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Diagnostic accuracy and reproducibility of tendency oriented perimetry in glaucoma

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PURPOSE. *To evaluate the diagnostic capability of tendency oriented perimetry (TOP) in glaucoma.*

METHODS. *A): The diagnostic accuracy of mean defect (MD), square-root of the loss variance (sLV), and number of pathologic points (NPP) was calculated in 295 normal and 414 glaucoma eyes (179 early, 112 moderate, and 123 advanced) examined with TOP. B): Threshold fluctuation (F) and its relationship with the loss variance (LV) was measured in 34 normal and 33 glaucoma eyes (mean MD=3 dB; SD=3.9) for TOP and for full-threshold perimetry (FT). C): Twenty-eight eyes with stable glaucoma (mean MD=9.5 dB; SD=7.2) were examined six times to quantify LV error. D): TOP and FT were tested with the simulation program PeriSim using different behavior models.*

RESULTS. *A): The best diagnostic index in early glaucoma (MD<6dB) was sLV (specificity=90.2%, sensitivity=84.9). The three indices had similar precision in moderate and severe glaucoma. B): Threshold fluctuation and sLV were better correlated in TOP (r=0.72, p<0.01) than in FT (r=0.62, p<0.01). For normal subjects, in FT the incidence of F<2 dB was 8.82% and sLV<1.5 dB 5.88%. The same frequencies in TOP were 67.65% and 55.88%. C): Averaging six examinations reduced the sLV value by 22%. D): The threshold estimation error increased 1 dB in TOP in relation to FT for the same patient's behavior, but the error in TOP was lower than in FT when the worst behavior was modeled.*

CONCLUSIONS. *TOP is a good discriminator between glaucoma and normality. Perimetry results overestimate the real sLV value. TOP's high diagnostic ability is probably associated to the algorithm design and to less contaminating influences during the examination. (Eur J Ophthalmol 2006; 16: 259-67)*

KEY WORDS. *Visual field, Perimetry, Glaucoma, Diagnosis*

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INTRODUCTION

Short perimetric strategies such as the Swedish interactive threshold algorithm (SITA) and tendency oriented perimetry (TOP) have gained acceptance in recent years as their diagnostic capability has been confirmed (1). Their advantages include a more efficient use of perimetric equipment; the feasibility of performing more frequent examinations, allowing better assessment of the stability or progression of the disease; the possibility of testing children (2); and increased patient comfort.

The standard bracketing full-threshold perimetry (FT) calculates the threshold of each point as completely independent from the surrounding ones. In contrast, tendency

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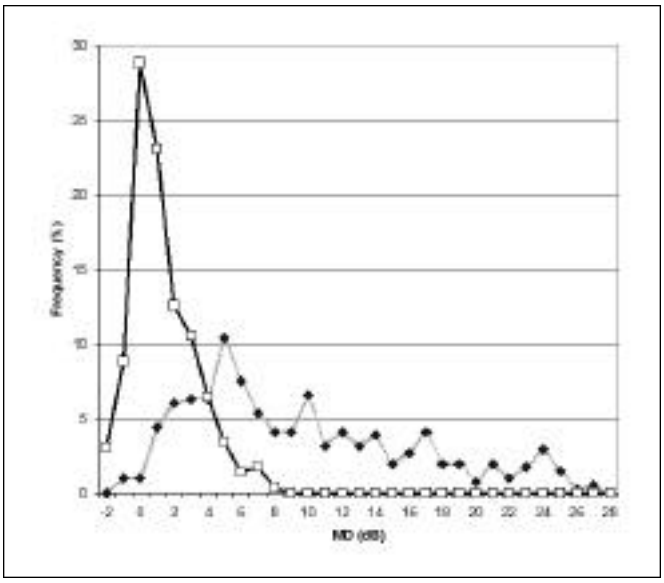

Fig. 1 - *Distribution of frequencies of mean defect (MD) value for control (black line) and glaucoma cases (gray line) in the whole sample.*

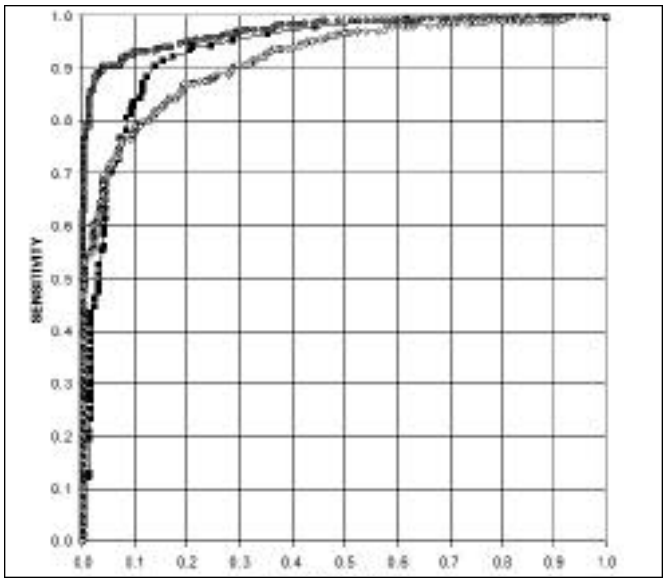

Fig. 2 - *Receiver operating characteristic curves corresponding to the whole sample (square-root of the loss variance = gray circles, number of pathologic points = black squares, mean defect = white rhomboids).*

oriented perimetry (TOP) relies upon the relationships of threshold sensitivities among different visual field locations (3). Thus, TOP uses these interpoint relationships to estimate the threshold of neighboring points, greatly reducing testing time.

Several studies have documented equivalent diagnostic capabilities between TOP and standard FT strategies (4-8). Better test-retest reproducibility may be achieved with TOP (9). However, it has been noted that TOP produces loss variance (LV) values slightly lower than FT (10), as a result of taking into account surrounding point values to calculate the individual thresholds. This observation has led some authors to suggest that the capability of TOP to detect early and subtle defects could be lower than FT's (11-13).

We review the concept of the main perimetric indices for better understanding: the mean defect (MD) index quantifies the overall reduction in sensitivity compared with an age-matched normal population. It is generally accepted that the MD is a robust perimetric index (14, 15). The LV (16), and its equivalent in Humphrey perimetry, the pattern standard deviation (PSD), quantifies the irregularity of defects across the visual field. These indexes have also been considered useful diagnostic tools, and appear to be better predictors of progression from ocular hypertension to glaucoma than MD (17, 18). The number of points with significantly reduced sensitivity, their grouping forming clusters (19), and the asymmetry between upper and lower thresholds (20) are criteria also utilized for diagnostic purposes.

Since the introduction of the quick perimetric strategy TOP, several studies have analyzed its sensitivity and specificity, using several diagnostic criteria: 1) the MD and LV cutoff points given by instrument manufacturers to discriminate between normality and pathology (1, 7, 21); 2) subjective normal or pathologic classification of visual fields by a specialist (7); and 3) the number of pathologic points and their grouping forming clusters (1, 6, 7). Some of these articles have reported high diagnostic accuracy of LV-TOP (21, 22).

Anderson (13), using a simulation model and theoretical visual fields, in which thresholds do not have proximity relations, has recently suggested that the lower LV values in TOP compared with FT are the consequence of ignoring isolated defects.

This article has been designed to evaluate the diagnostic accuracy, reproducibility, and performance of TOP clinically as well as using a simulation model (13). Four studies were designed: (A) evaluation of LV- TOP's diagnostic accuracy on a wide sample of patients from several health centers, using the traditional regular distribution of examination points (TOP-32) and irregular distribution, with higher density of central points, which is usual in Octopus perimeters (TOP-G1); (B) analysis of the relationship

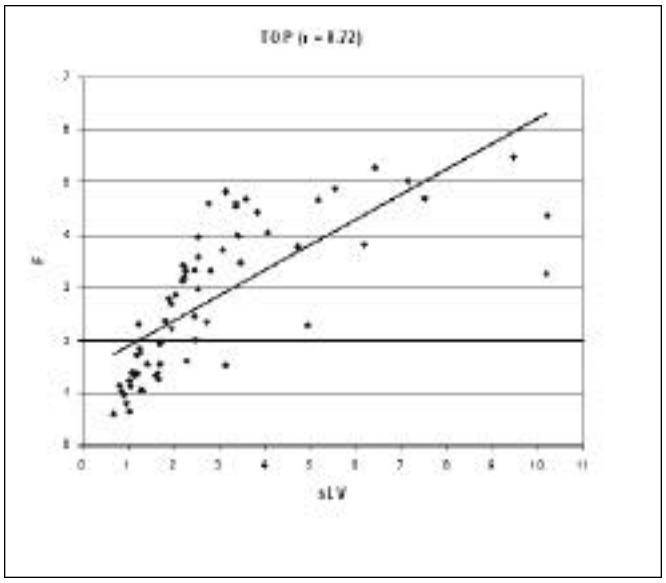

Fig. 3 - *Correlation between fluctuation (F) and square-root of the loss variance (sLV) using tendency oriented perimetry.*

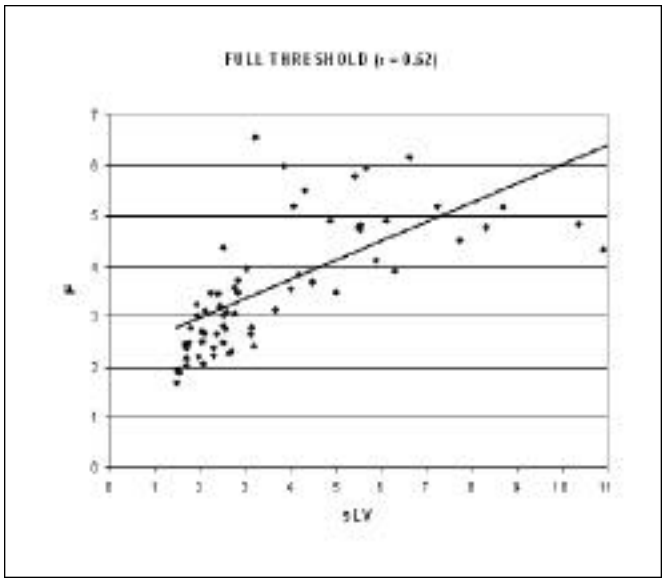

Fig. 4 - *Correlation between fluctuation (F) and square-root of the loss variance (sLV) using full threshold.*

between threshold test-retest fluctuation (F) and LV value in both strategies; (C) analysis of components that contribute to LV: real visual field irregularity, threshold fluctuation, and "noise," understanding noise as the threshold variability caused by the instrumental, strategy, and patient errors; and (D) TOP and FT accuracy estimation using a simulation program that allows modifying patient's reliability, modulating not just threshold fluctuation but also the main noise components.

MATERIALS AND METHODS

Study A: Diagnostic accuracy of the main perimetric indices

Chronic open angle glaucoma patients and normal subjects from four different academic institutions were included in this study. The glaucoma diagnosis was made by any of the following criteria: 1) glaucomatous appearance of the optic nerve (including a localized thinning or notch of the neuroretinal rim, cup-to-disc ratio >0.8, or vertical enlargement of the cup); 2) reproducible visual field defects on previous examinations on standard Bracketing perimetry (MD>2 dB, LV>6 dB, or three or more contiguous abnormal points – $p<0.05$ – in the arcuate area in the pattern deviation plot); 3) evidence of glaucomatous visual field progression; and/or 4) marked asymmetry between both eyes' visual fields or optic nerves (difference

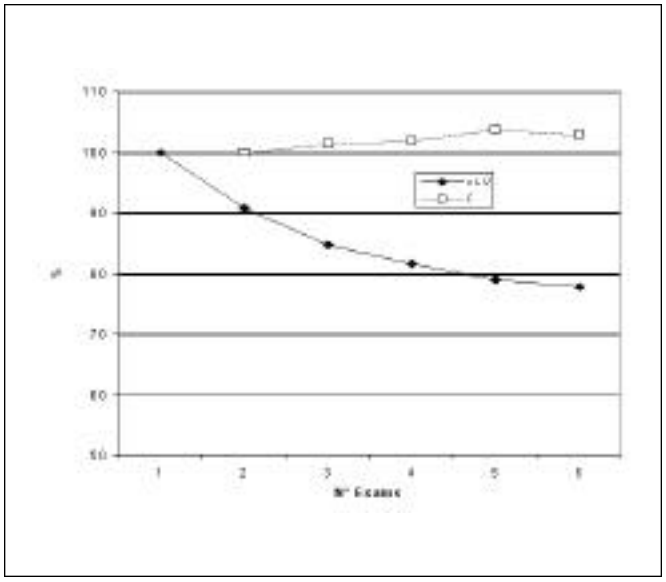

Fig. 5 - *Change of mean defect, fluctuation (F), and square-root of the loss variance (sLV) values after averaging several examinations of the same subjects.*

>0.2 of the cup-disc ratio, difference between eyes of > 2 dB of MD value). Anterior chamber angle was open. Glaucoma patients did not have any other ocular pathology. Controls had a normal ocular examination including optic disc appearance and intraocular pressure, without history of ocular disease.

Patient and control subjects had previous perimetric experience. Subjects using medication that could affect the visual field, with refractive errors higher than 6 diopters of

TABLE I - SIMULATION MODELS USED BY PeriSim MODIFYING THE PERCENTAGE OF FALSE POSITIVES (FP%) AND FALSE NEGATIVES (FN%), AVERAGE AMPLITUDE OF THE NORMAL (FOS-N) AND PATHOLOGIC (FOS-P) FREQUENCY OF SEEING CURVES, AND FATIGUE EFFECT (dB reduction for every 400 stimuli shown to the patient)

Model	FP%	FN%	FOS-N	FO-P	Fatigue
1	0	0	1.0	12	2.0
2	3	3	2.0	13	2.4
3	5	5	3.0	14	2.8
4	10	10	4.5	15	3.2
5	15	15	6.0	16	3.6
6	25	25	7.5	17	4.0

TABLE II - RECEIVER OPERATING CHARACTERISTIC (ROC) RESULTS FOR THE WHOLE SAMPLE

	sLV	sLV-c	NPP	MD
ROC area	0.971	0.972	0.934	0.921
Area st. error	0.006	0.006	0.009	0.010
Optimum cut off	2.66	2.66	9.48	3.85
Specificity	96.3	96.3	86.1	92.5
Sensitivity	89.9	90.6	90.6	76.6
Average	93.1	93.4	88.3	84.6

sLV-c = Corrected square-root of the loss variance; NPP = Number of pathologic points; MD = Mean defect

TABLE III - RECEIVER OPERATING CHARACTERISTIC (ROC) RESULTS FOR THE SAMPLE INCLUDING ONE EYE PER PATIENT

	sLV	sLV-c	NPP	MD
ROC area	0.975	0.976	0.951	0.940
Area st. error	0.006	0.006	0.009	0.010
Optimum cut off	2.66	2.66	10.48	2.63
Specificity	96.2	96.2	90.5	88.2
Sensitivity	91.8	92.4	90.4	86.3
Average	94.0	94.3	90.5	87.2

sLV-c = Corrected square-root of the loss variance; NPP = Number of pathologic points; MD = Mean defect

spherical equivalent or cataracts with visual acuity worse than 20/40, were excluded.

A total of 554 subjects (211 normal controls and 343 glaucomatous) were included. The number of normal and glaucomatous eyes was 295 and 414, respectively. In 155 subjects both eyes were examined. Due to the large sample size, bias associated with the inclusion of both eyes would not be expected (23, 24). As an additional precaution, further analysis was made, randomly choosing only one per patient. TOP algorithm (either TOP-32 or TOP-G1 program) and the Octopus 1-2-3 perimeter (Haag-Streit, Köniz, Bern, Switzerland) were used in all cases. A subanalysis to compare the performance of TOP-32 and TOP-G1 programs was also carried out.

The following indices were studied: MD, square root of the LV (sLV), and number of pathologic points (NPP) with a deviation higher than 5 dB from the age-matched normal value. Patients with very severe defects show a normalization of the sLV index because there are many points with identical sensitivity (0 dB). For that reason, sLV was considered as pathologic, whatever its value, for MD higher than 20 dB.

Receiver operating characteristic (ROC) curves, ROC areas, cutoff levels, and sensitivity and specificity values were calculated for each index. To fulfill the above criteria, two units were added to the sLV for the ROC analysis when MD was higher than 20dB (sLV-c = corrected sLV). Because program 32 tests 74 points and program G1 tests only 59, an additional analysis was performed for the NPP numeric index by multiplying NPP (G1) by 74/59 (that is, 1.254). Finally we proceeded to analyze the potential of the joint analysis of the three indexes utilizing logistic regression analysis, discriminating analysis, and regression trees (25) as well as correction of the NPP value by cluster analysis.

Study B: Relationship between fluctuation and LV

Thirty-four consecutive healthy subjects and 33 consecutive patients with glaucoma were selected. One eye per subject was included and examined twice with the TOP and FT strategies. Patients had a MD value of less than 15 dB.

The program TOP-32 and the Octopus 1-2-3 perimeter were used in all cases. The relationship between sLV and test-retest fluctuation (F) (26) was calculated using the formula $F=\sqrt{\sum}(X2-X1)2/(2n)$. The correlation coefficient (r) was estimated.

Study C: Quantification of error of LV estimation caused by threshold fluctuation and noise

Twenty-eight eyes from 28 consecutive patients with stable chronic open angle glaucoma were examined six times in a row using the TOP 32 program with intervals of 1 to 3 months. The threshold estimation of each examination was averaged with that obtained on all previous examinations, so that six MD and sLV estimations were achieved: e.g., the ones obtained with the first examination, those obtained from averaging the first and second examination, those obtained averaging the first, second, and third examination, and so on.

Study D: Estimation of the measuring error in TOP and FT using the PeriSim simulation pro - gram

Nineteen visual fields from 19 glaucomatous eyes with defects in different locations and of different depth were included. Each field was the result of averaging four visual fields: the threshold value at each point was the average of the results of two examinations with each of the two strategies (see study B) and was considered to be the reference standard, that is, the "true" visual field from which to measure the error of estimation. The PeriSim simulation program (by H. Bebie, Haag-Streit) was used to calculate the error of threshold estimation.

Six different patient behavior models were simulated, progressively increasing the percentage of positive and negative catch trials, the amplitude of the frequency of seeing curve in normal and pathologic points (range of the fluctuation between 16% and 84% percentiles, or mean ± 1 SD), and the fatigue effect (i.e., dB reduction for every 400 stimuli shown to the patient) (Tab. I).

A total of 30 TOP and FT simulations were carried out for each of the 19 model visual fields and for each of the six behavior models.

All examinations were conducted in accordance with the tenets of the Declaration of Helsinki and informed consent was obtained from each participant.

RESULTS

Study A: Diagnostic accuracy of the main perimetric indices

The sample consisted of 41.9% men and 58.1% women. Mean age was 49.2 years (SD=17.5) for the control group and 66.2 years (SD=12.5) for the glaucomatous group. Eighty-nine control and 178 glaucomatous eyes were tested with TOP-32 program and 206 control and 236 glaucomatous were tested with TOP-G1. According to MD values for the TOP examination, 179 eyes were classified as early glaucoma (MD<6 dB), 112 as moderate (6 dB<MD<12 dB), and 123 as advanced glaucoma (MD>12 dB).

Mean MD value was 0.8 dB (SD=1.9) for the control group and 9.1 dB (SD=6.7) for the glaucoma group (Fig. 1).

Correlation coefficient between MD and LV for controls and patients with glaucoma with an MD lower than 18 dB (658 cases) was 0.76. Correlation coefficient between MD and the sLV in these eyes was 0.83.

ROC analysis for the whole population requiring specificity higher than 95% (Tab. II and Fig. 2) showed that the best discrimination between patients with glaucoma and controls was achieved by the sLV with a cutoff level of 2.66 dB, and sensitivity and specificity average of 93.4%. The difference in diagnostic accuracy between sLV and NPP and MD indices was statistically significant ($p<0.05$).

The analysis carried out including one eye per patient

TABLE IV - RECEIVER OPERATING CHARACTERISTIC (ROC) ANALYSIS OF THE INDEXES MD, SLV, AND NPP IN PATIENTS WITH EARLY, MODERATE, AND ADVANCED GLAUCOMA

	MD<6dB			6dB<MD<12dB			MD>12dB		
	sLV	NPP	MD	sLV	NPP	MD	sLV	NPP	MD
Roc area	0.940	0.871	0.817	0.994	0.976	0.998	1.000	0.989	1.000
Area st. error	0.013	0.018	0.021	0.005	0.010	0.003	0.001	0.007	0.000
Optimum cut off	2.42	8.51	2.16	2.99	26.02	5.78	3.47	39.52	9.93
Specificity	90.2	84.7	80.0	98.6	95.6	98.0	99.7	97.6	100
Sensitivity	84.9	80.4	70.4	96.4	98.2	100	98.4	99.2	100
Average	87.5	82.6	75.2	97.5	96.9	99.0	99.0	98.4	100

sLV-c = Corrected square-root of the loss variance; NPP = Number of pathologic points; MD = Mean defect

gave similar results to those previously described (Tab. III).

ROC results for sLV with programs TOP 32 (specificity=92.1, sensitivity=93.2, ROC area=0.979, SE=0.008) and TOP G1 (specificity=95.6, sensitivity=91.1, ROC area=0.969, SE= 0.008) were similar.

Early glaucoma cases had an average MD value of 3.2 dB. The best discrimination between control and early glaucoma groups was obtained with sLV=2.42 dB, reaching an average between sensitivity and specificity of 87.5% (Tab. IV). Regarding moderate and severe glaucoma the differences in the diagnostic capability of the three indexes were not statistically significant (Tab. IV).

Cluster analysis of two, three, four, or five adjacent pathologic locations produced similar or worse diagnostic results than NPP and worse than those obtained with the sLV alone. Analysis of the NPP index between programs TOP G1 and TOP 32 did not show statistically significant differences. Logistic regression, discriminating analysis, and regression trees did not improve the results of the sLV index by itself.

Study B: Relationship between fluctuation and LV

The sample consisted of 30 men and 37 women. Mean age was 42.1 years (SD=22.2).

Mean MD value for TOP was 2.3 dB (SD=3.9). Regarding FT, mean MD value was 3.6 dB (SD=4.3), different from the one obtained with TOP ($p<0.0001$).

Mean sLV value in TOP was 2.9 dB (SD=2.2), ranging from 0.6 to10.4 dB. In FT mean sLV was 3.9 dB (SD=2.4), ($p<0.0001$).

Mean F value for TOP was 2.8 dB (SD=1.5). In FT, mean F value was 3.7 dB (SD=1.5) ($p<0.0001$).

Correlation coefficients between F and average sLV of the two examinations performed with each strategy were 0.72 ($p<0.01$) for TOP and 0.62 ($p<0.01$) for FT (Figs. 3 and 4). In normal subjects TOP often gave low F and sLV values (F<2 dB = 67.6%; sLV<1.5 dB = 55.9%). This was rare in FT (8.82% and 5.88%). Averaging the thresholds from first and second examinations resulted in an sLV value 9.3% lower than the two averaged original LVs. In FT the reduction of sLV was 8.5%.

TABLE V - AVERAGE RMS ERROR (SD) OF THE THRESHOLD ESTIMATION OF TENDENCY ORIENTED PERIMETRY (TOP) AND FULL-THRESHOLD PERIMETRY (FT) IN THE PeriSim PROGRAM, USING SIX DIFFERENT PATIENT BEHAVIOR MODELS AND 30 SIMULATIONS OF 19 VISUAL FIELDS

Model	FT	TOP
1	1.6 (0.3)	2.7 (0.6)
2	2.1 (0.2)	3.1 (0.6)
3	2.5 (0.2)	3.4 (0.6)
4	3.2 (0.2)	4.3 (0.6)
5	3.9 (0.2)	5.1 (0.4)
6	5.5 (0.3)	7.0 (0.8)

Study C: Quantification of error of LV estimation caused by threshold fluctuation and noise

The sample consisted of 11 men and 17 women. Mean age was 67.8 years (SD=8.5).

Mean MD value was 9.5 dB (SD=7.2). Mean sLV value was 5.1 dB (SD=2.3).

Averaging the MD (averaging two, three, four, five, or the six examinations) resulted in differences lower than 1% of the value obtained for the first examination (Fig. 5).

F estimation including the first three examinations was only 1.3% higher than analyzing the first two examinations. F estimation with the six examinations was only 2.9% higher than with the first two examinations (Fig. 5).

A 9.3% reduction of sLV was observed when the first and second examinations were averaged. Averaging the threshold value of six examinations with those of successive examinations resulted in a progressive reduction of sLV of up to 22.3% less than the initial estimation (Fig. 5).

Study D: Estimation of the measuring error in TOP and FT using the PeriSim simulation program

If identical collaboration was presumed for TOP and for FT, the error of threshold estimation was approximately 1 dB higher in TOP than in FT. If patient collaboration was assumed to be better in TOP than in FT due to its duration, the error of estimation could be lower in TOP than in FT (Tab. V).

DISCUSSION

The results from study A agree with another publication (22) that concluded that the sLV provided by TOP had better diagnostic capability than FT.

Cluster analysis did not offer advantages in TOP. This might be related to the way TOP works, by establishing lateral influences among the thresholds and intrinsically

favoring the detection of grouped abnormal points (3).

The high diagnostic accuracy of sLV observed in TOP 32 and TOP G1 (27) may be explained by the use of averaged values that reflect diffuse damage and loss of regularity of the visual field in the initial phases of glaucoma.

In early and moderate glaucomas, there is a linear relationship between the sLV and the MD (28). These results confirm previous reports that sLV and MD are better correlated in TOP than in FT (8). In very advanced glaucomas, sLV may not be a useful index. A low sLV value in a patient with end-stage glaucoma could be misleading for inexperienced observers (29) and may limit the usefulness of sLV as an index for automatic interpretation. In these cases, sLV should be considered as abnormal, whatever its value, for MD higher than 20 dB.

Study B indicated that threshold fluctuation in TOP is the main contributor for sLV in normal subjects and in the first stages of glaucoma. There is higher correlation between both indices (F and sLV) in TOP than in FT. In the case of FT, the lower correlation seems to indicate that the higher sLV value does not exclusively depend on threshold fluctuation, but that it is influenced by noise during the determination.

Some explanations of this fact could be the following: TOP's short duration reduces fatigue effect and patient distractions. In the case of FT, a patient error would irreversibly invert the direction of threshold search, thus falsely incrementing the sLV. In the case of TOP, response errors are partially compensated for by correct answers to surrounding points. Additionally, FT perimetry does not establish an upper limit to the possible threshold that can be reached. Some "happy-trigger" patients answer repeatedly during the examination. The maximum possible threshold in TOP is 18/16 the normal value, which makes it impossible to have extremely high thresholds known as white scotomas, which increase noise and sLV.

Study C showed that while visual field algorithms provide an accurate estimation of the MD, they overestimate the sLV. When averaging the threshold results of the same patient, the sLV is observed to be drastically reduced. Even though the repeated examinations have been performed using the TOP strategy, the results obtained in study B (averaging two examinations) indicate that a similar reduction of sLV values could be obtained using FT. Admitting that threshold is a probabilistic concept (i.e., stimulus with a 50% probability of being detected) these results point out that individual visual field results considerably overestimate the irregularity of the defects and the sLV. Therefore, the differences of the sLV magnitude between several strategies should not be directly interpreted as errors of one strategy in relation to the other, as suggested by Anderson (13). On the contrary, it is evident that the sLV results provided by FT erroneously overestimate the irregularity of the defects. The "corrected sLV" (or its equivalent in Humphrey perimetry, the corrected PSD) takes fluctuation into consideration in an attempt to reduce this overestimation. However, the results from this study indicate that such correction is insufficient, since the sLV reduction achieved by averaging several tests results in a much lower value.

The irregularity of the defects in the visual field (LV-PSD) depends on three components: 1) irregularities produced by functional defects, that is, the "signal" that we are trying to clinically measure, 2) physiologic or pathologic threshold fluctuation, and 3) contaminating components of the test that affect threshold estimation. These contaminating components may be called noise and are made up of many factors: learning effect, neurologic fatigue effect, losses of attention or hypnosis effect (30), and other possible artifacts.

Flammer et al (26) deduced that threshold fluctuation was the first sign of glaucoma. If correct, the LV value on the initial stages of the disease would depend on fluctuation and noise more than on local defects. Thus, those procedures with less noise would have a stronger relation between LV and threshold fluctuation. Such is the case of TOP compared with FT.

Previous studies (4, 7-10) have measured errors of threshold estimation of TOP and FT calculating the "error of X in relation to Y," which is a statistical index commonly used on lineal regression analysis. The average value of the error of threshold estimation using TOP in relation to the threshold estimation using FT was 4.9 dB. The average error of threshold estimation between two FT examinations on the same eye was 4.3 dB. The average value of the threshold estimation between two TOP examinations was 3.9 dB.

Therefore, in clinical examinations using FT perimetry, the test-retest error of threshold estimation is on the same range than the error observed with PeriSim in behavioral models 5 and 6, that is, assuming poor patient collaboration (Tab. V). The test-retest error of TOP in clinical examinations is similar to the one in behavioral models 3 and 4, that is, assuming better patient collaboration.

If patient's behavior on simulation was considered to be similar in FT and TOP the error of TOP would be 1 dB

higher. However, comparing clinical data, verification of higher diagnostic accuracy, lower fluctuation, better MD and sLV correlation, and sLV and LV correlation seem to indicate that patient performance is better in TOP than in FT, overcoming the theoretical differences pointed out by the simulation process. Overall, the results described in these studies show that isolated examinations overestimate the irregularity of the defects represented by the LV. Even the corrected LV overestimates the real LV value, which should be at least 22% lower than estimated with one only examination, and probably 30% lower if the averaged series of examinations was large. Therefore, the fact that the LV has lower values in TOP than in FT may be interpreted as strength of TOP rather than a limitation (13).

The first author has proprietary interest in the TOP strategy.

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