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Intraobserver reproducibility of retinal nerve fiber layer measurements using scanning laser polarimetry and optical coherence tomography in normal and ocular hypertensive subjects

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PURPOSE. *To evaluate quantitatively the intraobserver reproducibility of measurements of the retinal nerve fiber layer (RNFL) in healthy subjects and an ocular hypertensive population using two nerve fiber analyzers.*
METHODS. *Sixty eyes of normal (n=30) and ocular hypertensive subjects (n=30) were consecutively recruited for this study and underwent a complete ophthalmologic examination and achromatic automated perimetry. RNFL were measured using scanning laser polarimeter (GDx-VCC) and optical coherence tomography (OCT Model 3000). Reproducibility of the RNFL measurements obtained with both nerve fiber analyzers were compared using the coefficient of variation.*
RESULTS. *In both groups the authors found fair correlations between the two methods in all ratio and thickness parameters. The mean coefficient of variation for measurement of the variables ranged from 2.24% to 13.12% for GDx-VCC, and from 5.01% to 9.24% for OCT Model 3000. The authors could not detect any significant differences between healthy and ocular hypertensive eyes, although in normal eyes the correlations improved slightly. Nevertheless, the test–retest correlation was slightly better for GDx-VCC than for OCT Model 3000 (5.55% and 7.11%, respectively).*
CONCLUSIONS. *Retinal mapping software of both nerve fiber analyzers allows reproducible measurement of RNFL in both healthy subjects and ocular hypertensive eyes, and shows fair correlations and good intraobserver reproducibility. However, in our study, GDx showed a better test–retest correlation. (Eur J Ophthalmol 2004; 14: 523-30)*

KEY WORDS. *Reproducibility, Retinal nerve thickness measurements, Optical coherence tomography, Scanning laser polarimeter, Ocular hypertension*

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INTRODUCTION

Glaucoma is associated with a progressive loss of retinal ganglion cell axons. Examinations of the optic nerve head and the retinal nerve fiber layer (RNFL) sites make glaucomatous tissue damage clinically detectable. Because the clinical techniques to date have been subjective, new objective and accurate methods have been developed to supersede conventional photography (1). Currently, confocal scanning laser tomography, nerve fiber layer polarimetry, and optical coherence tomography (OCT) are the most pop-

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ular techniques (2) and raise high expectations in clinical practice (3).

These instruments, which allow us to analyze RNFL thickness and realize a morphologic study on the optic nerve, are useful tools in the early diagnosis of glaucoma and help detect glaucoma progression, because they can differentiate between normal and glaucomatous eyes with initial to moderate visual field loss (4), even when damage to the RFNL has occurred but no quantifiable visual field defects are evident (5). It is essential to be sure that these new techniques designed to quantify structural alterations are capable of making accurate, reliable, and reproducible measurements (6), because results of RNFL thickness measurements may vary according to the devices used (7).

The aim of this study was to evaluate quantitatively the intraobserver reproducibility and compare the test–retest variability of RNFL measurements in healthy subjects and an ocular hypertensive population using the scanning laser polarimeter with variable corneal compensation (SLP-VCC) and high-resolution OCT (OCT3).

MATERIALS AND METHODS

We carried out a prospective cross-sectional analysis involving 60 eyes of 60 consecutive patients who underwent RNFL measurements using OCT3 and SLP-VCC. All the procedures were conducted in accordance with the principles of the Helsinki Declaration. Detailed consent forms were obtained from each of the patients. The subjects were divided into two subgroups according to the presence of ocular hypertension: Group 1 included 30 healthy subjects and Group 2 included 30 age-matched ocular hypertensive eyes.

All the patients underwent a complete ophthalmic examination, including medical, ocular, and family history; best-corrected visual acuity; slit lamp biomicroscopy; diurnal applanation tonometry measurement; stereoscopic optic disc evaluation using a 78-diopter lens; corneal thickness measurements (Orbscan Topography System II, Orbscan, Inc, Salt Lake City, UT); achromatic visual field testing with SITA standard strategy (Humphrey 750 Visual Field Analyser program 24-2, Zeiss Humphrey Systems, San Leandro, CA); SLP-VCC (GDx-VCC, software version 5.1.0, Laser Diagnostic Technologies, San Diego, CA); and OCT imaging (OCT version 3.0, Carl Zeiss Meditec Inc., Dublin, CA).

Subjects with visual acuity <20/40, refractive error exceeding 5.00 diopters sphere and/or 2.00 diopters cylinder, evidence of vitreous or retinal disease (including pathologic features of the optic nerve or peripapillary atrophy by stereoscopic slit-lamp biomicroscopy), uveitis, prior incisional surgery, laser therapy, and unreliable automated achromatic perimetry (greater than 25% fixation losses, false-positive and false-negative rates) were excluded from the study. The optic discs were assessed by the same experienced examiner. Presence of glaucomatous optic neuropathy was defined as vertical asymmetry >0.2, cup-to-disc ratio >0.6, and altered neuroretinal rim with peripapillary hemorrhages, notches, localized pallor, or nerve fiber layer defect.

In addition, all patients in both groups had clear media (without corneal, lens, or vitreous body abnormalities), had normal visual field as judged by the Glaucoma Hemifield Test, and presented no cluster of three or more adjacent points depressed more than 5 dB or of two adjacent points depressed more than 10 dB; they had a healthy-looking optic disc and an intraocular pressure of 21 mmHg or less for normal subjects, and at least 25 mmHg on two consecutive separate visits in ocular hypertensive eyes, in accordance with other previously reported studies (8, 9).

The GDx Nerve Fiber Layer Analyzer is a commercially available SLP, designed to estimate RNFL thickness *in vivo*. The actual time spent in acquiring data is less than $^3/_4$ of a second. This technology has been described in detail elsewhere (10-12). A brief overview is described below. The SLP is based on the birefringent characteristics of axonal neurotubules and measures the linear retardation of light in order to calculate RNFL thickness. It uses a confocal scanning laser ophthalmoscope with an integrated polarimeter. A linearly polarized beam (780-nm diode laser) traversing the RNFL scans the back of the eye, is elliptically polarized, and changes its state of polarization. The amount of linear retardation at each corresponding retinal location is proportional to the RNFL thickness.

The high-resolution Zeiss Optical Coherence Tomography Model 3000 is a noncontact and noninvasive tech-

nology that allows high-resolution measurements and cross-sectional imaging of the human retina at histologic levels of resolution (approximately 10 µm). The image acquisition time is approximately 1 second for each scan. Detailed descriptions of the principles of OCT have already been published (13-15); however, a summary follows. OCT involves the analysis of two broad bandwidth near-infrared light beams (840 nm) from a super luminescent diode. One beam is used for reference, the other for measurement. A scanning low-coherence interferometer is used to obtain a cross section of the retina based on the reflectivity of the different layers of the retina by measuring the echo delay time of light that is reflected and backscattered from different microstructural features. A high reflectance layer located just under the inner surface of the retina that corresponds to the RNFL is measured with a computer algorithm to give RNFL thickness.

Nerve fiber layer analysis

The nerve fiber analyses were performed in a single session with both instruments. One well-trained operator performed all the repeated RNFL thickness measurements five consecutive times in each eye. The first time, the RNFL measurement was performed in a standardized fashion with the SLP-VCC in an undilated state along the visual axis and central cornea. Only high-quality images that had passed the internal software's automated quality control criteria were accepted. Images that were obtained during eye movement, as well as unfocused and poorly centered images, were excluded. Finally, the optic disc margin was approximated by a circle or ellipse placed around the inner margin of the peripapillary scleral ring by the experienced technician. Defaulted quadrant positions (supplied by the manufacturer) were applied: the peripapillary band was divided into superior and inferior segments of 120° each, a temporal segment of 50°, and a nasal segment of 70°.

The second time, after pupillary dilation with 1% tropicamide to a minimum diameter of 5 mm to maximize the likelihood of acquiring a high-quality image, the RNFL was scanned with the OCT3. Five circular scans of 3.4-mm diameter centered on the optic disc, judged to be of acceptable quality by an experienced observer, were obtained and stored for each eye tested. An internal fixation target offset nasally from the scan area was used, because it has previously been shown to give the highest reproducibility (16) and was therefore used for all image acquisition. The scan process was started and the image of the optic nerve head was focused and aligned using the real time video monitor. When the operator was satisfied with the focus and quality of the scan image, it was frozen and saved in a database.

Statistical analysis

Unpaired Student t-tests and descriptive statistics were conducted for statistical analysis of continuous variables. A p value of 0.05 or less was considered to denote statistical significance. Measurement reproducibility of the RNFL obtained with the two nerve fiber analyzers (NFA) was compared using the mean coefficient of variation (COV) of the optic disc topographic parameters of the five measurements in both subgroups. The COVs were calculated as follows:

$$COV = (SD/M) * 100$$

where SD is the standard deviation of the measurements and M is the mean of the measurements. The COVs were expressed in percentages. To evaluate the test-retest correlation, we used the average of the mean COV of all the variables studied in both NFA.

Five parameters generated by NFA available mapping software were selected from each instrument for the statistical analysis of the intraobserver variation. In the SLP-VCC, we evaluated the following: the calculation circle average thickness (TSNIT), the superior 120º average thickness (SAVG), the inferior 120º average thickness (IAVG), the calculation circle standard deviation (TSNIT SD), and the nerve fiber indicator (NFI). The parameters evaluated by the OCT3 were the maximum thickness in the superior quadrant (SMAX), the maximum thickness in the inferior quadrant (IMAX), the average thickness in the superior quadrant (SAVG), the average thickness in the inferior quadrant (IAVG), and the average thickness for the total circumference (AVG THICK).

One eye/subject was enrolled; if both eyes of a patient were eligible for the study, the right eye was selected in order to obtain the most unbiased data. The choice of limiting the study to the right eye instead of the left was made in a random fashion.

RESULTS

Table I describes the demographic characteristics of the study population. As previously described, the patients were divided into two groups according to the presence of ocular hypertension, and there were no differences between the groups with regard to sex, age, visual acuity, or refractive defect. However, subjects with ocular hypertension had a significantly higher intraocular pressure and central corneal thickness values (p=0.002 and p=0.001, respectively). All normal and ocular hypertensive eyes had normal achromatic visual fields.

Good quality images were acquired in every case, and no one eye demonstrated impracticable measurements. The mean, standard deviation, range, and reproducibility comparisons of the optic nerve head topographic variables of all the patients analyzed are shown in Tables II and III. In both imaging technologies, intraobserver reproducibility of retinal thickness measurements was excellent, with mean COV of less than 10% for all the parameters, except for the NFI in the SLP-VCC.

Nevertheless, the test–retest correlation was better with the SLP-VCC than for OCT3 with an overall mean COV of optic nerve head topographic measurements of 5.55% with the SLP-VCC and 7.11% with the OCT3. The best reproducible parameters were the ellipse average thickness (TSNIT) and the SAVG with the SLP-VCC, and the IMAX and AVG THICK with the OCT3.

The intraobserver parameters and the test-retest variability in both groups analyzed showed fair correlations, and we could not detect any significant differences between healthy and ocular hypertensive eyes, although in normal eyes the correlations improved slightly, as can be observed in Tables IV and V. Relative variations in measurements were small in both healthy and ocular hypertensive eyes, with overall mean reproducibility of 6.49% and 6.08%, respectively.

However, the COV showed lower values with the SLP-VCC than in the OCT3. In the healthy eyes group, the COVs of the RNFL thickness measurements were found to range between 2.83% and 13.36% with the SLP-VCC, and between 5.37% and 7.87% with the OCT3. In the ocular hypertensive group, the COVs of the RNFL thickness measurements ranged from 2.07% to 12.75% with the SLP-VCC, and from 3.59% to 11.30% with the OCT3. The parameters with the best reproducibility were the same as when the whole group was analyzed.

DISCUSSION

An objective, quantitative, and sensitive method to assess RNFL thickness is needed for diagnosing and monitoring optic nerve diseases. Therefore, the purpose of our investigation was to assess prospectively the reproducibility of the RNFL measurements obtained using the two NFA. Our results indicate that for quantifying RNFL thickness both OCT3 and SLP-VCC are highly reproducible, showing fair correlations

TABLE I - DEMOGRAPHICS AND CLINICAL DATA OF THE STUDY POPULATION
(expressed as number (%) of subjects or mean ±standard deviation)

Characteristics	Control group	Ocular hypertension group	p value*
Number of eyes	30	30	—
Women	17 (56.66)	18 (60)	—
Men	13 (43.33)	12 (40)	—
Age, yr	38.50±18.58	48.67±18.01	0.148
Visual acuity (Snellen lines)	0.93±0.16	0.88±0.17	0.404
Spherical equivalent (D)	-1.21±2.65	-2.60±5.64	0.368
GAT (mm Hg)	15.22±2.24	26.32±1.08	0.002
CCT (microns)	535±38	602±53	0.001
Visual field: MD (dB)	-0.39±1.18	-0.74±1.23	0.095
Visual field: PSD (dB)	1.21±0.52	1.38±0.68	0.127

* Unpaired Student's t-test
GAT = Goldmann applanation tonometry; CCT = Central corneal thickness; MD = Mean defect; PSD = Pattern standard deviation

TABLE II - DESCRIPTIVE STATISTICS AND REPRODUCIBILITY COMPARISONS OF THE PARAMETERS ANALYZED IN THE OPTIC NERVE HEAD WITH THE SCANNING LASER POLARIMETER (GDX–VCC)

	Mean	SD	Range	COV, %
TSNIT	57.96	1.33	69.76-43.63	2.24
SAVG	68.71	1.73	85.81-40.79	2.56
IAVG	68.02	1.93	90.1-47.64	2.90
TSNIT SD	22.75	1.52	33.65-12.5	6.95
NFI	15.98	2.14	28-2	13.12

SD = Standard deviation; COV = Coefficient of variability; TSNIT = Circle average thickness; SAVG = Superior 120º average thickness; IAVG = Inferior 120º average thickness; TSNIT SD = Calculation circle standard deviation; NFI = Nerve fiber indicator

TABLE III - DESCRIPTIVE STATISTICS AND REPRODUCIBILITY COMPARISONS OF THE PARAMETERS ANALYZED IN THE OPTIC NERVE HEAD WITH OPTICAL COHERENCE TOMOGRAPHY (OCT model 3000)

	Mean	SD	Range	COV, %
SMAX	159.95	12.37	198-102	8.90
IMAX	156.12	9.40	203-110	5.89
SAVG	124.82	9.73	153-98	9.24
IAVG	114.72	7.09	159-107	6.50
AVG THICK	94.52	4.58	123.16-86.08	5.01

SD = Standard deviation; COV = Coefficient of variability; SMAX = Maximum thickness in superior quadrant; IMAX = Maximum thickness in inferior quadrant; SAVG = Average thickness in superior quadrant; IAVG = Average thickness in inferior quadrant; AVG THICK = Average thickness for the total circumference

TABLE IV - DESCRIPTIVE STATISTICS AND REPRODUCIBILITY COMPARISONS OF THE PARAMETERS ANALYZED WITH THE SCANNING LASER POLARIMETER (GDX-VCC) FOR BOTH GROUPS

	Control group (n=30)		Ocular hypertension group (n=30)	
	Mean±SD	COV, %	Mean±SD	COV, %
TSNIT	57.77± 5.87	2.20	58.24± 8.22	2.29
SAVG	69.41± 6.84	2.83	67.67±10.15	2.14
IAVG	67.62±10.97	3.44	68.63±12.8	2.07
TSNIT SD	23.21± 5.33	7.39	22.06± 4.34	6.30
NFI	11.17± 7.28	13.36	20± 9.26	12.75

SD = Standard deviation; COV = Coefficient of variability; TSNIT = Circle average thickness; SAVG = Superior 120º average thickness; IAVG = Inferior 120º average thickness; TSNIT SD = Calculation circle standard deviation; NFI = Nerve fiber indicator

TABLE V - DESCRIPTIVE STATISTICS AND REPRODUCIBILITY COMPARISONS OF THE PARAMETERS ANALYZED WITH OPTICAL COHERENCE TOMOGRAPHY (OCT MODEL 3000) FOR BOTH GROUPS

	Control group (n=30)		Ocular hypertension group (n=30)	
	Mean±SD	COV, %	Mean±SD	COV, %
SMAX	164.58±22.45	7.71	153±24.24	10.70
IMAX	156.72±29.96	7.42	155.21±12.27	3.59
SAVG	127.75±20.49	7.87	119.92±22.08	11.30
IAVG	115.42±27.57	7.37	113.67±25.71	5.20
AVG THICK	97.15±14.71	5.37	90.57±15.4	4.46

SD = Standard deviation; COV = Coefficient of variability; SMAX = Maximum thickness in superior quadrant; IMAX = Maximum thickness in inferior quadrant; SAVG = Average thickness in superior quadrant; IAVG = Average thickness in inferior quadrant; AVG THICK = Average thickness for the total circumference

and good intraobserver reproducibility, with low test–retest variability, being both accurate and reproducible methods in topographic measurements of the optic nerve head.

Both imaging instruments provide an assessment of the RNFL structure by utilizing different optical properties. They can both differentiate glaucomatous from nonglaucomatous populations (8) and can complement the diagnostic armamentarium as a sensitive parameter for diagnosing and monitoring glaucomas (17).

The OCT evaluates reflectance of posterior segment structures and incorporates a mathematical algorithm capable of localizing the anterior and posterior limits of the RNFL. It then compares the echo time delays of light reflected from the retina with the echo time delays of the same light beam reflected from a reference mirror. Using this mechanism, the OCT3 provides quantitative measures of RNFL thickness and

is an excellent clinical tool ideally suited to the clinical assessment of glaucoma (18), and to monitoring progressive diseases such as glaucoma (19).

The SLP estimates RNFL thickness through measurement of retardation of polarized light passing through the birefringent RNFL and cornea. It has been proven to be an effective tool for screening for glaucoma (20, 21), and it could be useful to follow the progression of glaucoma. Recently, GDx was modified into the GDx-VCC, which includes a VCC using macular-based strategies for neutralization of corneal birefringence if the Henle layer is not disrupted by macular pathology. It eliminates the anterior segment contribution to the total birefringence measured, and provides more valuable and repeatable information on RNFL loss (22, 23), especially in the mean-based retardation parameters: average thickness, superior average, inferior average, ellipse average, and superior integral.

The reproducibility of RNFL measurements has been assessed previously using both SLP and OCT, in healthy, ocular hypertensive, or glaucomatous eyes. An acceptable reproducibility and similar variability were found for most retardation parameters using SLP in healthy patients and patients with glaucomatous damage (24, 25). A high intraobserver reproducibility has been reported using the Nerve Fiber Analyser type I (26), the Nerve Fiber Analyser type II (mean COV of all integral values ranged from 3.67% to 4.92%) (27, 28), and the SLP third generation, the GDx (29), and the reproducibility of measurements hardly differed between single images and mean images.

Peripapillary RNFL thickness assessment using OCT has been studied previously, and high intraoperator reproducibility for both normal and glaucomatous eyes (16) was reported, which is consistent with the properties of RNFL (30). The mean COV for OCT measurements reported ranged between 4.33% and 6.9% in normal eyes (31, 32), but COV worsened to 8% for quadrant measurements and to 9% with further subdivision into 12 segments (33).

Comparisons in the reproducibility of the RNFL measurements between the different NFA have been studied by several authors, and the SLP yielded the most reliable results, which agrees with our results. Therefore, mean-based SLP parameters generated with SLP-VCC showed a greater correlation with visual function and RNFL thickness assessment obtained with OCT (23), and data obtained by SLP showed the lowest COV values (7%), followed by those obtained by Heidelberg Retina Tomograph (COV 12%), and finally the OCT showed the lowest degree of reproducibility (COV 15%) (7). However, none of the instruments provided sensitivity and specificity that justify summary data reports when used alone (4).

Different studies have reported the causes for poor reproducibility or measurements bias using SLP. In this respect, the presence of a vitreous opacity (34) or eyes with corneal grafts or edema, keratic precipitates, anterior uveitis, posterior subcapsular cataract, vitreous opacity, peripapillary atrophy, posterior staphyloma, and high axial myopia (35) can affect SLP measurement reliability. None of these circumstances was presented in our patients. On the other hand, contact lens wear and refractive power ranging from +4 diopters to -8.5 diopters do not significantly affect SLP measurements (36).

SLP-VCC software provides a specially constructed retardation parameter, the NFI, which indicates the likelihood that glaucoma is present, distinguishes normal and glaucomatous eyes, and is able to reflect disease severity. The sensitivity and specificity of this "number" has been evaluated, and acceptable sensitivity and specificity values at a critical value of 23 (37) were found and showed close relationship with RNFL average thickness and visual field status in glaucoma (38). But the neural network number has showed less reproducibility in normal eyes and eyes with initial glaucomatous damage (COV 12.4%) (25).

In our study, the NFI showed the worst COV in all the parameters analyzed, even though we were meticulous in centering the ellipse placement over the optic nerve head. We recommend cautious interpretation of the GDx "number" and clinicians must be careful in clinical decisions based only on this parameter. These high technology instruments should never replace the clinical judgment of expert observers in order to distinguish between normal individuals and those with glaucoma, particularly in the group with initial glaucoma.

We were unable to identify significant statistical differences in reproducibility between normal and ocular hypertensive eyes, and neither NFA could differentiate normal from ocular hypertensive eyes. Although RNFL thickness measured with OCT tended to be greater in normal than in ocular hypertensive eyes, this difference was not statistically significant. These find-

ings were consistent with other studies (8, 9) that reported that ocular hypertensive eyes with normal achromatic automated perimetry could not be distinguished from normal subjects by using SLP and OCT.

In conclusion, our results for repeated quantitative assessment of RNFL thickness in individuals with normal and ocular hypertensive eyes using current imaging instruments showed that both SLP-VCC and OCT3 can provide reproducible measurements of retinal thickness, showing good intraobserver reproducibility of these measurements, with a low range of test–retest variability. However, in our study, GDx showed slightly better test–retest correlation.

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