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Combined spatial, contrast, and temporal functions perimetry in mild glaucoma and ocular hypertension

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PURPOSE. *To evaluate the diagnostic ability of a new perimetric procedure in glaucoma.*
METHODS. *Pulsar perimeter shows white circular sinusoidal grating patterns with decreasing amplitude, 5° in diameter, 500 msec in duration in 66 locations. The stimuli scale combines spatial resolution and contrast. The stimuli were shown with centrifugal wave motion at 8 cyl/deg (K6W) or pulse at 30 Hz (T30W). Fifty-six normal eyes and 82 eyes with ocular hypertension and mild glaucoma were included. These 82 cases were classified into four levels of diagnostic certainty, from 0 (ocular hypertension) to 3 (mild glaucoma).*
RESULTS. *Mean examination time was 3:49 min. Specificity was 96.4% (T30W) and 94.6% (K6W). Sensitivities for levels 0 and 3 were 34.5% to 100% (T30W) and 24.1% to 75% (K6W). The receiver operating characteristic (ROC) curve areas for T30W at levels 1, 2, and 3 were 0.88, 0.94, and 0.99. The ROC areas for K6W were 0.83, 0.91, and 0.97. There was good correlation between both Pulsar perimetries (r=0.88), but it was lower with conventional perimetry (r=0.58 for T30W and r=0.59 for K6W).*
CONCLUSIONS. *The novel Pulsar T30W perimetry may be helpful for the study of mild glaucoma and ocular hypertension. (Eur J Ophthalmol 2004; 14: 514-22)*

KEY WORDS. *Contrast, Glaucoma, Perimetry, Temporal modulation, Visual field*

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INTRODUCTION

Defining the initial phases of glaucoma as well as the precise moment of glaucoma onset is challenging. The definitions of ocular hypertension, glaucoma suspect, and glaucoma refer to a continuous process that goes from normality to blindness. We know that many patients with ocular hypertension are never going to develop glaucoma, but it is also true that normality diagnosis is complex and that our knowledge of initial glaucoma and ocular hypertension is limited (1). The boundaries of these phases will keep moving as long as our knowledge of the disease keeps progressing.

During the last few years, new and alternative methods have been proposed to establish a diagnosis of glaucoma. Peripheral spatial resolution is probably a function of the parvocellular system and has been studied by high pass resolution perimetry (2). A large research effort has been focused on the examination of

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the koniocellular system using short wavelength automated perimetry, although some researchers proposed that this is a function of large parvocellular cells (3, 4). Other studies have been done on the magnocellular system by, for example, contrast perception (5), in the belief that large ganglion cells are first affected by glaucomatous damage (6).

The contrast sensitivity function (CSF) was first studied for central vision (7) and was applied to the study of glaucoma in the fovea (8). Although several examination techniques have been designed, none of them has reached useful sensitivity and specificity levels for the diagnosis of glaucoma (9-12).

The changes of the CSF in relation to retinal eccentricity are characterized by a displacement of the curve toward lower spatial frequencies due to the reduction of visual acuity in the peripheral retina. With respect to high spatial frequencies, the curves are parallel, representing equivalent cortical projection areas (12-15). We have verified the shape of these curves in the 66 points of the central visual field with the same instrument that we used in this article (16) (Fig. 1).

The examination of the CSF in the peripheral visual field seems to be a reasonable alternative for early glaucoma diagnosis, since that area is more sensitive to glaucoma damage than the fovea. So far, few authors have attempted this kind of study (17, 18).

The most studied temporal functions so far have been motion (19-25), critical flicker fusion frequency (26, 27), and temporal modulation perimetry (28).

The combined examination of these two visual functions (CSF and temporal functions) had never been suggested for the early examination of glaucoma, although they had both been proposed separately. This encouraged us to design a procedure able to simultaneously examine both functions. This study was designed to evaluate the usefulness of a perimeter prototype called Octopus Pulsar Perimeter for evaluating visual functions in glaucoma. The prototype has the ability to examine some of the visual functions described above, including spatial resolution, contrast perception, motion, and temporal modulation. The results of this procedure in normal subjects have been described (16, 29). Interindividual variability and short-term fluctuation, as well as the threshold reduction with age, had characteristics that were similar to those known for conventional perimetry. Sensitivity decreased sharply from the center toward the periphery, mostly on the nasal field.

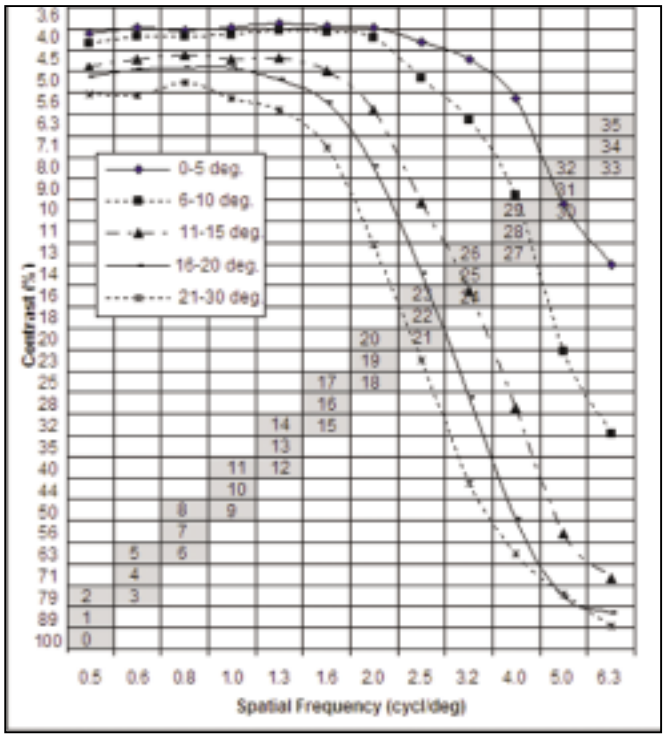

Fig. 1 - *Contrast sensitivity curves in relation to eccentricity calculated with the Pulsar perimeter (16) are similar to the ones calculated by Rovamo et al (13). The descending phases of the curves are parallel and correspond to central vision to the right (high spatial frequencies and good visual acuity) and to peripheral vision to the left (corresponding to low spatial frequencies and low visual acuity). The combined scale (gray) intercepts them in an approximately perpendicular way.*

MATERIALS AND METHODS

Fifty-six normal subjects (one eye per subject) were examined. Twenty were male and 36 female. The sample of subjects was evenly distributed in homogeneous age groups between 19 and 75 years.

Eighty-two eyes from 82 patients diagnosed with mild chronic primary open angle glaucoma (with characteristic changes of the optic disc and/or visual field defects) or ocular hypertension (with intraocular pressure higher than 21 mmHg measured at least twice, normal visual fields, and normal optic discs, without asymmetry between eyes and no progression) were included in the study. Subjects with closed anterior chamber angle on gonioscopic examination and ex-

treme corneal thickness (optical Orbscan central thickness lower than 510 microns or higher than 615 microns) were excluded. Thirty-two were male and 50 female. All patients had a mean defect value (MD) lower than 7 dB in conventional white-white perimetry (WW). One eye per patient was evaluated. Because the purpose was to compare two functional examination techniques, perimetry only was used for glaucomatous patient subclassification. Three criteria were used to define the visual field as pathologic. The first criterion was seven abnormal points in relation to the age-corrected mean threshold value ($p<0.05$), at least three of them forming a cluster. This criterion of pathology, derived from another study (30), has been evaluated with positive results in other studies (31, 32). The other two criteria were defined by the normal statistical levels established by the instrument manufacturers for the MD and loss variance (LV): MD>2 dB and LV>6 dB 2.

The 82 patients were classified into four diagnostic categories. Level 0 was made up of those cases with ocular hypertension and normal visual field results (n=29). Level 1 consisted of all visual fields with at least one abnormal criterion (53 cases). Level 2 consisted of those with two abnormal indices: MD>2 dB and more than seven points deviated more than 5 dB from the normal value (n=35). Level 3 consisted of those with three abnormal criteria and MD higher than 3 dB (20 cases).

All normal subjects underwent a complete ocular examination, including personal and family history, to rule out any ocular pathology or systemic pathology that could affect vision. Exclusion criteria for both groups included clinically detectable lens opacities, ocular disease other than glaucoma or ocular hypertension, systemic disease or medication that could affect vision, refractive error greater than 4 diopters (spherical equivalent), corrected visual acuity less than 6/7.5 (0.8), pupil diameter less than 3 mm, and perimetric catch trials outside the normal range.

The visual field tests were performed with distance refractive correction for the Octopus 1-2-3 and with near vision correction for Pulsar. At least two previous perimetric examinations were required (33-35). All examinations were performed in the same session, in a random order, and allowing rest periods of at least 10 minutes between each examination.

All procedures were reviewed and approved by the local ethics committee and the study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

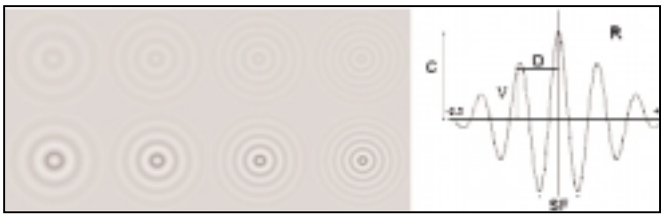

Fig. 2 - *Aspect and formula of the stimulus shown by the Pulsar perimeter. The examples correspond to two different contrast levels and spatial frequency between 1.3 cycles/deg and 2.5 cycles/deg . All stimuli are 2.5 degrees in radius (R). Contrast at each point in the image (V) depends on the global central contrast selected (C), the chosen spatial frequency (SF), and distance from the center (D), following the formula V=Cont. x cos ([2p x SF x D]- p) x (1- [D/R]).*

The Pulsar perimeter consists of an examination screen made up of a 21' (Sony GDM-F500, Sony Corporation, Tokyo, Japan) computer CRT monitor photometrically calibrated by a specific photopic photometer with oscilloscopic functions to control temporal stimuli. The screen resolution is 1600x1200 pixels, vertical frequency 60 Hz, and color temperature 6500∞K. This allows the examination of 66 points in the central visual field: 30 degrees in the nasal and temporal regions and 24 degrees in the superior and inferior regions.

Background of 100 asb is chosen to perform Pulsar perimetry. The screen displays round stimuli, 5 degrees in diameter, 500 msec in duration, shaped as a wave decreasing in amplitude towards the edges, and with mean luminance equal to that of the background (Fig. 2). The stimulus has been designed to keep the same level of contrast in all edges, to avoid stimulation of those cells that selectively respond to a given orientation. The stimulus wave can be modulated in spatial resolution (from 0.5 to 6.3 cycles per degree in a scale of 12 logarithmic steps), contrast (32 logarithmic levels from 3 to 100%), color (white, red, green, and blue), centrifugal motion velocity (from 2 to 20 cycles per second in a logarithmic scale of 11 levels), or temporal frequency for oscillations in phase and counter-phase (10, 15, or 30 Hz).

For spatial resolution, the scale was established from the minimum spatial resolution (0.5 cycles/deg) using the following formula: spatial frequency level (dLog) = 10 x Log (spatial frequency/0.5).

For motion, the levels were calculated in relation to

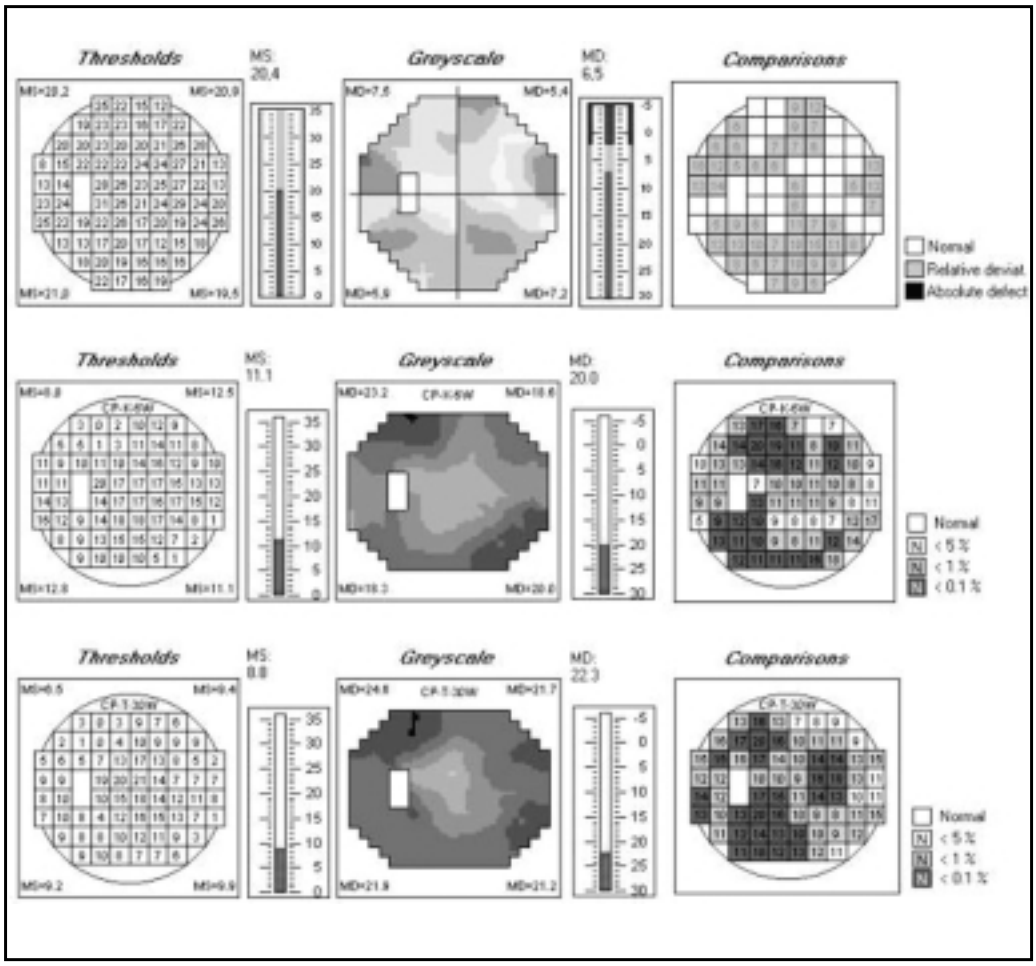

Fig. 3 - *Results for a glaucoma subject (level 3) on white-white perimetry (top images), K6W perimetry (center images), and T30W perimetry (lower images). Left: numeric thresholds table. Center: gray map. Right: numeric table of deviations*

the minimum velocity (2 cycles/sec), using the following formula: motion level (dLog) = 10 x Log (motion/2).

Because the contrast is above and below the background, the following formula was used: contrast = –20 x Log (central amplitude from background/background intensity).

The photometer used is own made (FOT9851). It uses a photopic photodiode and was calibrated by means of a photometer-colorimeter (Tektronix J17 LumaColor) provided with a reading head designed for measuring screens (J1820). The chromatic coordinates used in the monitor were X=0.325, Y=0.278, Z=0.397 (CIE 1931). Immediately before each examination, the 256 RGB screen scale was photometrically calibrated.

Due to the difficulties encountered when measuring the CSF for each position of the visual field, which requires a search for the contrast threshold for several spatial resolutions, we chose to examine just one point in the contrast sensitivity curve. For this purpose, we used a combined scale that varies spatial resolution and contrast at the same time (Fig. 1). As previously mentioned, the curves that relate both factors at different eccentricities are parallel on the descending tails, in the area of high spatial frequencies (36). Therefore, the scale is approximately perpendicular to each of the curves that relate spatial resolution and contrast. This way, it is adapted to any position of the visual field.

The scale is made up of 36 spatial resolution-contrast units (src). The stimuli become progressively less visible as the spatial resolution increases and contrast decreases. The range goes from spatial resolution 0.5 cycl/deg and 100% contrast (step 0 src) to spatial resolution 6.3 cycl/deg and 6% contrast (step 35 src).

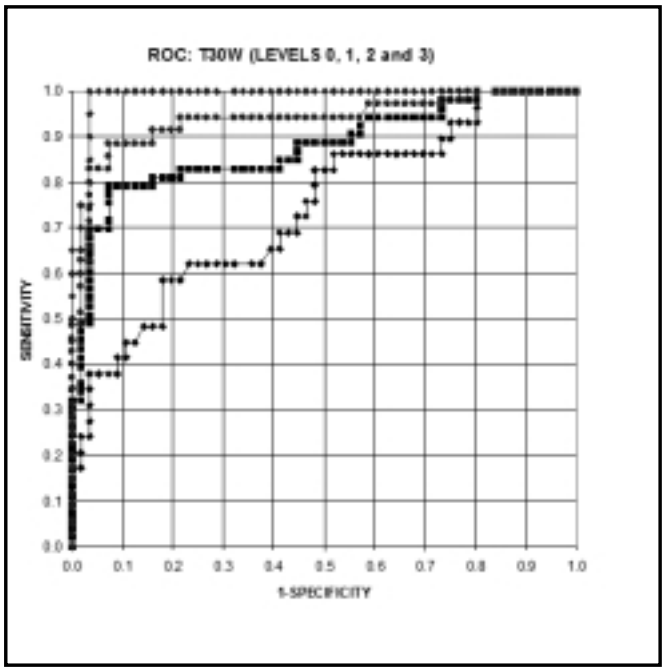

Fig. 4 - *Receiver operating characteristic areas for T30W perimetry. Results for levels 0 (ocular hypertension), 1, 2, and 3 (glaucoma) from right to left. The points in the graph represent several cutoff levels.*

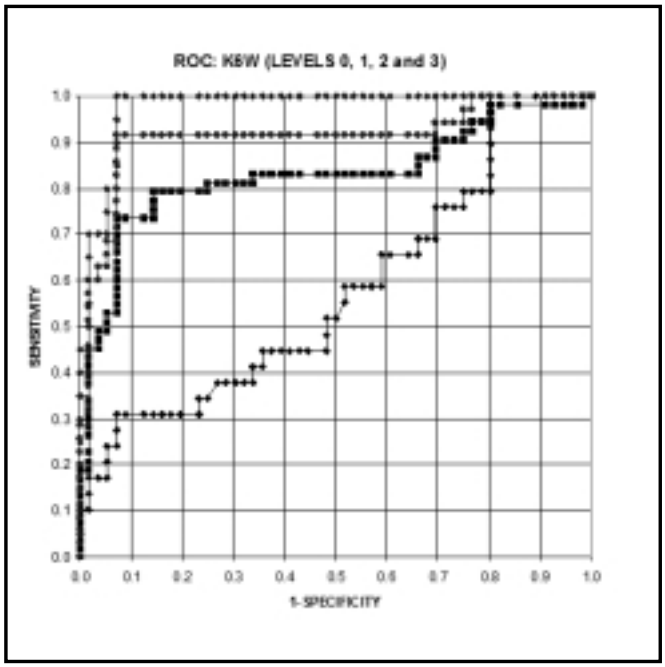

Fig. 5 - *Receiver operating characteristic areas of K6W perimetry. Results for levels 0 (ocular hypertension), 1, 2, and 3 (glaucoma) from right to left. The points in the graph represent several cutoff levels.*

The sequence of stimulus presentation is adapted to the patient's response time and there is an additional random delay in order to avoid rhythmic responses.

In this study, we have used two Pulsar tests: (1) white stimuli with centrifugal motion at 8 cycl/sec for motion perimetry (K6W perimetry) and (2) white stimuli pulsing in phase and counterphase at 30 Hz for temporal modulation perimetry (T30W perimetry).

To determine the threshold level, we used the previously reported TOP strategy (tendency oriented perimetry), which has been favorably compared to the conventional bracketing full-threshold strategy (31, 36-41). Figure 3 shows examples of the topographic information given by WW and Pulsar perimetries.

For WW perimetry we used the Octopus 123 Perimeter (Interzeag AG, Schlieren-Zürich, Switzerland), the TOP strategy, and a 32 test pattern.

The normality values and deviations with age previously described (29) were used for calculating the MD in the Pulsar perimetries (29). The results were analyzed by descriptive analysis, Kolmogorov-Smirnov test for the normal distribution of our data, Student t-test with adjustment by Bonferroni method in the case of comparing more than two groups simultaneously, t-test power analysis, and Pearson's r coefficient, to compare perimetric results between groups.

The distributions of probability scores for normal control subjects and each group of patients were then compared by means of receiver operating characteristic (ROC) curves.

RESULTS

Mean examination time was 3:49 min for Pulsar perimetries. Mean age and standard deviation of the normal, ocular hypertension, and glaucoma groups were 45.18 ± 17.62, 59.62 ± 11.87, and 60.70 ± 15.59 years. The mean ages of the glaucoma and ocular hypertension groups did not have significant differences with the control group ($p>0.05$).

The results of the Kolmogorov-Smirnov test for the different groups indicated that a normal distribution could be assumed ($p>0.20$). The average MD value for T30W perimetry in the normal group was 0.0 src (SD=1.7) and for the four levels of ocular hyperten-

TABLE I - RECEIVER OPERATING CHARACTERISTIC (ROC) ANALYSIS FOR T30W AND K6W PERIMETRIES

		Level 0	Level 1	Level 2	Level 3
	No Cases	29	53	35	20
T30W	Roc Area	0.74	0.88	0.94	0.99
	Specificity	96.4	96.4	96.4	96.4
	Sensitivity	34.5	69.8	82.9	100
	Pos Pre Value	83.3	94.9	93.5	90.9
	Neg Pre Value	74.0	77.1	90.0	100
K6W	Roc Area	0.58	0.83	0.91	0.97
	Specificity	94.6	94.6	94.6	94.6
	Sensitivity	24.1	50.9	65.7	75.0
	Pos Pre Value	70.0	90.0	88.5	83.3
	Neg Pre Value	70.7	67.1	81.5	91.4

Cut off value 3 spatial resolution contrast units.
Group Ø, ocular hypertension cases; groups 1 to 3, glaucoma cases.

sion and glaucoma: 2.1 src (SD=2.7), 4.5 src (SD=3.5), 5.8 src (SD=3.5), and 7.3 src (SD=3.2), respectively. The difference with the normal group for the four levels was statistically significant ($p<0.0001$). The average MD value for K6W perimetry for the normal group was 0.0 src (SD=1.6). For each of the four levels of ocular hypertension and glaucoma, the MD was 1.1 src (SD=2.6), 3.4 src (SD=3.1), 4.5 src (SD=2.9), and 5.6 src (SD=2.8). The difference from the normal group was statistically significant for level 0 ($p<0.05$) and highly significant for the other levels ($p<0.0001$). The power value of the t-test was calculated with the data obtained. In the most unfavorable case, the comparison between the ocular hypertension patients (group 0) and the normal subjects gave a value of 0.98 for T30W and 0.63 for K6W.

For all levels, MD was significantly higher for T30W than for K6W ($p<0.001$). For levels 1 to 3, K6W perimetry gave defects 0.26, 0.32, and 0.82 units deeper than WW and T30W gave defects 1.4, 1.6, and 2.6 units deeper than WW perimetry.

The MD values of both Pulsar perimetries had a moderate correlation with WW conventional perimetry, reaching $r=0.58$ for T30W ($p<0.01$) and $r=0.59$ for K6W ($p<0.01$). The MD values for both Pulsar perimetries were best correlated with each other ($r=0.88$) ($p<0.01$).

When calculating the square root of the LV (sLV), no significant differences were found between normal subjects (2.6 src, SD=0.7) and ocular hypertensives from level 0 (2.3 src, SD=0.9) in K6W perimetry ($p>0.05$). For levels 1, 2, and 3 the mean sLV value was 3.1, 3.4, and 3.7, with statistically significant differences from the normal group ($p<0.001$). For T30W, there were no significant differences on the sLV of the normal group (2.7 src, SD=0.7) and that of level 0 (2.4 src, SD=0.7) ($p>0.05$). Mean sLV for the three glaucoma levels was 3.3, 3.6, and 3.9, with significant differences from the normal group ($p<0.01$). sLV values were always slightly higher for T30W than for K6W, but the differences reached statistical significance ($p<0.05$) only in level 1.

Both perimetric indices (MD and sLV) had similar correlation in the three types of perimetry for the whole sample. The correlation coefficients were $r=0.69$ ($p<0.01$) for WW perimetry, $r=0.62$ ($p<0.01$) for K6W perimetry, and 0.63 ($p<0.01$) for T30W perimetry.

For sensitivity and specificity analysis, a cut off level of MD=3 src was established for Pulsar perimetry. As shown in Table I and Figure 4, the ROC areas for T30W were very high for all patients with anomalies in WW perimetry. The areas under the curve for T30W at levels 1, 2, and 3 were 0.88, 0.94, and 0.99, respectively. Specificity was 96.4%. Sensitivity was 69.8, 82.9, and 100%, respectively. Among ocular hypertensives with no abnormal signs on WW perimetry (level 0), 34% had abnormal results, with a positive predictive value of 83.3%.

In the case of K6W perimetries (Tab. I and Fig. 5) the ROC areas had high values, but lower than those found for T30W in patients with anomalies in WW perimetry. The area under the curve for K6W at levels 1, 2, and 3 were 0.83, 0.91, and 0.97, respectively. Specificity was 94.6%. The lower ability to diagnose with this strategy is manifest on a sensitivity of 75% for level 3 and much lower predictive values. The percentage of abnormal results in the ocular hypertensive group with no abnormal signs on WW perimetry reached 24.1% with a positive predictive value of 70%. For these patients, the ROC area is much higher for T30W perimetry than for K6W and WW.

DISCUSSION

In glaucomatous optic neuropathy there is no accurate delimitation of the boundaries between nor-

mality and pathology with our current diagnostic methods. Most diagnostic tests reported in the literature have sensitivity and specificity values around 80 to 90% (42-44). The most striking result of this study was the fact that the 29 patients with ocular hypertension (level 0) had slightly negative MD values (average=–0.4dB) in WW perimetry, which is slightly higher (hypernormal) than the age-matched value. On the other hand, with Pulsar perimetry, the results were deviated toward the opposite direction; that is, toward pathologic levels, up to 1.1 src for K6W perimetry and 2.1 for T30W perimetry, with very highly statistically significant differences compared with normal subjects. Therefore, our results indicate that Pulsar perimetries, and mostly T30W, show abnormal values of the visual function in patients with ocular hypertension. However, the sensitivity and positive predictive value of the patients in group 0 should be understood as an ability of the examination to distinguish between normal and ocular hypertension subjects and not for the detection of typical glaucoma defects. Additionally, in glaucoma subjects, defects appear to be deeper than those found in conventional perimetry. Its sensitivity in detecting abnormalities in patients with defects that could be considered mild or moderate (MD between 3 and 7 dB in WW perimetry) is close to 100%.

The results of the research point out that ocular hypertensives with abnormal results in Pulsar have an altered physiologic function when compared to normal subjects. In subjects with mild or moderate visual field defects, it is even more altered than in WW. Indeed, a longitudinal evaluation of these subjects would be needed to check the hypothesis that these functional defects may lead to glaucoma.

It is difficult to compare our results with those of other procedures proposed for the early diagnosis of glaucoma, due to the influence of the population sample selected and the gold standard used to define glaucoma.

Frequency doubling technique (FDT) examines the contrast associated with the phenomenon of frequency doubling for a fixed spatial frequency. FDT studies in mild glaucoma subjects have reported specificity values of 61.1% (45), 84% (46), 90% (47), and 100% (48), and sensitivities of 72% (48), 75% (45), 78 to 86% (46), and 85% (47). It seems that it does not detect defects in ocular hypertensive subjects with normal WW perimetry, because the frequency of abnormal tests in these cases has been estimated to be 6% (49), 9% (50), and 10% (51), except when cases with proven defects on blue-yellow perimetry or optic nerve head topography are selected (52). Flicker perimetry, which measures the critical fusion frequency in the central visual field, has shown similar sensitivity and specificity results (53). However, flicker perimetry may be a more difficult test for the subject, since it works with recognition thresholds, while Pulsar perimetries, similar to WW perimetry, use detection thresholds, needing a simple answer: seen or not seen.

With regard to static contrast sensitivity, the stimulus scale used by Pulsar analyzes the threshold for high spatial frequencies, adapted to each region of the visual field. To this effect, the examination would favor the study of the parvocellular system. However, the use of high temporal frequencies using T30W and relatively slow motion using K30W would favor the examination of the magnocellular system and finding better results with T30W may also suggest alterations in that system (54). It could also be that, before axonal death happens, a slight reduction in the transmission velocity of the axon under stress results in its inability to transmit much information per unit time and more if that information is limited by related characteristics such as spatial frequency and contrast. It must be borne in mind that ocular hypertension is only one of the risk factors associated with glaucoma. Therefore, it would be interesting to widen this type of study to include patients with other related risk factors. There may also be racial and genetic differences that make it mandatory to carry out new studies in order to obtain general conclusions.

We have started longitudinal and comparative studies with other diagnostic procedures, such as computer optic nerve head analysis (HRT II), FDT, and nerve fiber thickness using laser polarimetry (GDx) in order to study the diagnostic possibilities of this procedure.

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