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Sector-based analysis of frequency doubling technology sensitivity and optic nerve head shape parameters

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PURPOSE. *To evaluate which Heidelberg Retina Tomograph (HRT) parameter is the best predictor of frequency doubling technology (FDT) sensitivity by using a sector based analysis between FDT and optic nerve head shape parameters such as cup shape measure (CSM) and rim area (RA), which have been shown to have the best correlation with FDT indices among all the HRT parameters.*

METHODS. *One eye was randomly chosen from 100 patients with primary open angle glaucoma (abnormal visual field and/or abnormal optic nerve and untreated intraocular pressure above 21 mmHg). All the patients were examined with Humphrey field analyzer (HFA), program 24-2, SITA standard, FDT program C 20, and HRT. RA and CSM for the HRT analysis and mean deviation, pattern standard deviation, and the sensitivity of each tested point for the FDT test were considered in this study. All the parameters were calculated as both global and sector measurements. Findings were analyzed using Pearson's correlation coefficient and linear regression model.*

RESULTS. *Significant ($p<0.001$) correlation was found between FDT indices and HRT RA and CSM. Significant ($p<0.001$) sector correlation was found between FDT sensitivity and RA and CSM, but when a linear regression model was applied, RA was the most predictive parameter of FDT. Temporal CSM was more strongly correlated to FDT fovea sensitivity than temporal RA. Furthermore, sector HRT parameters were better correlated to HFA than to FDT.*

CONCLUSIONS. *In this glaucomatous group, cup shape measure and RA were significantly correlated to FDT indices. RA was more predictive of FDT abnormality than CSM in all the considered sectors except in the temporal one. However, HFA was a stronger predictor of HRT parameters than FDT. (Eur J Ophthalmol 2007; 17: 223-9)*

KEY WORDS. *Frequency doubling technology, Standard threshold perimetry, Nonconventional perimetry, Indices, Heidelberg Retina Tomograph, Confocal scanning laser*

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INTRODUCTION

Several authors have shown that both optic nerve head (ONH) analysis and unconventional perimetry tests, such as frequency doubling technology (FDT, Welch-Allyn, Skaneateles, NY, Zeiss-Humphrey, San Leandro, CA, USA), could be able to detect glaucomatous changes earlier than

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white/white visual field defects (1-5).
It has been found that Heidelberg Retina Tomograph (HRT, Heidelberg Engineering, Heidelberg, Germany; software version 2.01) cup shape measure (CSM) and rim area (RA) were correlated to standard automated perimetry (SAP) indices in a population of glaucomatous subjects and that RA was the most predictive parameter of Humphrey Field Analyzer (HFA) indices (6). Furthermore, CSM and RA were the most useful parameters to detect early glaucomatous ONH changes (7-9). In particular, CSM is the parameter which is almost always present in all the discriminant analysis formulas and RA is the parameter used by the Moorfields Regression Analysis (7, 10, 11).
The aim of this study was to evaluate which HRT parameter, CSM or RA, which have been shown to have the best correlation with FDT indices among all the HRT parameters (12), was the best predictor of FDT sensitivity by using a sector-based analysis.

PATIENTS AND METHODS

This was a cross-sectional study. The research followed the tenets of the Declaration of Helsinki and informed consent was asked of all considered patients. One eye was randomly chosen from 100 patients with primary open angle glaucoma (POAG). Neither HRT nor FDT was used to classify patients. Patients were not excluded on the basis of sex, age, or race. The refractive error ranged from –7 to +7 diopters. Visual fields were assessed by HFA 750 (Humphrey, Inc.), 24-2 SITA (Swedish Interactive Threshold Algorithm) standard, program full threshold, which tested the central 24 degrees of the visual field. Patients were excluded when either HFA or FDT visual field testing was considered unreliable (false-negative and false-positive responses >30% and fixation losses >20%) (8, 13). Furthermore, to avoid any learning effect defects, all the included patients were experts in visual field testing (they have already had at least three visual field tests in the last 3 years). In addition, patients with an HRT mean image with a standard deviation higher than 30 were excluded.
Patients were classified as having POAG when they had a typical glaucomatous visual field and/or a typical abnormal optic nerve head, open angle at gonioscopy, intraocular pressure (IOP) > 21 mmHg with no treatment, and no clinically apparent secondary cause for their glaucoma (14).
Patients were classified as having a glaucomatous visual field if they had on the pattern deviation plots 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 (8, 15). Mean deviation (MD) and pattern standard deviation (PSD) were considered in the study.
An ONH was classified as abnormal when there was an optic rim notch or diffuse/generalized loss of optic rim tissue, vertical cup/disc diameter ratio asymmetry unexplained by side differences in optic disc size, or a disc hemorrhage.
All the patients' visual fields were assessed by FDT, program C 20, threshold program, and both ONHs of each patient were analyzed by confocal scanning laser tomograph.

Frequency doubling technology

The FDT allows a relatively fast assessment of the central visual field. The reliable detection of glaucomatous visual field defects is well established. This technique has shown high sensitivity and specificity and can quantify visual field loss accurately (3, 4). Technical details were published earlier (13, 16-18).
For the analysis, FDT-mean deviation (FDT-MD), FDT-pattern standard deviation (FDT-PSD), and the sensitivity of four quadrants were considered and used to calculate the correlation. Using the FDT sensitivity map printout, the sensitivity of each quadrant was calculated manually. To avoid any learning effect the second FDT test was selected (10, 19, 20).

Heidelberg retina tomograph

The ONH were morphometrically evaluated by using the HRT. Details of this technique were previously published (21-26). The HRT is a confocal scanning diode laser with a wavelength of 670 nm. A series of 32 confocal images are obtained at consecutive focal planes, each 256 x 256 pixels, that the computer converts into a single topographic image. The depth of

TABLE I - DESCRIPTIVE STATISTICS

	Mean	SD	Minimum	Maximum
RA	1.46	0.46	0.23	3.23
T RA	0.24	0.11	0.07	0.72
TS RA	0.17	0.07	0.00	0.48
TI RA	0.17	0.08	0.00	0.41
NS RA	0.21	0.07	0.00	0.50
NI RA	0.22	0.07	0.00	0.47
CSM	–0.12	0.12	–0.34	0.77
T CSM	–0.06	0.10	–0.27	0.33
TS CSM	–0.04	0.13	–0.30	0.34
TI CSM	–0.05	0.13	–0.40	0.32
NS CSM	–0.12	0.15	–0.56	0.39
NI CSM	–0.13	0.20	–0.59	1.47
FDT MD	–3.38	5.32	–20.32	1.92
FDT PSD	3.63	2.91	0.00	14.10
Fovea	27.70	6.92	0.00	38.00
NI	24.75	9.04	0.00	39.00
NS	23.83	9.19	0.00	39.75
TI	25.26	7.90	0.00	52.75
TS	24.74	7.37	0.00	43.25
HFA MD	–4.69	6.60	–27.68	2.79
HFA PSD	4.12	3.45	0.98	14.18

RA = Rim area; T = Temporal; TS = Temporal superior; TI = Temporal inferior; N = Nasal; NS = Nasal superior; NI = Nasal inferior; CSM = Cup shape measure; FDT = Frequency doubling technology; MD = Mean deviation; PSD = Pattern standard deviation; HFA = Humphrey field analyzer

TABLE II - PEARSON r CORRELATION COEFFICIENT

	FDT-MD	FDT-PSD
RA	0.43	–0.44
	p<0.001	p<0.001
CSM	–0.34	0.27
	p<0.001	p=0.001
Fovea		
TRA	0.27	
	p<0.001	
TCSM	–0.39	
	p<0.001	

FDT = Frequency doubling technology; MD = Mean deviation; PSD = Pattern standard deviation; RA = Rim area; CSM = Cup shape measure; TRA = Temporal RA; TCSM = Temporal CSM

each topographic image series ranges between 0.5 mm and 4.0 mm in 0.5-mm increments depending on individual differences in the optic disc morphology. For each eye, three 10° confocal scanning laser tomographic images were obtained. The HRT mean standard deviation was 28.0±17.6 µm. The reproducibility and reliability of this technique have already been described in detail elsewhere (21-26).

We measured both global and sector HRT predefined (as for software vs 2.01) RA and CSM in this study.

TABLE III - PEARSON r CORRELATION COEFFICIENT FOR EACH SECTOR

	NI FDT	NS FDT	TI FDT	TS FDT
TS CSM	–0.39			
	p<0.001			
TI CSM		–0.37		
		p<0.001		
NS CSM			–0.32	
			p<0.001	
NI CSM				–0.11
				p=0.188
TS RA	0.48			
	p<0.001			
TI RA		0.53		
		p<0.001		
NS RA			0.46	
			p<0.001	
NI RA				0.32
				p<0.001

TS = Temporal superior; TI = Temporal inferior; N = Nasal; NS = Nasal superior; NI = Nasal inferior; FDT = Frequency doubling technology; CSM = Cup shape measure; RA = Rim area

Statistical analysis

All data were analyzed by Student *t*-test and Pearson r coefficient when the distribution of the data was normal and by Spearman coefficient correlation and Mann-Whitney test when the distribution of the data was not normal. A linear regression model was also used to determine the independent contribution of variables included in the model. Because multiple statistical comparisons were performed, a p value ≤0.001 was considered significant to avoid any correlation just for chance.

RESULTS

One hundred patients were included in the study. The details of the glaucomatous patients are listed in Table I. Significant correlation was found between the two HRT parameters and FDT indices (Tab. II). FDT fovea sen-

TABLE IV - LINEAR REGRESSION MODEL

	B	SE	Beta	p value
FDT MD vs				
RA	3.98	0.94	0.35	<0.001
CSM	–8.43	3.70	–0.19	0.024
FDT PSD vs				
RA	–2.53	0.52	–0.40	<0.001
CSM	2.21	2.04	0.09	0.279

FDT = Frequency doubling technology; MD = Mean deviation; RA = Rim area; CSM = Cup shape measure

TABLE V - LINEAR REGRESSION MODEL

	B	SE	Beta	p value
FDT NI vs				
RA TS	47.30	10.69	0.39	<0.001
CSM TS	–11.47	5.98	–0.17	0.057
FDT NS vs				
RA TI	56.96	10.38	0.48	<0.001
CSM TI	–6.69	6.27	–0.09	0.288
FDT TI vs				
RA NS	43.40	9.11	0.39	<0.001
CSM NS	–8.07	4.36	–0.15	0.066
FDT TS vs				
RA NI	31.72	8.41	0.32	<0.001
CSM NI	0.07	3.06	0.00	0.982

FDT = Frequency doubling technology; NI = Nasal inferior; RA = Rim area; TS = Temporal superior; CSM = Cup shape measure; NS = Nasal superior; TI = Temporal inferior

sitivity was significantly correlated to temporal RA and CSM: CSM had a stronger correlation than RA (Tab. II). When sector HRT parameters and quadrant FDT indices were considered, significant correlation was found among the four different sectors, except for NI CSM vs TS FDT (Tab. III).

Since both HRT parameters were significantly correlated to FDT quadrant sensitivities, a multiple linear regression model was used to determine the independent contribution of these parameters to detect glaucomatous optic discs. When global parameters were considered and the most important predictor of FDT MD and FDT PSD was calculated, RA was the only predictor parameter (Tab. IV). When the multiple linear regression model was applied to determine the independent contribution of the HRT parameters for each considered sector, RA was the most important predictor of FDT quadrant sensitivity (Tab. V).

TABLE VI - LINEAR REGRESSION MODEL

	B	SE	Beta	p value
HFA MD vs				
RA	5.31	1.12	0.38	<0.001
CSM	–13.59	4.38	–0.25	<0.001
HFA PSD vs				
RA	–2.94	0.60	–0.40	<0.001
CSM	5.04	2.35	0.18	0.033
RA vs				
HFA MD	0.03	0.01	0.37	0.001
FDT MD	0.02	0.01	0.18	0.090
RA vs				
HFA PSD	–0.05	0.02	–0.34	0.003
FDT PSD	–0.03	0.02	–0.19	0.085
CSM vs				
HFA MD	–0.01	0.00	–0.35	0.002
FDT MD	0.00	0.00	–0.10	0.372
CSM vs				
HFA PSD	0.01	0.00	0.34	0.004
FDT PSD	0.00	0.00	0.01	0.931

HFA = Humphrey field analyzer; MD = Mean deviation; RA = Rim area; CSM = Cup shape measure; PSD = Pattern standard deviation; FDT = Frequency doubling technology

Furthermore, significant ($p<0.001$) correlation was found between HFA MD and CSM ($r=–0.41$) and RA ($r=0.49$) and between HFA PSD and CSM ($r=0.35$) and RA ($r=–0.48$). The most important predictor of both HFA MD and HFA PSD was calculated, and RA was the only predictor parameter (Tab. VI). Then a multiple linear regression model was applied to determine the independent contribution of HFA and FDT indices for HRT and both HFA indices were the most important predictors of HRT parameters (Tab. VI).

DISCUSSION

Many psychophysical tests are being investigated since it is clinically relevant to detect glaucomatous functional damage at an early stage (3-5, 16, 27, 28). The correlation between structure and function is of great interest. Different studies support the existence of correlations between SAP and morphometric parameters (6, 8, 29-32). Which functional or structural parameter is the first to detect glaucomatous alteration depends broadly on the sensitivity of each examination

technique. Previous studies have demonstrated the usefulness of morphologic parameters to elucidate the deviation from normal in early stages of glaucoma (7, 11, 33); however, the results are mainly influenced by which parameter is used as the gold standard to be challenged.

Different authors showed significant correlation ($p<0.0001$) between HRT parameters and SAP indices (6, 31, 32). In particular, when a multiple regression model was applied, RA was the most important predictor of MD and PSD, followed by CSM (6).

Significant correlation was found between SAP and FDT in different studies (3, 33). FDT had a high sensitivity to differentiate normal subjects from patients with glaucoma and was able to quantify glaucoma damage (3, 4, 16, 17). Medeiros et al showed that functional abnormalities detected by FDT perimetry were predictive of the future onset and location of standard threshold perimetry loss among glaucoma suspect subjects (34). In a recent study, Iester et al showed some correlation between HRT and FDT, in particular in the glaucoma subgroup rather than in ocular hypertension subgroup (12).

In this study, significant sector and global correlations were found between HRT and FDT in patients with glaucoma, but when sector parameters were used, RA had the strongest correlation with both perimetric techniques. Furthermore, when the regression model was used to determine which perimetric technique was the most predictive of RA or CSM, HFA indices were the most important predictor of HRT parameters.

The presence of significant correlation between SAP and HRT is well known, and between FDT and SAP, and it has been shown that HRT and FDT could detect glaucomatous damage earlier than standard threshold perimetry, but the data of this study suggested that HRT CSM and RA are better correlated to HFA than FDT, even when sector measurements were considered.

Theoretically, sector correlation should be stronger than global because of the loss of the measurement noise and the damage location is analyzed without considering all the other data; however, from this study the correlation coefficients were similar. Temporal HRT parameters had a stronger correlation than nasal HRT ones, suggesting that the temporal ONH sides are more useful to check in the follow-up.

Since both perimetric techniques seem to be able to detect early glaucomatous damage with good sensitivity and specificity, we compared FDT quadrants with HRT sectors to evaluate which HRT parameter was the best indicator of FDT indices. RA was the most important predictor of visual field indices in the detection of visual field loss (6, 7); however, different studies showed that CSM had the highest diagnostic capacity among the HRT parameters (9, 35). Furthermore, a significant correlation was found between FDT foveal sensitivity and both temporal CSM and RA, suggesting that the papilla-fovea bundle could be involved in glaucomatous disease earlier than in the latest stages (Tab. II). Furthermore, CSM was found to have a stronger correlation than RA, suggesting the temporal RA is smaller than in the other sectors and the analysis of the shape could be more useful.

The study suggested the possibility that FDT and HRT assessed different types of cells even if using two completely different methods. In particular, HRT and standard threshold perimetry could assess all the ganglion cells, while FDT should evaluate only a subgroup of ganglion cells. We could speculate that HRT and HFA assess ganglion cells in two different ways: morphometrically and functionally, respectively. If all the ganglion cells are considered together, due to a redundancy effect, standard threshold perimetry is not able to detect any early loss of cells, but HRT should be able to assess the loss of axons because of a volumetric change.

In conclusion, our data showed that in a sector analysis there was a correlation between HRT sectors and FDT quadrants; furthermore, by multiple linear regression analysis, while RA and CSM were equally strong predictors of HFA MD, only RA was strong predictor of HFA PSD, FDT MD, and FDT PSD. By sector, only RA was strong predictor of FDT quadrant sensitivity, while temporal CSM was more significantly correlated to FDT fovea sensitivity. Overall, HFA was a stronger predictor of HRT parameters than FDT.

None of the authors has a proprietary interest in the development and marketing of any products mentioned in the article.

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REFERENCES

1. Kamal DS, Viswanthan AC, Garway-Heath DF, et al. Detection of optic disc change with the HRT before confirmed visual field change in ocular hypertensives converting to early glaucoma. Br J Ophthalmol 1999; 83: 290-4.
2. Chauhan BC, McCormick TA, Nicolela MT, LeBlanc RP. Optic disc and visual field changes in a prospective longitudinal study of patients with glaucoma. Arch Ophthalmol 2001; 119: 1492-9.
3. Quigley HA. Identification of glaucoma-related field abnormality with the screening protocol of frequency doubling technology. Am J Ophthlamol 1998; 125: 819-29.
4. Sponsel WE, Arango S, Trigo Y, Mensah J. Clinical classification of glaucomatous visual field loss by frequency doubling perimetry. Am J Ophthlamol 1998; 125: 830-6.
5. Iester M, Altieri M, Vittone P, et al. Detection of glaucomatous visual field defect by nonconventional perimetry. Am J Ophthalmol 2003; 135: 35-9.
6. Iester M, Mikelberg FS, Courthright P, Drance SM. Correlation between the visual field indices and Heidelberg Retina Tomograph parameters. J Glaucoma 1997; 6: 78-82.
7. Wollstein G, Garway-Heath DF, Hitchings RA. Identification of early glaucoma cases with the scanning laser ophthalmoscope. Ophthalmology 1998; 105: 1557-63.
8. 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: 371-6.
9. Iester M, Mikelberg FS, Swindale NV, Drance SM. ROC analysis of Heidelberg Retina Tomograph optic disc shape measure in glaucoma. Can J Ophthalmol 1997; 32: 382-8.
10. Iester M, Capris P, Pandolfo A, et al. Learning effect, short term fluctuation and long-term fluctuation in frequency doubling technique. Am J Ophthalmol 2000; 130: 160-4.
11. Iester M, Mardin CY, Budde WM, et al. Discriminant analysis formulas of optic nerve head parameters measured by confocal scanning laser tomography. J Glaucoma 2002; 11: 97-104.
12. Iester M, Traverso CE, De Feo F, et al. Correlation between frequency doubling technology and Heidelberg Retina Tomograph. J Glaucoma 2005; 14: 368-74.
13. Johnson CA, Demirel S. The role of spatial and temporal factors in frequency-doubling perimetry. In: Wall M, Heijl A, eds. Perimetry Up-date 1996/97. Amsterdam/New York: Kugler Publications, 1997; 13-9.
14. European Glaucoma Society 1998. Terminology and Guidelines for Glaucoma. Savona: Dogma, 1998; 64-5.
15. Caprioli J. The contour of the juxtapapillary nerve fiber layer in glaucoma. Ophthalmology 1990; 97: 358-66.
16. Johnson CA, Samuels SJ. Screening for glaucomatous visual field loss with frequency-doubling perimetry. Invest Ophthalmol Vis Sci 1997; 38: 413-25.
17. Iester M, Mermoud A, Schnyder C. Frequency doubling technique in patients with ocular hypertension and glaucoma. Ophthalmology 2000; 107: 288-94.
18. Heijl A, Bengtsson B. The effect of perimetric experience in patients with glaucoma. Arch Ophthalmol 1996; 114: 19-22.
19. Matsuo H, Tomita G, Suzuki Y, Araie M. Learning effect and measurement variability in frequency-doubling technology perimetry in chronic open-angle glaucoma. J Glaucoma 2002; 11: 467-73.
20. Horani A, Frenkel S, Yahalom C, et al. The learning effect in visual field testing of healthy subjects using frequency doubling technology. J Glaucoma 2002; 11: 511-6.
21. Dreher AW, Tso PC, Weinreb RN. Reproducibility of topographic measurements of the normal and glaucomatous nerve head with the laser tomographic scanner. Am J Ophthalmol 1991; 111: 221-9.
22. Kruse FE, Burk ROW, Völcker HE, et al. Reproducibility of topographic measurements of the optic nerve head with laser tomographic scanning. Ophthalmology 1989; 96: 1320-4.
23. Cioffi GA, Robin AL, Eastman RD, et al. Confocal laser scanning ophthalmoscope: reproducibility of optic nerve head topographic measurements with the confocal scanning laser ophthalmoscope. Ophthalmology 1993; 100: 57-62.
24. Weinreb RN, Lusky M, Bartsch DU, Morsman D. Effect of repetitive imaging on topographic measurements of the optic nerve head. Arch Ophthalmol 1993; 111: 636-8.
25. Mikelberg FS, Wijsman K, Schulzer M. Reproducibility of topographic parameters obtained with the Heidelberg Retina Tomograph. J Glaucoma 1993; 2: 101-3.
26. Chauhan BC, LeBlanc RP, McCormick TA, Rogers JB. Test-retest variability of topographic measurements with confocal scanning laser tomography in patients with glaucoma and control subjects. Am J Ophthalmol 1994; 118: 9-15.
27. Sample P, Weinreb RN. Progressive colour visual field loss in glaucoma. Invest Ophthalmol Vis Sci 1992; 33: 2068-71.
28. Birt CM, Shin DH, McCarty B, et al. Comparison between high-pass resolution perimetry and differential light sensitivity perimetry in patients with glaucoma. J Glaucoma 1998; 7: 111-6.
29. Funk J, Bornscheuer C, Grehn F. Neuroretinal rim area and visual field in glaucoma. Graefes Arch Clin Exp Ophthalmol 1988; 226: 431-4.
30. Jonas JB, Gusek GC, Naumann GOH. Optic disc morphometry in chronic primary open-angle glaucoma. Graefes Arch Clin Exp Ophthalmol 1988; 226: 531-8.

31. Brigatti L, Caprioli J. Correlation of visual field with scanning confocal laser optic disc measurements in glaucoma. Arch Ophthalmol 1995; 113: 1191-4.
32. Tole DM, Edwards MP, Davey KG, Menage MJ. The correlation of the visual field with scanning laser ophthalmoscope measurements in glaucoma. Eye 1998; 12: 686-90.
33. Iester M, Jonas JB, Mardin CY, Budde WM. Discriminant analysis models for early detection of glaucomatous optic disc changes. Br J Ophthalmol 2000; 84: 464-8.
34. Medeiros FA, Sample PA, Weinreb RN. Frequency doubling technology perimetry abnormalities as predictors of glaucoma visual field loss. Am J Ophthalmol 2004; 137: 863-71.
35. Uchida H, Brigatti L, Caprioli J. Detection of structural damage from glaucoma with confocal laser image analysis. Invest Ophthalmol Vis Sci 1996; 37: 2393-401.