EXTENDED REPORT

An enhancement module to improve the atypical birefringence pattern using scanning laser polarimetry with variable corneal compensation

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Aim: To examine the repeatability and effect of an enhancement module on the severity of atypical birefringence patterns (ABP) using scanning laser polarimetery (SLP) with variable corneal compensation (VCC).

Methods: 16 patients with perimetric glaucoma (PG), 24 glaucoma suspect and pre-perimetric glaucoma (GSPPG), and 12 normal volunteers (N) were included. One randomly selected eye of each volunteer was scanned three times using VCC and enhanced corneal compensation (ECC) at the same session by the same examiner. Typical scan scores (TSS) were calculated to evaluate the ABP. Coefficients of variability (CoV), coefficients of repeatability (CoR), and intraclass correlation coefficients (ICC) were calculated.

Results: The mean TSS using ECC (n = 97.3 (5.5), GSPPG = 98.3 (3.5), PG = 99.2 (2.3)) was significantly higher (p = 0.02, 0.01, and 0.006, respectively) compared with VCC (86.5 (14.4), 88.2 (18.2), and 83.4 (2.2), respectively). VCC parameters had a CoR of 1.2–6.5, CoV of 1.9%–8.6%, and ICC of 0.8–0.9. ECC parameters had a CoR of 0.5–4.0, CoV of 0.3%–5.1%, and ICC of 0.2–0.9. TSNIT average was the overall best performing parameter with the highest repeatability and least variability using both techniques (CoR<2.1, CoV<2%).

Conclusion: The enhancement module significantly reduced the severity of ABP and maintained a high level of repeatability of retardation measurements.

The basic pathological change in glaucoma is loss of retinal ganglion cells and their axons resulting in retinal nerve fibre layer (RNFL) atrophy and the optic nerve head changes characteristic of glaucoma. Scanning laser polarimetry (SLP, GDx; Carl Zeiss Meditec Inc, Dublin, CA, USA) is a confocal scanning laser ophthalmoscope with an integrated polarimeter that measures the amount of retardation (phase shift) of a polarised near infrared laser beam as it passes through the RNFL.[1–7] Linearly polarised light traversing the RNFL is elliptically polarised and the amount of linear retardation of light at each corresponding retinal location is proportional to the RNFL thickness.

As all birefringent structures cause a change in the polarisation of an illuminating beam, the total retardance of a beam illuminating the parapapillary retina consists largely of contributions from the cornea and RNFL. The accuracy of RNFL measurements with SLP depends on the ability to extract the RNFL retardance from the total measured retardance. In order to neutralise the confounding influence of corneal birefringence on RNFL thickness, the latest commercial polarimeter has an integrated variable corneal compensator, which determines and neutralises eye specific corneal polarisation axis and magnitude using the concept of the macula as an intraocular polarimeter.[3 8 9] Several studies have shown that SLP with variable corneal compensation (GDx-VCC) significantly improves the structure-function relation,[10–12] the agreement with other imaging technologies,[11 13–15] and the discriminating power for glaucoma detection[4 9 16] compared to scanning laser polarimetry with fixed corneal compensation. Macular pathology, however, may introduce error in the strategy used for corneal compensation and alternative strategies have been proposed.[13 17]

It has been reported that in a subset of eyes, GDx-VCC scans have atypical birefringence patterns (ABP) such that the brightest areas of the retardation maps are not consistent with the histologically thickest portions of the peripapillary RNFL located along the superior and inferior arcuate bundles. Eyes with ABP are characterised by variable areas of high retardation arranged in a spoke-like peripapillary pattern, or "splotchy" areas of high retardation nasally and temporally.[18] Proposed mechanisms for atypical images include older age, myopia, and thinner retinal pigment epithelium. A support vector machine score (typical scan score, TSS) ranging from 0–100 has been reported to be highly predictive of ABP; lower scores are highly correlated with atypical patterns and may confound the detection of glaucoma.[18 19]

An enhancement module (enhanced corneal compensation, ECC) has been recently described to improve the signal to noise ratio and eliminate artefacts associated with ABP.[19 20] The ECC algorithm introduces a predetermined large birefringence bias to shift the measurement of the total retardation to a higher value region to remove noise and circumvent the problem of atypical patterns.[19] The amount of birefringence bias is determined using the birefringence pattern of the macular region, and then is mathematically removed point by point from the total birefringence pattern of the VCC to improve the signal and obtain a retardation pattern of the RNFL with least noise.[19 21]

The purpose of this study was to examine the effect of the ECC module on the severity of ABP and to study the

Abbreviations: ABP, atypical birefringence patterns; CoR, coefficients of repeatability; CoV, coefficients of variability; ECC, enhanced corneal compensation; GSPPG, glaucoma suspect and pre-perimetric glaucoma; ICC, intraclass correlation coefficients; IOP, intraocular pressure; PG, perimetric glaucoma; RNFL, retinal nerve fibre layer; RPE, retinal pigment epithelium; SLP, scanning laser polarimetry; TSNIT, temporal, superior, nasal, inferior, temporal; TSS, typical scan scores; VCC, variable corneal compensation

repeatability in normal volunteers, glaucoma suspects, and patients with perimetric glaucoma.

PATIENTS AND METHODS

Normal (N), glaucoma suspect and pre-perimetric glaucoma (GSPPG), and eyes with perimetric glaucoma meeting eligibility criteria were enrolled in this prospective study. Informed consent was obtained from all subjects by means of a consent form approved by the institutional review board for human research of the University of Miami Miller School of Medicine and was in agreement with the provisions of the Declaration of Helsinki. All patients underwent complete ophthalmic examination including slit lamp biomicroscopy, gonioscopy, ultrasound pachymetry, Goldmann applanation tonometry, dilated stereoscopic examination and photography of the optic disc, and two reliable visual field examinations. Standard automated perimetry (SAP) was performed with the Humphrey field analyser (Carl-Zeiss Meditec, Dublin, CA, USA) utilising a SITA-Standard strategy, program 24–2. One eye per subject was randomly selected for enrolment.

Normal subjects had no history of ocular disease and had intraocular pressure (IOP) less than or equal to 21 mm Hg by Goldmann applanation tonometry, normal optic disc appearance based upon clinical examination, and review of stereodisc photography, and normal SAP. Absence of glaucomatous optic neuropathy was defined as vertical cup-disc asymmetry less than 0.2, intact neuroretinal rim without peripapillary haemorrhages, notches, localised pallor, or RNFL defect. Normal visual field indices were defined as a mean deviation (MD) and pattern standard deviation (PSD) within 95% confidence interval limits and a glaucoma hemifield test result within normal limits. The GSPPG group consisted of subjects who had normal SAP and at least one of the following risk factors: ocular hypertension (IOP $\geqslant$24 mm Hg in one eye and IOP $\geqslant$22 mm Hg in the fellow eye) and/or optic nerve or RNFL defect visible on slit lamp biomicroscopy and stereoscopic optic disc photography. Subjects with perimetric glaucoma (PG) were defined as glaucomatous optic disc or RNFL abnormality associated with a repeatable SAP abnormality following confirmatory visual field testing. Visual field abnormality was defined as GHT outside normal limits and PSD of probability $<$5%.

Inclusion criteria common to all groups consisted of best corrected visual acuity better than or equal to 20/40, age between 40 and 79 years, refractive error between −7.00D and +3.00D, reliable Humphrey SITA-Standard 24-2 visual fields defined as a less than 33% rate of fixation losses, false positives and false negatives; and no previous intraocular surgery except for uncomplicated cataract extraction. Eyes with ocular disease other than glaucoma or cataract, visual acuity less than 20/40, peripapillary atrophy extending to 1.7 mm from disc centre, retinal disease, or unreliable SAP were excluded from this investigation.

GDx imaging (software version 5.5.0.11) was performed using a circular scan centred on the optic disc as described previously.[11 13 14 22–25] Each subject had three consecutive scans using VCC and three scans using ECC on the same day by the same examiner. A primary scan was acquired before each measurement to compensate for the corneal birefringence. Each image had a quality scan score of 8 or more. One eye of each volunteer was randomly selected for the analysis. All scans were acquired on undilated pupils. Unfocused and poorly centred images and images that were obtained during eye movements were excluded. A fixed concentric measurement band centred on the optic disc with a 3.2 mm outer and a 2.4 mm inner diameter was used and peripapillary retardation measurements were generated. The typical scan score (TSS), average thickness (TSNIT average), superior average, inferior average and the standard deviation of the average thickness (TSNIT standard deviation) were selected from both the GDx-VCC and GDx-ECC images as the outcome variables for the analysis. TSS scores were obtained using an electronic data export after the completion of image acquisition. ABP was defined as a TSS value of 60 or lower. This was based upon a previous report[18] that demonstrated a 100% probability of ABP in images with TSS scores of 60 or less using multiple logistic regression analysis.

Statistical analysis was performed using SPSS version 13.0 (SPSS Inc, Chicago, IL, USA). The intraclass correlation coefficient (ICC) was calculated as a measure of agreement of values within cases based on the variance between and within subjects.[26] The relative measure of dispersion was examined using the coefficient of variation (CoV) and was calculated as the standard deviation divided by the mean. The coefficient of repeatability (CoR) was also calculated as a measure of the within subject standard deviation of the replicates and was calculated as 1.96 times the standard deviations of the differences between the measurements.[27] Lower CoV and CoR mean lower variability and better repeatability of the diagnostic test.

RESULTS

Fifty two volunteers (31 females, mean age 63.3 (9.0), range 44–77) were recruited. Sixteen PG patients (nine females, mean age 65.3 (7.0), range 54–77), 24 patients in the GSPPG group (16 females, mean age 60.1 (9.0), range 44–77) and 12 normal volunteers (six females, mean age 62.8 (11.0), range 45–76) were examined.

Table 1 demonstrates the clinical characteristics of the study population. The visual field MD and PSD were significantly worse in the PG group compared to N ($p = 0.003$) and GSPPG groups ($p = 0.003$). There was no difference between the MD and PSD in the N and GSPPG groups ($p = 0.7$).

As demonstrated in figure 1, the mean TSS using ECC (N = 97.3 (5.5), GSPPG = 98.3 (3.5), PG = 99.2 (2.3)) was significantly higher ($p = 0.02$, 0.01, and 0.006, respectively) using ECC compared with VCC (86.5 (14.4), 88.2 (18.2), and 83.4 (21.8), respectively). The range of TSS values was greater using VCC (N = 54–100, GSPPG = 21–100, PG = 18.3–100) compared to ECC (N = 83–100, GSPPG = 86–100, PG = 91–100). Using a cut-off TSS value of $\leqslant$60, 4/52 subjects (7.7%) had ABP using VCC (one N, one GSPPG, and two PG); there were no subjects with ABP using ECC.

The CoR (table 2) and the CoV (table 3) were evaluated for five retardation parameters using VCC and ECC. VCC parameters had a CoR of 1.9–6.5 and CoV of 1.9%–8.6%. ECC parameters had a CoR of 0.5–4.0, and CoV of 0.3%–5.1%. TSNIT average was the overall best performing parameter with the highest repeatability and least variability using both VCC and ECC (CoR$<$2.1, CoV$<$2%).

The intraclass correlation coefficient (ICC) was evaluated for five retardation parameters using VCC and ECC (table 4).

Figure 2 illustrates a glaucomatous left eye with abnormal birefringence pattern characteristics. The left column demonstrates advanced glaucomatous cupping with thinning of the inferior neural rim associated with a superior arcuate visual field defect noted on grey scale and pattern deviation plot (bottom). The middle column illustrates the GDx-VCC image (top) with atypical birefringence pattern characterised by variable areas of high retardation arranged in a spoke-like peripapillary pattern. Note normal retardation parameters (bottom) and the TSS value of 22. The right column illustrates the GDx-ECC image with diffuse RNFL atrophy (top), abnormal retardation parameters (bottom, $p<0.5\%$), and TSS value of 93.

Table 1 Clinical characteristics of the study population

	Normal (n = 12)		Suspects (n = 24)		Glaucoma (n = 16)	
Mean age (years) (SD)	62.8 (11)		60.1 (9)		65.3 (7)	
Gender						
Female	6		16		9	
Male	6		8		7	
Race						
White	11		19		14	
Hispanic	1		3		1	
Asian	0		1		1	
Black	0		1		0	
Mean central corneal thickness (μm) (SD)	537.2 (21.8)		563.4 (38.7)		548.1 (44.0)	
Mean visual field mean deviation (dB) (SD)	−0.58 (1.69)		−0.83 (1.72)		−4.37 (3.75)	
Mean visual field pattern standard deviation(dB) (SD)	1.69 (0.73)		1.65 (0.49)		5.55 (4.21)	
	VCC	**ECC**	**VCC**	**ECC**	**VCC**	**ECC**
Mean TSS values (SD)	86.5 (14.4)	97.3 (5.5)	88.2 (18.2)	98.3 (3.5)	83.4 (21.8)	99.2 (2.3)
Mean TSNIT average (μm) (SD)	55.2 (5.2)	51.5 (4.0)	53.3 (6.4)	50.6 (5.1)	46.3 (6.3)	42.7 (6.0)
Mean Superior average (μm) (SD)	64.7 (8.3)	64.0 (7.6)	63.1 (7.6)	62.7 (6.8)	52.8 (8.5)	51.6 (8.5)
Mean Inferior average (μm) (SD)	61.0 (7.0)	60.0 (5.0)	61.3 (10.2)	62.4 (8.9)	50.9 (9.9)	50.6 (9.5)
Mean TSNIT SD (μm) (SD)	21.2 (3.6)	24.4 (3.4)	21.3 (4.7)	24.3 (4.2)	16.2 (3.5)	19.1 (4.2)

SD, standard deviation; VCC, variable corneal compensation; ECC, enhanced corneal compensation; TSS, typical scan score; TSNIT, temporal, superior, nasal, inferior, temporal.

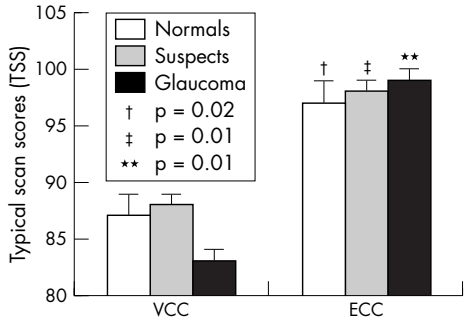

Figure 1 Histogram illustrating the mean and standard error of the typical scan scores obtained using GDx-VCC and GDx-ECC in normal (†), glaucoma suspect (‡), and glaucomatous eyes (♦♦).

DISCUSSION

Identifying and correcting sources of ocular imaging artefact are critical for technological advancement. It has been recognised that anterior and posterior segment pathology can produce spurious RNFL measurements using SLP.[28 29] The latest commercial polarimeter has an integrated variable corneal compensator, which determines and neutralises eye specific corneal polarisation axis and magnitude.[3 8 9 30 31] Macular pathology may disrupt the birefringence characteristics of the Henle fibre layer and limit the efficacy of corneal compensation strategies; alternative strategies in such eyes have been described.[13 17] Despite the introduction of variable corneal compensation, recent data[18 32] reveal that atypical birefringence images exist in a subset of normal and glaucomatous eyes. It has been hypothesised that ABP images occur in the presence of low signal to noise ratio resulting from loss/diminution of reflectivity from the retinal pigment epithelium (RPE) and occur more commonly in elderly myopic patients. A quantitative measure (TSS value) is associated with atypical images and TSS scores $\leqslant 60$ have a high probability of atypical images.

Recent data suggest that an enhancement module to the commercially available polarimeter may reduce the atypia of retardation maps resulting in lower RNFL thickness values.[19 20] In the absence of atypia, RNFL thickness parameters are similar using ECC and VCC.[19]

Our data confirm that ECC may significantly reduce the severity of ABP in normal, suspect, and glaucomatous eyes as determined by TSS values. Using a cut-off TSS value of $\leqslant 60$ for defining atypia, we found no patients with ABP when imaged using ECC compared with almost 8% of subjects imaged with VCC. Furthermore, there was a significant reduction in the severity of atypia as judged by the mean TSS value using ECC.

Good intraoperator measurement reproducibility has been demonstrated by several investigators.[33–35] Swanson *et al*[36] found significant interoperator variability using the NFA I. Hoh *et al*[28 37] reported good intraoperator and interoperator reproducibility among a series of normal eyes using the NFA II. Rhee *et al*[38] reported good reproducibility in pseudophakic normal and glaucomatous eyes. We found that GDx-ECC had high levels of reproducibility comparable with VCC using

Table 2 Coefficients of repeatability among the groups

	Normal (n = 12)		Suspects (n = 24)		Glaucoma (n = 16)	
	VCC	**ECC**	**VCC**	**ECC**	**VCC**	**ECC**
TSS	6.1	2.2	6.5	4.0	2.3	0.5
TSNIT average	1.9	1.3	2.1	1.5	1.2	1.3
Superior average	2.2	2.5	2.5	2.7	1.8	2.6
Inferior average	3.7	2.4	5.9	3.7	4.4	2.7
TSNIT SD	2.4	0.7	4.0	2.1	1.7	1.5

TSS, typical scan score; TSNIT, temporal, superior, nasal, inferior, temporal; VCC, variable corneal compensation; ECC, enhanced corneal compensation; SD, standard deviation.

Table 3 Coefficients of variability among the groups

	Normal (n = 12)		Suspects (n = 24)		Glaucoma (n = 16)	
	VCC	ECC	VCC	ECC	VCC	ECC
TSS	4.6%	1.8%	6.1%	2%	3.8%	0.3%
TSNIT average	1.9%	1.7%	1.9%	1.9%	1.9%	1.7%
Superior average	2%	2.8%	2.1%	2.8%	2%	2.6%
Inferior average	2.9%	2.8%	4.8%	4.2%	5.4%	3.2%
TSNIT Std. Dev.	5.7%	5.0%	8.6%	5.1%	6.6%	4.5%

TSS, typical scan score; TSNIT, temporal, superior, nasal, inferior, temporal; VCC, variable corneal compensation; ECC, vnhanced corneal compensation; SD, standard deviation.

Table 4 Intraclass correlation coefficients among the study groups

	Normal (n = 12)		Suspects (n = 24)		Glaucoma (n = 16)	
	VCC	ECC	VCC	ECC	VCC	ECC
TSS	0.95	0.98	0.98	0.25	0.99	0.98
TSNIT average	0.98	0.98	0.98	0.99	0.99	0.99
Superior average	0.99	0.97	0.99	0.97	0.99	0.98
Inferior average	0.96	0.94	0.91	0.92	0.95	0.99
TSNIT SD	0.93	0.96	0.87	0.96	0.95	0.98

TSS, typical scan score; VCC, variable corneal compensation; ECC, enhanced corneal compensation; TSNIT, temporal, super, nasal, inferior, temporal; SD, standard deviation.

various statistical approaches including CoV, CoR, and ICC. Of note, we observed that the ICC value for TSS in the GSPPG group was worse compared with other groups. The ICC represents a measure of inter-subject and intra-subject variance; lower ICC values are associated with greater intra-subject variance which may in part explain this observation.

In summary we found that the ECC module significantly reduced the frequency and severity of ABP in normal, glaucoma suspect, and glaucomatous eyes using scanning laser polarimetry. A high level of reproducibility was maintained comparable to VCC software. Further research is warranted to evaluate the ability of ECC to discriminate between normal and glaucomatous eyes.

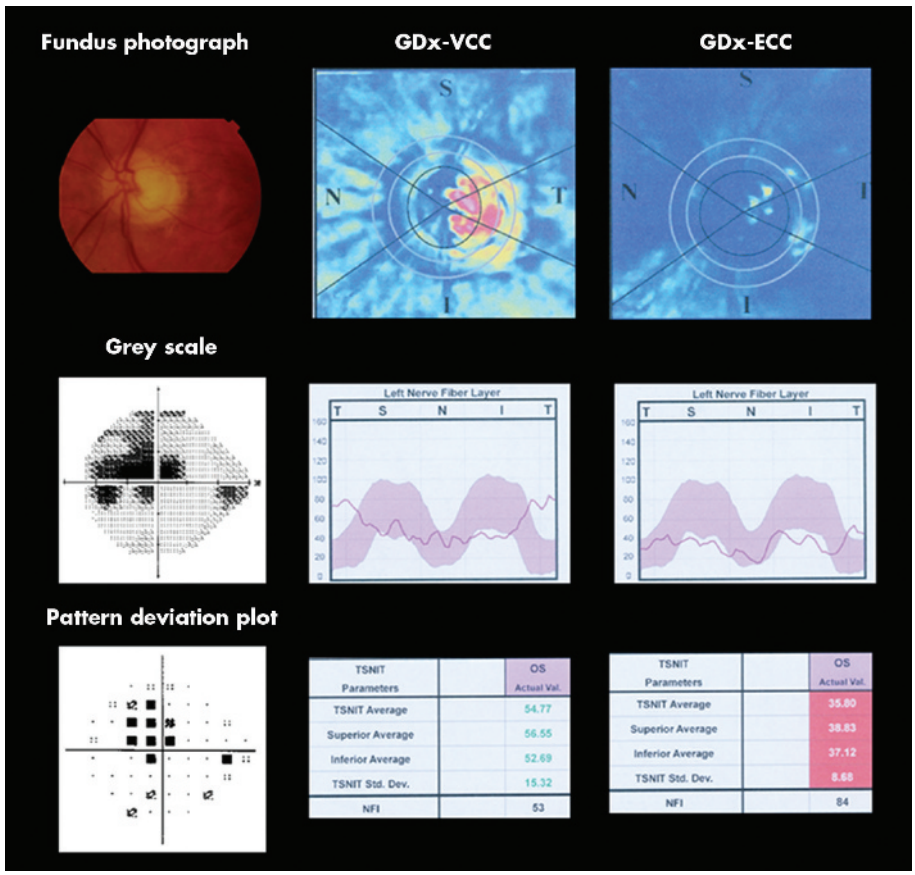

Figure 2 Illustrates a glaucomatous left eye with abnormal birefringence pattern characteristics.

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