for data analysis. Visual fields were assessed by HFA, HRP, and FDT perimetry. HRP global deviation (HRP-GD), HRP local deviation (HRP-LD), FDT-mean deviation (FDT-MD), and FDT-pattern standard deviation (FDT-PSD) were considered for the analysis. Clinical agreement between HRP and FDT was evaluated. All data were analyzed by Pearson *r* coefficient when the distribution of the data was normal and by Spearman coefficient correlation when the distribution of the data was not normal. A *P* < .05 was considered statistically significant.

- **RESULTS:** Fifty-two eyes (52 patients) were classified as glaucoma and 30 eyes (30 patients) as ocular hypertension. In the entire group, a significant (*P* > .001) correlation was found between the HFA indices and those of either HRP or FDT. A significant (*P* < .001) correlation was found between HRP-GD and FDT-MD as well as between HRP-LD and FDT-PSD. In 14% of the glaucomatous patients and in 33% of the subjects with ocular hypertension, FDT and HRP showed different clinical features.

- **CONCLUSIONS:** Our data suggest that FDT and HRP are useful for detection of early glaucomatous visual field damage. (Am J Ophthalmol 2003;135:35–39. © 2003 by Elsevier Science Inc. All rights reserved.)

Accepted for publication Aug 12, 2002.

From the Department of Neurological and Vision Sciences, Ophthalmology (M.I., M.A., G.C., C.E.T.), University of Genoa, and the Division of Ophthalmology (M.I., P.V.), the G. Gaslini Institute, Genoa, Italy.

Professor Mario Zingirian died on August 5, 2001.

Inquiries to Michele Iester, MD, Viale Teano 71/1, 16147 Genoa, Italy; fax: (+39)010-3538494. e-mail: m_ Lester@hotmail.com

STANDARD THRESHOLD PERIMETRY (STP) IS BASED ON the detection by the patient of localized light spots showed on a homogeneously illuminated background. At each tested point, it is possible to differentiate normal from abnormal sensitivity. Many different perimetric techniques are used to assess visual field in patients with primary open-angle glaucoma (POAG).^{1–7}

Retinal ganglion cells are classified on the basis of their anatomic and functional features, and perimetry can theoretically test different ganglion cell pathways using different types of stimuli. The P cells are classified as type I when they have small axons with slow conduction and are sensitive to high spatial and low temporal frequency stimuli.⁸ The loss of type I P cells is detected very well by high-pass resolution perimetry ([HRP] Nikon-High Tech Vision, Malmö, Sweden). High-pass resolution perimetry, unlike STP, is based on resolution or acuity targets. High-pass resolution perimetry has been proposed as an alternative to standard threshold perimetry to identify early visual field defects.^{9,10} High-pass resolution perimetry has shown a strong capability for detection of early visual field dishomogeneity in patients with glaucomatous damage.⁶ Type II P cells have larger bodies, larger axons, and slower conduction than type I cells and are sensitive to blue stimuli, making their loss more readily detectable by short-wave automatic perimetry.⁸ Type III are M cells, with large axons and fast conduction, and are sensitive to discriminant white/black stimuli and to low spatial and high temporal frequency stimuli.⁸ One subgroup of M cells, called the My cells, is particularly capable of carrying the latter stimuli. These cells constitute approximately 20% of total M cells, corresponding to 3% to 5% of the total number of optic nerve axons. The frequency-doubling technology ([FDT] Welch Allyn, Skaneateles, New York, USA; Zeiss Humphrey, San Leandro, California, USA) is a recently introduced perimetric technique, based on low spatial and high temporal frequency stimuli.^{5,6,11,12}

The aim of this study is to report the correlations among the Humphrey Field Analyzer 750 ([HFA 750] Humphrey, San Leandro, California, USA), HRP, and FDT perimetry in glaucoma patients and ocular hypertension (OH) patients.

DESIGN

THIS WAS A CROSS-SECTIONAL STUDY.

METHODS

EIGHTY-TWO EYES OF 82 CONSECUTIVE PATIENTS WITH POAG or OH were included in this study. One eye of each patient was randomly selected for data analysis. Patients were not excluded on the basis of gender, age, or race. Visual fields were assessed by an HFA 750, 30-2 program full threshold, which tested the central 30 degrees of the visual field. The refractive error ranged from -7 to 7 diopters.

Patients were classified as having POAG when they had a typical glaucomatous visual field or a typical abnormal optic nerve head, open angle at gonioscopy, and no clinically apparent secondary cause for their glaucoma.¹³ Patients were classified as having a glaucomatous visual field if they had at least: (1) three adjacent points depressed by 5 dB, with one of the points depressed by at least 10 dB; (2) two adjacent points depressed by 10 dB; or (3) a 10-dB difference across the nasal horizontal meridian in two adjacent points. None of the points could be edge points unless immediately above or below the nasal horizontal meridian.^{14,15} In addition, visual field testing was considered reliable only when false-negative responses were less than 30% and fixation losses were less than 20% on HFA.

Patients with OH were identified if they had high intraocular pressure (more than 21 mm Hg without any treatment), normal visual field, and normal optic nerve head and retinal nerve fiber layer.¹³

All patients were assessed by HRP and FDT.

For HRP, thresholds are determined by varying the size of the stimuli, which have fixed luminance characteristics. The stimulus is ring shaped. Each ring is made of a bright core with darker boundaries with a luminance 25 cd/m^2 and 15 cd/m^2 , respectively. Stimuli below threshold are not visible because they vanish into the 20 cd/m^2 background. Subjects are instructed to fixate a small central black-and-white cross in the center of the video screen, to refrain from gazing at eccentric stimuli, and to depress a response button each time they detect a stimulus being presented. The refractive error was corrected using the HRP set of lenses. With this technique, as soon as the patient sees the stimulus, he or she also perceives its shape. Thresholds for perception (the identification of a stimulus without recognition) and for recognition (the identification of the shape and margins of the stimulus) overlapped and were generally obtained simultaneously. Since the perception of a stimulus coincides with the recognition of the stimulus, this test theoretically challenges a function involving neuronal systems sensitive to the high frequency levels of the parvocellular chain.^{6,9,10}

The FDT provides a fast test for detecting glaucomatous and neurologic visual field defects. The technique demonstrates high sensitivity and specificity and can quantify visual field loss accurately.^{5,7,11} The FDT presents stimuli on a black-and-white video monitor with specialized control circuitry interfaced to a microprocessor. An optical system is used to display the stimulus at optical infinity, with an eyepiece adjustment provided to correct for spherical refraction errors up to 7 diopters. During program C-20, full-threshold, 17 points are tested, 1 round centrally and 16 square ones in the periphery up to 20 degrees eccentricity. The stimulus angular width is approximately 10×10 degrees peripherally and 5×5 degrees in diameter for the central one. Each stimulus consists of a 0.25 cycle per degree sinusoidal grating undergoing 25-Hz (50 times/s) counterphase flicker (contrast reversal of light and dark bars). For all stimuli the total exposure time is 2 seconds with a 1-second interval between trials. The test time for the full-threshold test ranges between 4 minutes, 30 seconds and 5 minutes per eye, while the screening test takes less than 1 minute per eye. The location for each stimulus presentation is randomly selected, and the contrast between black and white bars is modified according to the conventional "bracketing" threshold strategy of the automated standard perimetry. The threshold value for each test location is defined by the minimal contrast of the pattern that is perceived.

The frequency-doubling phenomenon is described by the patient as a quick flickering of the bars with a horizontal flicker. The age of each patient was entered in the system by the examiner, and the instrument compares subjects' responses to normal values from an age-normal database.

Subjects are instructed to fixate on a small central black square on the video monitor, to refrain from gazing at eccentric stimuli, and to depress a response button each time they detect a stimulus being presented. The unique character of the pattern makes it independent from refractive errors (up to ± 7 diopters) and other types of interferences, theoretically reducing false-positive and learning effect.^{11,16}

From the HRP indices global deviation (HRP-GD) and local deviation (HRP-LD) and from the FDT indices FDT-mean deviation (FDT-MD) and FDT-pattern standard deviation (FDT-PSD) were considered for the analysis.

All data were analyzed by Pearson r coefficient when the distribution of the data were normal and by Spearman coefficient correlation when the distribution of the data was not normal. A $P < .05$ was considered statistically significant. A linear regression model was used to determine the independent contribution of variables included in the model.

Clinical agreement among the three techniques was evaluated; for HFA the criteria are mentioned above,

TABLE 1. Mean Values and Standard Deviation (SD) in Glaucomatous and Ocular Hypertensive Patients

	POAG (n = 52)		OH (n = 30)	
	Mean	SD	Mean	SD
Age	62.22	10.43	65.42	12.08
Refraction	0.68	4.27	1.92	2.42
HFA-MD	-9.08	6.52	-0.26	1.20
HFA-PSD	6.76	3.85	2.60	1.21
HRP-GD	2.55	1.60	0.91	0.39
HRP-LD	1.11	0.35	0.90	0.38
FDT-MD	-6.46	6.02	-1.21	2.35
FDT-PSD	6.35	2.79	4.54	2.27

FDT = frequency-doubling technology; GD = global deviation; HFA = Humphrey field analyzer; HRP = high-pass resolution perimetry; LD = local deviation; MD = mean deviation; n = number of eyes; OH = ocular hypertension; POAG = primary open-angle glaucoma; PSD = pattern standard deviation.

whereas FDT was considered abnormal when at least one point had less than 5% probability to be abnormal, as each location was 10 square degrees. When the abnormal points were adjacent to the blind spot, and if the patient had a myopic refractive error, two locations were necessary before the test was considered abnormal. The visual field finding had to be present in at least two consecutive tests. High-pass resolution perimetry was considered abnormal when two of the following conditions were present: at least three adjacent points were "deep dent," global deviation, local deviation, and functional channel were outside the normal range as for software Ophthimus system version 2.0.

Clinical agreement between HRP and FDT was evaluated using the kappa test. Kappa measures change-corrected agreement on a scale of -1.0 to 1.0, with 1.0 indicating perfect agreement. We used weights suggested by Landis and Koch¹⁷: kappas of 0.0 or less were considered poor; 0.0 to 0.2, slight; 0.21 to 0.4, fair; 0.41 to 0.6, moderate; 0.61 to 0.8, substantial; and 0.81 to 1, almost perfect.

RESULTS

TABLE 1 LISTS THE DEMOGRAPHIC DATA OF THE PATIENTS considered. Fifty-two patients were classified as having glaucoma (24 male and 28 female) and 30 as having ocular hypertension (17 male and 13 female).

When the entire group was analyzed, significant correlation was found between the HFA indices and the indices for HRP and FDT. Similar correlation between STP and the other two techniques was also found when the glaucomatous group was considered in isolation. Strong corre-

TABLE 2. Correlations Among Different Indices of Different Perimetric Techniques

	Entire Group	POAG	OH
FDT MD vs HFA MD	0.76*	0.73*	0.18 NS
HRP GD vs HFA MD	0.67*	-0.47*	-0.31 NS
HRP GD vs FDT MD	-0.57*	-0.29*	-0.19 NS
FDT PSD vs HFA PSD	0.43*	0.30*	0.15 NS
HRP LD vs HFA PSD	0.72*	0.62*	0.37 NS
HRP LD vs FDT PSD	0.55*	0.36*	0.47†

FDT = frequency-doubling technology; GD = global deviation; HFA = Humphrey field analyzer; HRP = high-pass resolution perimetry; LD = local deviation; MD = mean deviation; NS = not significant; OH = ocular hypertension; POAG = primary open-angle glaucoma; PSD = pattern standard deviation.

* $P < .001$.

† $P < .01$.

lation was found between HRP-GD and FDT-MD as well as between HRP-LD and FDT-PSD both for the entire group and the glaucomatous group. In the ocular hypertensive group a significant correlation was found between HRP-LD and FDT-PSD (Table 2). As there was some correlation between the various visual field parameters we used a multiple linear regression model to determine the independent contribution of these parameters to detect glaucomatous optic disks. For the most important predictor of HFA-MD no difference was found between FDT-MD ($b = 0.618$, $SE = 0.111$, $t = 5.574$; $P < .001$) and GD ($b = -1.449$, $SE = 0.364$, $t = -3.939$; $P < .001$). The most important predictor of HFA-PSD was HRP-LD ($b = 6.868$, $SE = 0.935$, $t = 7.343$; $P < .001$), no other predictor was present (FDT-PSD ($b = 0.238$, $SE = 1.22$, $t = 1.946$; $P = .056$).

In 14% (seven patients) of the glaucomatous patients the clinical diagnosis did not agree using the two techniques: three patients had normal FDT and abnormal HRP, whereas four had abnormal FDT and normal HRP. In 33% (10 patients) of the subjects with ocular hypertension the results of FDT and HRP did not agree: four patients had normal FDT with abnormal HRP, whereas six patients had abnormal FDT and normal HRP (Table 3).

When the agreement between HFA and HRP was tested in the entire group, kappa was 0.326 ($SE = 0.1$; 95% confidence interval [CI]: 0.125 to 0.529), whereas when the agreement between HFA and FDT was tested, kappa was 0.255 ($SE = 0.11$; 95% CI: 0.049 to 0.462). When the agreement between FDT and HRP was tested, in the entire group kappa was 0.356 ($SE = 0.14$; 95% CI: 0.084 to 0.629), in the glaucoma group kappa was -0.071 ($SE = 0.376$; 95% CI: -0.808 to 0.667), in the ocular hypertension group kappa was 0.324 ($SE = 0.17$; 95% CI: -0.018 to 0.666).

TABLE 3. Agreement Among Different Perimetric Techniques

OH (n = 30)	POAG (n = 52)	HFA	FDT	HRP
0	36	Abnormal	Abnormal	Abnormal
8	0	Normal	Normal	Normal
12	9	Normal	Abnormal	Abnormal
4	1	Normal	Normal	Abnormal
6	2	Normal	Abnormal	Normal
0	2	Abnormal	Abnormal	Normal
0	2	Abnormal	Normal	Abnormal

FDT = frequency-doubling technology; HFA = Humphrey field analyzer; HRP = high-pass resolution perimetry; n = number of eyes; OH = ocular hypertension; POAG = primary open-angle glaucoma.

DISCUSSION

THE CORRELATION BETWEEN STP INDICES AND THE INDICES of the other perimetric techniques are of great interest for early detection of glaucomatous visual field loss. Pederson and Anderson¹⁸ showed that the glaucomatous alteration of ONH and RNFL caused by nerve fiber loss anticipates the perimetric defect. Because it is clinically relevant to detect glaucomatous damage to the visual field at an early stages, many psychophysical tests are being investigated. Furthermore many new perimetric techniques are available for the detection of very early visual field damage, including HRP, FDT, short-wave automatic perimetry, motion perimetry, and flicker perimetry. Each is based on a different theoretic concept. Many studies have shown correlation between standard threshold perimetry and some of these new techniques. Sponsel and associates¹⁹ also showed a good correlation between FDT and Humphrey 30-2 perimetry results, while Iester and associates showed a significant correlation between FDT and Octopus (Interzeag AG, Schlieren, Switzerland) visual field.¹¹

Using HRP, Dannheim and associates²⁰ and Chauhan and associates²¹ demonstrated a strong correlation between the indices of standard threshold perimetry and the indices of HRP.

From our data in glaucomatous patients a significant correlation was found between FDT-MD and HRP-GD, and between FDT-PSD and HRP-LD. Another significant correlation was found between indices such as FDT-PSD and HRP-LD, which showed localized damage of the visual field in ocular hypertensive group.

These results confirm that early glaucomatous visual field damage often starts with a localized depression of sensitivity. These data suggest that FDT and HRP are useful to screen populations and to detect early glaucomatous visual field progression in early and moderate stages of the disease. The significant correlation could also suggest

that early glaucomatous damage of the visual field generally start with localized depression of sensitivity. When the regression model was used, no predictor of HFA-MD was found, outlining that all the three perimetric indices tested similar sensitivity. High-pass resolution perimetry local deviation was found to be the most important predictor of HFA-PSD, suggesting the possibility that HFA and HRP techniques test the visual field similarly.

In 14% of glaucomatous patients and 33% of ocular hypertensive patients HRP and FDT results did not agree (Table 3). The reason for this disagreement could be due to the different neuronal optical pathways tested or to the different size and shape of the visual field changes tested. High-pass resolution perimetry examinations inside roughly 30 central degrees whereas FDT tested 20 central degrees. Frequency-doubling technology was able to detect 29 subclinical visual fields among the entire group with normal HFA, whereas HRP detected 26 abnormal visual fields.

When clinical agreement was studied among the glaucomatous patients, there was full agreement in 36 subjects; in 9 glaucomatous patients HFA was normal and FDT and HRP were abnormal, supporting the theoretical ability of FDT and HRP to detect early visual field. In 9 glaucomatous patients visual fields were in disagreement among the three different techniques. In 8 OH patients there was full agreement among the three perimetric techniques; in 12 subjects there was an agreement between FDT and HRP, but both techniques disagreed to HFA. In 10 cases FDT and HRP disagreed. The kappa statistic showed slight agreement among all the three techniques; however, the strongest agreement was found between FDT and HRP (kappa: 0.356).

Our data supported the potential usefulness of FDT and HRP to detect glaucoma. The results, however, are not completely explained. The findings of normal HFA and abnormal FDT or HRP would imply the capacity of these techniques to detect an abnormal visual field. The contrary results are more difficult to explain, however; the disagreement found in the same eyes between the two techniques could be the result of falsely positive or negative answers intrinsic to psychophysical techniques.

The agreement found between the two techniques prevents appreciation of any difference between the two tested corticonneuronal pathways (P cells and M cells). It is possible to assume a contemporary loss of P cells and M cells in glaucoma. Our data failed to demonstrate whether the two techniques actually challenged different neuronal pathway, although both perimetric techniques appeared to measure ganglion cell loss.

In conclusion, the data from this study suggest that both FDT and HRP could be useful to identify glaucomatous visual field damage in early and moderate stages of the disease. Our data failed to demonstrate whether the two techniques actually challenged different neuronal path-

way, although both perimetric techniques appeared to measure ganglion cell loss.

ACKNOWLEDGMENT

This paper is dedicated to the memory of Professor Mario Zingirian, who was a great "perimetrist".

REFERENCES

1. Lindblom B. High-pass resolution perimetry: a new method for the early detection of visual field. *Chibret Int J Ophthalmol* 1990;7:33-41.
2. Chauhan BC, House PH. Intratest variability in conventional and high-pass resolution perimetry. *Ophthalmology* 1991;98:79-83.
3. Douglas GR, Drance SM, Mikelberg FS, Schulzer M, Wijsman K. Variability of the Frisen ring perimetry. *Ophthalmology* 1991;98:79-83.
4. Birt CM, Shin DH, McCarty B, Kim C, Lee DT, Chung HS. Comparison between high-pass resolution perimetry and differential light sensitivity perimetry in patients with glaucoma. *J Glaucoma* 1998;7:111-116.
5. Quigley HA. Identification of glaucoma-related field abnormality with the screening protocol of frequency doubling technology. *Am J Ophthalmol* 1998;125:819-829.
6. Frisén L. High-pass resolution perimetry. Recent developments: In: Heijl A, editor: *Perimetry up-date 1988/89*. Amsterdam, Kugler and Ghedini, 1989:369-375.
7. Johnson CA, Samuels SJ. Screening for glaucomatous visual field loss with frequency-doubling perimetry. *Invest Ophthalmol Vis Sci* 1997;38:413-425.
8. Wiesel TN, Hubel DH. Spatial and chromatic interactions in the lateral geniculate body of the rhesus monkey. *J Neurophysiol* 1966;29:1115-1155.
9. Frisén L. High-pass resolution perimetry. *Doc Ophthalmol* 1993;83:1-25.
10. Frisén L. A computer-graphic visual field screener using high-pass spatial frequency resolution targets and multiple feedback devices. *Doc Ophthalmol Proc Ser* 1987;49:441-446.
11. Iester M, Mermoud A, Schnyder C. Frequency doubling technique in patients with ocular hypertension and glaucoma. *Ophthalmology* 2000;107:288-294.
12. Johnson CA, Demirel S. The role of spatial and temporal factors in frequency-doubling perimetry. In: Wall M, Heijl A, editors. *Perimetry up-date 1996/97*. Amsterdam: Kugler, 1997:9-13.
13. European Glaucoma Society 1998. Terminology and guidelines for glaucoma. Savona: Dogma, 1998:64-65.
14. Iester M, Swindale NV, Mikelberg FS. Sector-based analysis of optic nerve head shape parameters and visual field indices in healthy and glaucomatous eyes. *J Glaucoma* 1997;6:371-376.
15. Caprioli J. The contour of the juxtapapillary nerve fiber layer in glaucoma. *Ophthalmology* 1990;97:358-366.
16. Iester M, Capris P, Pandolfo A, Zingirian M, Traverso CE. Learning effect, short term fluctuation and long-term fluctuation in frequency doubling technique. *Am J Ophthalmol* 2000;130:160-164.
17. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977;33:159-174.
18. Pederson JE, Anderson DR. The mode of progressive disc cupping in ocular hypertension and glaucoma. *Arch Ophthalmol* 1980;58:14-19.
19. Sponsel WE, Arango S, Trigo Y, Mensah J. Clinical classification of glaucomatous visual field loss by frequency doubling perimetry. *Am J Ophthalmol* 1998;125:830-836.
20. Danheim F, Abramo F, Verlhor D. Comparison of automated conventional and spatial resolution perimetry in glaucoma: In: Heijl A, editor. *Perimetry up-date 1988/89*. Amsterdam: Kugler and Ghedini, 1989:383-392.
21. Chauhan BC, LeBlanc RP, McCormick TA, Rogers JB. Comparison of high-pass resolution perimetry and pattern discrimination perimetry to conventional perimetry in glaucoma. *Can J Ophthalmol* 1993;28:306-311.