Intraobserver Reproducibility of Retinal Nerve Fiber Layer Measurements Using Scanning Laser Polarimetry with Variable Corneal Compensation in Glaucoma Suspect Patients

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Abstract

***Purpose*:** To quantify the intraobserver reproducibility of retinal nerve fiber layer (RNFL) measurements using scanning laser polarimetry with variable corneal compensation in glaucoma suspect patients.

***Methods*:** Twenty-six eyes of 26 glaucoma suspect patients were included. Complete ophthalmologic examination and standard automated perimetry were performed for all of them. RNFL measurements were done using GDx-VCC (Laser Diagnostic Technologies, San Diego, CA) by an experienced operator. The test repeated immediately by the same operator.

***Results*:** Patients were 24 to 70 years old (55.9±11.5 years). Twenty patients were female and 6 patients were male. Eighteen patients were ocular hypertensive and 8 patients had large cup to disk ratios. None of them had glaucomatous field defect in standard perimetry. The mean coefficient of variation for measurements of TSNIT average (Avg), superior Avg, inferior Avg, TSNIT-SD and nerve fiber indicator (NFI) were 0.77, 0.95, 0.91, 0.81, and 0.98 respectively. The mean coefficient of variation of GDx-VCC was 88.4 for the 5 main parameters (TSNIT Avg, superior Avg, inferior Avg, TSNIT-SD, and NFI).

***Conclusion*:** GDx-VCC showed a good test-retest correlation and acceptable intraobserver reproducibility. NFI may be the most reproducible major GDx-VCC parameter in glaucoma suspect patients.

***Keywords*:** scanning laser polarimetry, reproducibility, GDx-VCC, glaucoma suspect

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Introduction

There is increasing evidence that in most cases a structural retinal nerve fiber layer (RNFL) defect precedes the functional loss due to glaucomatous optic neuropathy.[1-4] By the time a visual field (VF) defect is present on automated achromatic perimetry, as many as 40% of the retinal ganglion cell pool may be already lost.[3] In order to detect RNFL thinning, in vivo, objective and quantitative measurements can be obtained by scanning laser polarimetry (SLP). Polarized laser light passing through tissues with physical properties of form birefringence undergoes retardation, linearly related to thickness in a primate model.[5] The most recent generation of polarimeters (GDx-VCC) provides a customized compensation of anterior segment birefringence whose incomplete removal produced sometimes inaccurate RNFL measurements when scans were caught by instrument with fixed corneal compensator.[6-10]

It is essential to be sure that this new technique designed to quantify structural alterations is capable of making accurate, reliable, and reproducible measurements. Although *Lacono* et al showed a reproducible measurement of GDx in normal and glaucomatous persons[11-13] there are few articles measuring its reproducibility in glaucoma suspect patients.[14]

Thus we conducted a study to quantitatively assess the reproducibility of the GDx-VCC parameters in the glaucoma suspect patients.

Methods

Design

Cross-sectional study.

Subjects

Twenty-six glaucoma suspect patients were recruited for this study. All of them were gathered from the glaucoma clinic of *Farabi* eye hospital. All the subjects were white. Twenty patients were female and 6 patients were male. All the patients underwent a complete ophthalmologic examination. Corneal thickness was measured by ultrasound. Achromatic visual field testing with SITA standard strategy (Humphrey field analyzer program 24-2, Zeiss Humphrey System, San Leandro, CA) was performed.

There were two kinds of patients in our study. The first group was ocular hypertensive (IOP consistently above 24 mm Hg without other signs of glaucoma). The second group had isolated large cup to disk ratio (larger than $^{6}/_{10}$) without other signs of glaucoma. No glaucomatous field defect was noted in the perimetry of any patients.

Patients with corneal disease, advanced cataract, peripapillary/retinal atrophy, high myopia, clinically relevant floater, keratorefractive surgery, best-corrected visual acuity worse than $^{20}/_{40}$ in either eye, previous intraocular surgery, secondary causes of elevated IOP, anatomically narrow angles, other diseases that can cause visual field loss, background diabetic retinopathy and optic disc abnormalities that can produce visual field loss or obscure the interpretation of the optic disc were excluded from the study.

Measurements

A single experienced examiner scanned each patient by SLP-VCC (GDx-VCC, Laser Diagnostic Technologies, San Diego, CA). Two separate tests performed on each patient. The quality of all images represented as Q by software was above 8. Ellipse placed around the inner margin of the peripapillary scleral ring was modified (if necessary) by the operator.

Statistical analysis

Data were analyzed using SPSS software. Coefficient of variation and Cronbach`s alpha reliability were calculated for each of 17 GDx-VCC parameters.

Results

Twenty-six patients were collected for this study. Twenty patients were female and 6 patients were male. All of them were glaucoma suspects. Eighteen patients were ocular hypertensive and 8 patients had large cup to disk ratio. The mean±SD of age was 55.9±11.5 (24-70) years. The mean IOP was 27.1±3.2 mm Hg and 14.3±2.1 mm Hg for the ocular hypertensive cases and the group with large cup to disk ratio respectively. The mean central corneal thickness for the first group was 531.5±35.2 (453-610) µm and for the second group was 522.4±30.5 (446-606) µm.

The results of the 52 tests performed (2 for any patient) are showed in table 1 (suffix 1 and 2 denotes the first and second test respectively).

Table 2 shows the coefficient of variation (CV) between the results of two tests for 17 GDx-VCC parameters. The mean CV for measurements of TSNIT average(Avg), superior Avg, inferior Avg, TSNIT-SD and nerve fiber indicator (NFI) was 0.77, 0.95, 0.91, 0.81, and 0.98 respectively. The mean±SD CV of GDx-VCC for the 5 main parameters (TSNIT Avg, Superior Avg, Inferior Avg, TSNIT-SD and NFI) was 88.4. The Cronbach`s alpha reliability for each of the GDx-VCC parameters is also shown in table 2. It ranges from 0.86 (TSNIT Avg) to 0.98 (NFI).

Table 1. Mean results of 17 parameters of the 52 tests performed in glaucoma suspect patients (two times for any patient)

	Test 1 Mean±SD	**Test 2 Mean±SD**
TSNIT average	52.00±7.33	53.19±8.54
Superior average	62.25±9.54	62.44±9.88
Inferior average	59.83±10.11	60.37±11.17
TSNIT SD	20.78±4.65	20.93±5.51
NFI	23.15±15.89	23.35±16.79
Symmetry	0.96±0.12	00.96±0.09
Superior ratio	3.23±0.98	3.16±0.92
Inferior ratio	3.34±0.95	3.30±0.97
Superior/nasal	2.29±0.58	2.34±0.55
Max modulation	2.51±0.87	2.40±0.89
Superior maximum	71.50± 9.71	72.30±10.81
Inferior maximum	75.03±13.69	76.15±13.80
Ellipse modulation	3.68±1.27	3.75±1.54
Normalized superior area	0.1222±0.0315	0.1227±0.0299
Normalized inferior area	0.1292±0.0299	0.1296±0.0326
Ellipse SD	20.79±4.65	20.93±5.51
Ellipse average	52.35±7.20	52.15±7.44

SD: Standard Deviation; TSNIT: Circle average thickness, NFI: Nerve Fiber Indicator

Table 2. Coefficient of variation and Cronbach`s alpha reliability for 17 GDx-VCC parameters in glaucoma suspect patients

	Coefficient of variation	Cronbach`s alpha
TSNIT average	0.77	0.86
Superior average	0.95	0.97
Inferior average	0.91	0.95
TSNIT SD	0.81	0.88
NFI	0.98	0.98
Symmetry	0.76	0.83
Superior ratio	0.88	0.93
Inferior ratio	0.83	0.90
Superior/nasal	0.86	0.92
Max modulation	076	0.86
Superior maximum	0.91	0.95
Inferior maximum	0.86	0.92
Ellipse modulation	0.78	0.87
Normalized superior area	0.93	0.96
Normalized inferior area	0.88	0.93
Ellipse SD	0.81	0.88
Ellipse average	0.94	0.97

SD: Standard Deviation; TSNIT: Circle average thickness, NFI: Nerve Fiber Indicator

Discussion

In the detection of glaucoma, IOP measurement has a relatively poor discriminating power. Approximately 32–53% of patients with glaucoma on first presentation have an IOP within the normal range (14-21 mm Hg).[15,16] It is difficult to differentiate physiological optic disc variation from pathological cupping, particularly in early glaucoma.[17] The main weakness of screening using automated perimetry is the subjective nature of the test and the high variability of the results.[18] In addition, histological studies have found that as many as half of all ganglion cells can be lost before a field defect can be detected.[3]

The GDx-VCC is a scanning laser polarimeter that measures RNFL thickness using polarized light. The advantage of the GDx-VCC over previous models is the ability of the instrument to measure and individually compensate for anterior segment birefringence, thereby eliminating measurement inaccuracies in RNFL thickness.[19] Objective RNFL data are provided

that are compared with an extensive normative database. The GDx-VCC software has been tested in many clinical trials. GDx-VCC variables are calculated by two methods—using a total of 1500 pixels per quadrant peripheral to an ellipse of 1.75 disc diameters or using pixels within the 10 pixel-wide elliptical band that is automatically positioned concentric with the disc margin outline and 1.75 disc diameters from the centre of the optic disc.[6,9]

The aim of this study was to evaluate the intraobserver reproducibility of GDx-VCC quantitatively. As the main aim of this device is to diagnose the early glaucoma, the study group was collected from the glaucoma suspect patients.

Each of the 26 glaucoma suspect patients underwent the test twice. As is obvious from the results (Table 2), high correlation existed between the parameters obtained by the first and second tests. The mean CV of GDx-VCC for the 5 main parameters (TSNIT Avg, Superior Avg, Inferior Avg, TSNIT-SD and NFI) was 88.4. Nerve fiber index (NFI) which is one of the most important factors in the printout had the highest CV(0.98) in our study and the least CV was of TSNIT Avg (0.77).

The reproducibility of RNFL measurements has been assessed previously using both GDx and optical coherence tomography (OCT), in healthy, or glaucomatous eyes.[12,13] *Shauman*[21] reported high intraoperator reproducibility of peripapillary RNFL thickness using OCT, which is consistent with properties of RNFL. The mean CV reported range between 4.33% and 6.9%.[14,20]

Lleo-Perez et al evaluated quantitatively the intraobserver reproducibility of measurements of the RNFL in healthy subjects (n=30) and an ocular hypertensive (n=30) population using GDx-VCC and OCT. In both groups the authors found fair correlations between the two methods in all ratio and thickness parameters. They could not detect any significant differences between healthy and ocular hypertensive eyes, although in normal eyes the correlations improved slightly. Their study showed a better test-retest correlation with GDx.[14] *Blumenthal* also showed a good interdevice reproducibility of RNFL thickness measurements obtained with the commercially available GDx-VCC.[21] Item reliability (Cronbach's alpha) for their five GDx parameters were: TSNIT Avg: 0.97, Superior Avg: 1.00, Inferior Avg: 0.84, TSNIT-SD: 0.99, NFI: 0.99.

Comparisons in the reproducibility of the RNFL thickness measurements between different nerve fiber analyzers have been studied by several authors, and the GDx yielded the most reliable results.[14] *Bagga* et al showed that GDx-VCC parameters had greater correlation with visual function than OCT.[6] Also data obtained by GDx showed the lowest CV, followed by those obtained by Heidelberg Retina Tomograph, and OCT.[22]

Measurement bias using GDx has been studied previously. Presence of vitreous opacity, dense posterior subcapsular cataract, peripapillary atrophy, posterior staphyloma, and high axial myopia can affect GDx measurements.[23] In our study, none of patients had these circumstances. Performing the second test immediately after the first one eliminates the confounding factors such as changes in environment, pupil size, and media clarity and disease status and resulted in a high CV.

NFI is a special retardation parameter in GDx-VCC that indicates the likelihood that glaucoma present. It has a close relationship with RNFL thickness and visual field status in glaucoma. But in normal eyes and eyes with initial glaucomatous damage the number reported to be less reproducible.[13,14] Although some studies reported that NFI might have the worst CV in all major parameters,[14] other studies did not.[21,24] Interestingly, In our study, NFI showed the highest reproducibility.

Conclusion

Interdevice, interexaminer, intrasession, intersession, and intraobserver reproducibility as well as short- and long term variability are all important for any new diagnostic technology. Our study showed that GDx-VCC had a good test-retest correlation and acceptable intraobserver reproducibility. It was a highly reproducible test for RNFL analysis in glaucoma suspect patients. NFI might be the most reproducible major GDx parameter in glaucoma suspect patients. Further studies with a larger number of patients and in different clinical conditions are needed to establish this hypothesis.

References

1. Kass MA, Heuer DK, Higginbotham EJ, Johnson CA, et al. The ocular hypertension treatment study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. Arch Ophthalmol 2002;120:701–713.
2. Pederson JE, Anderson DR. The mode of progressive optic disc cupping in ocular hypertension and glaucoma. Arch Ophthalmol 1980;98:490–495.
3. Quigley HA, Addicks EM, Green RW. Optic nerve damage in human glaucoma. III. Quantitative correlation of nerve fiber loss and visual defect in glaucoma, ischemic neuropathy, papilledema, and toxic neuropathy. Arch Ophthalmol 1982;100:135–146.
4. Sommer A, Katz J, Quigley HA, Miller NR, et al. Clinically detectable nerve fiber layer atrophy precedes the onset of glaucomatous field loss. Arch Ophthalmol 1991;109:77–83.
5. Weinreb RN, Dreher AW, Coleman A, Quigley H, et al. Histopathologic validation of Fourier-ellipsometry measurements of retinal nerve fiber layer thickness. Arch Ophthalmol 1990;108:557–560.
6. Bagga H, Greenfield DS, Feuer WJ, Knighton RW. Scanning laser polarimetry with variable corneal compensation and optical coherence tomography in normal and glaucomatous eyes. Am J Ophthalmol 2003;135:521–529.
7. Greenfield DS, Knighton RW, Huang XR. Effect of corneal polarization axis on assessment of retinal nerve fiber layer thickness by scanning laser polarimetry. Am J Ophthalmol 2000;129:715–722.
8. Knighton RW, Huang XR. Linear birefringence of the central human cornea. Invest Ophthalmol Vis Sci 2002; 43:82–86.
9. Weinreb RN, Bowd C, Zangwill LM. Glaucoma detection using scanning laser polarimetry with variable corneal polarization compensation. Arch Ophthalmol 2002; 120:218–224.
10. Weinreb RN, Bowd C, Greenfield DS, Zangwill LM. Measurement of the magnitude and axis of corneal polarization with scanning laser polarimetry. Arch Ophthalmol 2002;120:901–906.
11. Lacono P, Da Pozzo S, Fuser M, Marchesan R, et al. Intersession reproducibility of retinal nerve fiber layer thickness measurements by GDx-VCC in healthy and glaucomatous eyes. Ophthalmologica. 2006;220:266-271.
12. Kook MS, Sung K, Park RH, Kim KR, et al. Reproducibility of scanning laser polarimetry (GDx) of peripapillary retinal nerve fiber layer thickness in normal subjects. Graefes Arch Clin Exp Ophthalmol. 2001;239:118-121.
13. Rhee DJ, Greenfield DS, Chen PP, Schiffman J. Reproducibility of retinal nerve fiber layer thickness measurements using scanning laser polarimetry in pseudophakic eyes. Ophthalmic Surg Lasers 2002;33:117-122.
14. Lleo-Perez A, Ortuno-Soto A, Rahhal MS, Martinez-Soriano F, et al. Intraobserver reproducibility of retinal nerve fiber layer measurements using scanning laser polarimetry and optical coherence tomography in normal and ocular hypertensive subjects. Eur J Ophthalmol 2004;14:523-530.
15. Sommer A, Tielsch JM, Katz J, Quigley HA, et al. Relationship between intraocular pressure and primary open angle glaucoma among White and Black Americans. Arch Ophthalmol 1991;109:1090–1095.
16. Collaborative Normal Tension Glaucoma Study Group. Natural history of normal tension glaucoma. Ophthalmology 2001;108:247–53.
17. Quigley HA, Katz J, Derick RJ, Gilbert D, et al. An evaluation of optic disc and nerve fiber layer examinations in monitoring progression of early glaucoma damage. Ophthalmology 1992;99:19–28.
18. Keltner JL, Johnson CA, Quigg KE, Cello KE, et al. Confirmation of visual field abnormalities in the ocular hypertension treatment study. Arch Ophthalmol 2000;118:1187–1194.
19. Weinreb RN, Bowd C, Zangwill LM. Glaucoma detection using scanning laser polarimetry with variable corneal polarization compensation. Arch Ophthalmol 2003;121:218–224.

20. Schuman JS, Pedut-Kloizman T, Hertzmark E, Hee MR, et al. Reproducibility of nerve fiber layer thickness measurements using optical coherence tomography. Ophthalmology 1996;103:1889-1898.
21. Blumenthal EZ, Frenkel S. Inter-device reproducibility of the scanning laser polarimeter with variable cornea compensation. Eye 2005;19:308-311.
22. Klemm M, Rumberger E, Walter A, Richard G. Reproducibility of measuring retinal nerve fiber density. Comparison of optical coherence tomography with the nerve fiber analyzer and the Heidelberg retinal tomography device. Ophthalmologe 2002;99:345-351.
23. Hoh ST, Greenfield DS, Liebmann JM, Maw R, et al. Factors affecting image acquisition during scanning laser polarimetry. Ophthalmic Surg Lasers 1998; 29:545-551.
24. Zangwill L, Berry CA, Garden VS, Weinreb RN. Reproducibility of retardation measurements with the nerve fiber analyzer II. J Glaucoma 1997;6:384-389.