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CLINICAL STUDY

Accuracy of GDx variable corneal compensation polarization measurements in normal human eyes: effect of accommodation, cycloplegia, focus, pupil size, and eye selection on reproducibility

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Abstract

Purpose **To evaluate the reproducibility of variable corneal compensation (VCC) and the effect of accommodation, cycloplegia, eye selection, focus, and pupil size on this measurement of polarization.**

Methods **Using a GDx scanning laser polarimeter, multiple measurements of the VCC were obtained from each eye of 33 healthy, young adults under differing conditions. Pupil size and refraction were independently measured with a pupillometer and an autorefractometer. The effects of eye, instrument focus, pupil diameter, cycloplegia, and accommodation were statistically assessed.**

Results **The reproducibility of a single retardation measurement and its axis, as determined by the standard deviations (SD) of repeated measurements, is ± 1.58 nm and 2.10°, respectively. There is a difference in retardation between right and left eyes, of 5.26 ± 9 nm, $P = 0.002$. Increasing pupil size increases retardation. Cycloplegia or defocusing decreases retardation, and pharmacologically induced accommodation has no effect on retardation.**

Conclusions **The retardation and its axis are highly reproducible measurements when the pupil is of physiologic size and the GDx is properly focused. There is a consistent difference in VCC retardation between the paired right and left eyes. This difference may reflect equipment-induced measurement artefact and/or an anatomic asymmetry between the paired eyes of the subjects studied. Clinicians should be cautious when comparing interocular VCC measurements between paired right and left eyes and using data pooled from both eyes for age-adjusted, normalized standards.**

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Keywords: scanning laser polarimetry; pupil size; focus; accommodation; cycloplegia; GDx VCC

Introduction

The scanning polarimeter is used clinically in glaucoma to measure peripapillary retinal nerve fibre layer (RNFL) thickness.[1,2] In order to remove non-RNFL components from the total retardation measurement, a method was developed to measure the eye-specific, nonretinal components contributing to the polarimetric measurement of retardation. This measurement is referred to as variable corneal compensation (VCC).[3–8] The optical pathway for determining the VCC includes the cornea,

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pupil, lens, vitreous, and the central macula. Since the central macula contains few polarizing ganglion cell axons and the fibres of Henle (which also polarize light) are symmetrically arranged and thought to be in quantitative balance with regard to the fovea, the measured polarization of the reflected beam is principally due to nonretinal tissues. The magnitude of this VCC retardation, at its specific axis of polarization, is subtracted from total peripapillary retardation to give the eye-specific, RNFL polarization measurements.[3–8] Therefore, the reliability of the measurement of RNFL polarization is critically dependent on the accuracy of its VCC measurement.

This study was undertaken to determine the intra- and intereye reproducibility of the VCC and the effects of pupil size, accommodation, cycloplegia, and focus on this measurement. Pupil size and accommodation were pharmacologically controlled and objectively quantified.

Methods

Commercially available scanning laser polarimeters with variable compensator (Model: GDx VCC Nerve Fiber Analyzer using Software version 5.2.1, Zeiss, formerly Laser Diagnostic Technologies Inc., San Diego, CA, USA) were employed in research mode for the measurement of central visual axis retardation and its axis. The data from the replicate VCC measurements were obtained directly from the computer source files.

Two experienced technicians performed all of the polarimetric measurements.[9,10] There were no statistical differences in paired comparisons of their GDx VCC measurements. All retardation measurements were associated with a 'quality score'. The maximum obtainable score with Software version 5.2.1 is '8'. All data employed had this maximum 'quality score' of 8, except that from studies in which the quality score was itself a variable. In such studies, measurements associated with a 'quality score' of 5 or better were permitted. Retardation measurements were obtained from an area centred on the fovea and having a sampling diameter of 930 μm.

Pupil size was determined with a pupillometer (Model: P2000, Part # A100010-1A, Procyon Instruments Ltd, 29 Abington Road, London W8 6AH, UK). The distance refractive error was quantified with an autorefractometer (Model # WV-500, Ryusyo Industrial Co. Ltd, 2-1-8 Minamihomachi, Chuo-ku, Osaka-Shi, Osaka, Japan).

This study adhered to the tenets of the Declaration of Helsinki and written informed consent was obtained only after the nature and possible untoward consequences of the study were explained. This study was HIPAA compliant. There were 33 subjects who participated in this study (age range: 18–22 years) (Table 2). A comprehensive ophthalmic examination on each subject did not reveal any ocular pathology, other than correctable refractive errors.

Multiple VCC measurements were obtained from four eyes of two subjects to establish the reproducibility of the VCC measurement. There were four sessions of equal duration required to obtain these data. Each pair of measurements (ie right and left eyes) at each session was a unique event, with the subject standing between measurements and then repositioning the head on the chin rest for the next measurement.

In all 33 subjects, the GDx instrument's focus was precisely adjusted to the subject's baseline subjective distance refraction. This refraction was verified by automated refractometry to be within 0.5 D of the objective measurement. A baseline set of 10 VCC measurements with a normal pupil was obtained, alternately from the right and the left eyes, in each subject. Prior to and following each set of 10 VCC measurements, pupillometry was performed.

Then, the internal focus of the GDx was increased by $+5$ D in the right eye. This was carried out to simulate the condition of a maximally defocused GDx image during measurement of the VCC. The other eye was defocused by -6 D. This was carried out to simulate the condition of a maximally defocused GDx image at the opposite extreme during the VCC measurement of the retardation. A full set of 10 VCC measurements was repeated with the eyes defocused.

The internal focus of the GDx instrument was returned to the prior baseline distance refractions for each subject. Phenylephrine 10% was instilled in both eyes and, after 20 min, another set of 10 VCC measurements and pupillometric measurements was obtained. Then, arbitrarily selecting the right eye, we instilled 2% cyclopentolate into its cul-de-sac and 4% pilocarpine into that of the other eye.

Automated refractometry was repeated 20 min after instillation of these drops. With the instrument focus based upon this new refraction, another set of VCC measurements was obtained, followed by pupillometry. The GDx internal focus was again changed, adding -6 D to the right eye and setting the focus in the left eye to its initial baseline refractive power. A final set of 10 VCC measurements was obtained, followed by pupillometry. Differences in retardation were evaluated for significance using the two-tailed '*t*-test', ANOVA, and Bland–Altman tests.[11,12]

Results

Using multiple VCC measurements obtained at eight different sessions from four eyes of two subjects, $n = 83$

and 96, respectively, the standard deviation (SD) of the VCC measurement was found to be ± 1.58 nm and 2.10° (Figures 1 and 2). Although the mean retardation and axis of these four eyes were themselves different, $P < 0.0001$ (Table 1; one-way ANOVA analysis), the accuracy$_{99\%}$ (99% probability range) of the VCC measurement was found to be ± 4.8 nm and $\pm 6.3°$.

There was a significant difference in the mean retardation between right and left eyes of 33 young subjects (Tables 2 and 3, row 1). Pupillary dilation with phenylephrine was associated with an increase in VCC retardation (Table 3, row 2). Following cyclopentolate, the pupil size increased and the retardation decreased (Table 3, rows 3 and 4). Pilocarpine induced miosis did not alter VCC retardation or its axis when compared to normal baseline or phenylephrine dilated pupils, as long as the polarimeter was properly refocused for any pharmacologically induced refractive change (Table 3, rows 5 and 6). However, defocus of the polarimeter, whether it was in the plus or minus direction, always caused a decrease in VCC retardation (Table 3, rows 7–9; Figure 3). With normal-sized pupils, the myopically defocused images were associated with lower-quality image scores (Figure 3). However, when the pupil size was altered in addition to defocusing of the image, a much greater percentage of the measurements demonstrated lower image quality scores (Table 3, rows 8 and 9; Figure 4). Change in pupil size alone did not significantly alter the quality score (Figure 5). There were

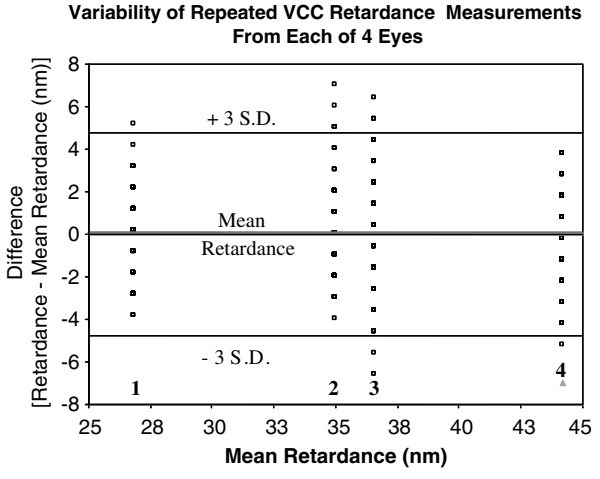

Figure 1 A Bland–Altman plot to determine the accuracy any single GDx VCC retardation measurement. The accuracy of an individual GDx VCC retardation measurement is determined from data obtained by repeated measurements of four eyes. The standard deviation (SD) of the retardation is ± 1.58 nm. Based upon this calculation, there is a 99% probability that any individual GDx VCC reading is within ± 4.8 nm of its actual retardation value ($3\,SD = \pm 4.75$ nm).

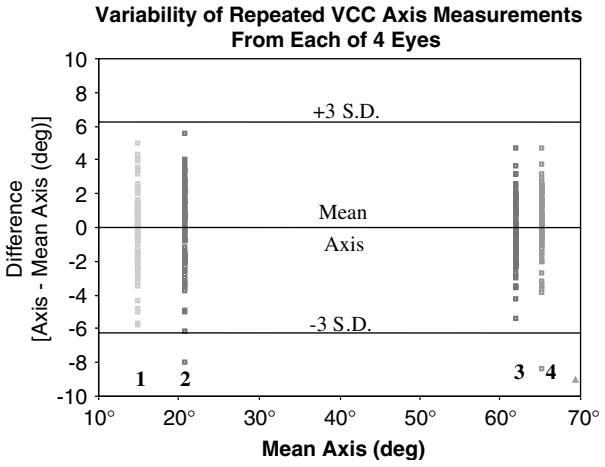

Figure 2 A Bland–Altman plot to determine the accuracy of an individual GDx VCC axis measurement based upon repeated measurements from four eyes. The standard deviation (SD) of the axis is $\pm 2.10°$. Based upon this calculation, there is a 99% probability that any individual GDx VCC reading is within $\pm 6.3°$ of the actual axis value ($3\,SD = \pm 6.29°$).

no adverse events associated with participation in this study.

Discussion

Our results indicate that the VCC measurement is highly reproducible under stable physiologic conditions with pupils of normal size. Pharmacologic dilation of the pupil with phenylephrine alone (mean pupil increase of 2.46 mm) causes an increase in VCC retardation when compared to that with a baseline pupil, $P < 0.0001$. When both phenylephrine and cyclopentolate are used together (mean pupil increase of 3.61 mm), the effect is opposite in direction, with a decrease in retardation when compared with that at the baseline pupil, $P = 0.029$. When the retardation with both phenylephrine and cyclopentolate together is compared to that with phenylephrine alone (mean pupil difference of 1.31 mm), the effect is a decrease in retardation, $P = 0.025$. Since this sample is modest in size, $n = 33$, with small, but significant differences and relatively large SDs, the possibility exists that the magnitude and directionality of these differences could be just random events.

Even if this were the case, what is clear is that dilatation markedly increases variability of the retardation measurement (Table 3, rows 2–4). Contrast these SDs with the SD of repeat retardation measurements with normal pupils of the same 33 subjects, where the SD is ± 2.3 and ± 2.5 (Table 2). The reason for the increase in variability of the VCC retardation measurement could be due to the difficulty of alignment of the GDx instrument after pupillary dilatation.

Table 1 VCC polarization differences between right and left eyes

Subject	N	*Retardation (nm)*					*Axis (degrees)*				
		Mean		*SD*		*Right minus left*	*Mean*		*SD*		*Right minus left*
		Right	*Left*	*Right*	*Left*		*Right*	*Left*	*Right*	*Left*	
1	83	27	35	2	2	−8	21	15	3	2	6
2	96	37	44	2	1	−8	62	65	2	2	−3
Total	179	32	40	2	2	−8	43	35	3	2	8

Table 2 Mean[10] of 10 paired and repeated VCC measurements from each of 33 young subjects (ages 18–22 years)

Subject	*Retardation (nm)*					*Pupil size (mm)*		
	Right	±*SD*	*Left*	±*SD*	*OS−OD difference*	*Right*	*Left*	*OD−OS difference*
1	29.8	3.4	32.4	2.0	2.6	4.7	4.5	0.2
2	64.9	1.8	61.5	1.8	−3.4	4.6	4.9	−0.3
3	46.2	1.6	61.2	5.0	15.0	4.2	4.1	0.1
4	40.8	3.9	42.2	2.9	1.4	4.8	4.9	−0.1
5	59.3	1.3	58.8	1.6	−0.5	4.3	4.4	−0.1
6	51.1	2.8	61.5	3.1	10.4	3.6	3.7	−0.2
7	38.5	1.8	31.4	2.0	−7.1	3.5	3.6	−0.1
8	39.5	2.4	44.6	1.6	5.1	5.2	5.2	0.0
9	30.6	3.1	31.6	2.2	1.0	4.4	4.2	0.2
10	61.1	2.6	77.0	2.4	15.9	3.4	4.2	−0.9
11	41.7	2.3	56.7	3.2	15.0	4.0	4.4	−0.3
12	37.0	4.8	38.0	2.9	1.0	5.1	5.3	−0.2
13	44.7	0.9	50.3	2.1	5.7	4.2	4.1	0.1
14	12.3	3.3	17.7	3.6	5.4	4.4	4.6	−0.1
15	47.0	2.8	56.9	1.5	9.9	4.7	4.6	0.0
16	30.2	1.9	37.5	3.0	7.3	5.1	5.4	−0.3
17	24.9	3.8	31.5	2.3	6.6	5.1	5.2	0.0
18	42.3	1.5	45.9	2.1	3.7	4.1	4.0	0.0
19	42.2	1.9	38.7	1.8	−3.5	3.5	3.5	0.0
20	15.4	1.3	31.8	1.0	16.4	4.3	4.4	−0.2
21	40.4	1.3	64.0	2.6	23.6	4.2	4.4	−0.3
22	41.1	2.6	51.2	1.7	10.1	4.7	4.8	0.0
23	18.0	3.5	32.6	3.7	14.6	4.8	4.8	0.0
24	32.5	2.9	43.1	2.3	10.6	5.2	5.2	0.0
25	23.9	0.5	35.0	2.3	11.1	3.9	4.2	−0.3
26	34.4	1.4	38.6	2.4	4.2	3.7	3.5	0.2
27	60.5	1.6	36.0	0.9	−24.5	5.1	5.1	0.0
28	69.6	3.3	77.5	3.6	7.9	3.9	3.9	0.0
29	39.2	1.4	37.6	1.7	−1.6	4.4	4.2	0.2
30	65.2	1.3	76.8	3.0	11.6	5.2	5.5	−0.3
31	62.6	3.9	51.8	5.0	−10.8	4.4	4.5	0.0
32	13.0	2.3	19.9	3.9	6.9	4.5	4.2	0.3
33	30.0	1.6	32.0	2.6	2.0	3.1	3.3	−0.1
Mean	40.3	±2.3	45.6	±2.5	5.3	4.4	4.4	−0.1
Probability of a difference (two-tailed '*t*'-test)				$P=0.002$			$P=0.07$	

The pupil itself is an unstable reference for purposes of obtaining and maintaining alignment of the GDx's optical axis for each eye. Its shape, size, and relative position are dynamically altered by ambient illumination and the pharmacologic agents employed.[13,14] The pupil moves nasally, with reference to the centre of the cornea, during miosis.[15–17] The dependence on the pupil as a reference to achieve optical alignment may explain the observed changes in VCC retardation associated with pupillary dilatation. The basis for the effect of increased pupil size on retardation may be related to this off-axis scanning and the associated corneal and lenticular optical aberrations.[17]

Some have reported that pupillary size does not affect the statistical evaluation of the parameters associated with polarimetric assessment of the peripapillary RNFL thickness.[18] This observation suggests that under the conditions of their experiment, the reproducibility of the GDx peripapillary RNFL measurements may be insufficient to identify the effect of pupil size on the retardation measurement. Others indicate that nerve fibre layer measurements with the GDx (without corneal compensation) are influenced by drugs affecting pupillary diameter.[19] These observations add importance to the changes we have documented in VCC retardation associated with changes in pupil size. By the reduction of all controllable sources of variability, the sensitivity of the GDx measurement may be enhanced and its utility augmented.

Although not evaluated in this study, no relationship has been reported between the baseline refractive error and the magnitude or axis of VCC polarization retardation. In this study, we assessed the effect of pilocarpine-induced accommodation and found it to have no effect on the magnitude of VCC retardation (Table 3, row 5).

We found a consistent and significant difference of 5.26 ± 9 nm, $P < 0.002$, in VCC retardation between the right and left eyes in our population of young adults at baseline (Table 3, row 1). By contrast, the intraocular reproducibility of a single retardation measurement is ± 1.58 nm. This large interocular difference in VCC retardation has not been reported previously, but has been confirmed by the manufacturer of the GDx at some of its study sites, following reanalysis of its polarization

Table 3 Mean$_{[10]}$ of 10 paired and repeated VCC measurements. Effect of pupil size, focus, accommodation, and intereye comparisons

No. of eyes	*Parameter*	*33 subjects between 18 and 23 years of age*				
		Retardation difference ± SD (nm)	*Axis difference ± SD (degrees)*	*Pupil size difference ± SD (mm)*	*Refraction difference ± SD (diopters)*	*Probability of difference in retardation by the two-tailed 't'-test*
33	RETARDATION Difference between RIGHT and LEFT EYES	OS > OD +5.26 ± 9.1 $[CI]_{95\%} = [\pm 3.10]$		None, pupils at baseline	None, refraction at baseline	$P = 0.002$
36	Effect Of DILATION with Phenylephrine Compared To Baseline Pupil	+1.63 ± 2.81 $P < 0.0001$		2.46 ± 0.71 $P < 0.0001$	None, refraction at baseline	$P < 0.0001$
33	Effect Of DILATION with Phenylephrine & Cyclopentolate Compared To Baseline Pupil	−1.37 ± 3.44 $P = 0.029$		3.61 ± 0.96 $P < 0.0001$	0.29 ± 0.44 $P = 0.0006$	$P = 0.029$
33	Effect Of DILATATION Phenyl + Cyclo Compared To Phenyelphine Alone	−2.86 ± 4.92 $P = 0.025$	5.46 ± 7.78 $P = 0.008$	1.31 ± 1.44 $P = 0.001$		$P = 0.025$
33	Effect of PILOCARPINE Compared To Baseline	0.66 ± 2.59 $P =$ NS		−0.91 ± 1.24 $P = 0.0002$	−5.87 ± 2.55 $P < 0.0001$	$P =$ NS
18	Effect of PILOCARPINE Compared To 10% Phenylephrine	−1.98 ± 6.04 $P =$ NS	+3.27 ± 6.88 $P = 0.060$	−3.49 ± 1.37 $P < 0.0001$		$P =$ NS
16	Effect of DEFOCUS of the Fixation with Baseline Pupil	OD −3.01 ± 3.36 $P = 0.003$	OS −4.42 ± 4.16 $P = 0.001$	None, pupils at baseline, 4.43 ± 0.57	Amt of defocus OD = +4.86 D OS = −5.79 D	$P = 0.003$
25	Effect of DEFOCUS of Fixation Following Phenyl + Pilo	−5.28 ± 5.72 $P = 0.0001$	−1.23 ± 2.20 $P = 0.01$	None, pupils constricted to 3.53 ± 1.09	Amt of defocus +5.87 ± 2.55 $P < 0.0001$	$P = 0.0001$
25	Effect of DEFOCUS of Fixation Following Phenyl + Cyclo	−4.71 ± 4.73 $P < 0.0007$		None, eyes dilated to 7.97 ± 1.16	Amt of defocus OD = −5.79 D	$P < 0.0007$

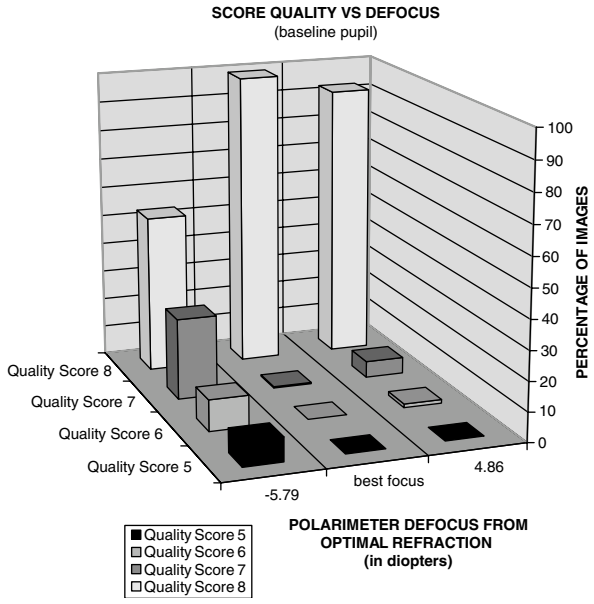

Figure 3 The three-dimensional graph shows the effect of defocusing the refraction in the GDx from its optimal level on the 'quality score'. The baseline condition was obtained when these 16 eyes were fully relaxed, had the best-corrected focus, pupils were physiologic, and no topical pharmacologic medications had been employed. Myopic defocus was obtained by subtracting a mean of 5.79 D from the baseline refractive setting, and hyperopic defocus was obtained by adding a mean of 4.86 D to the baseline refractive setting. The distributions of 'quality score' associated with either myopic or hyperopic defocus are demonstrated. Defocus causes a reduction in the 'quality' of the scores, that is, a shift toward lower quality. This is most apparent with myopic defocus.

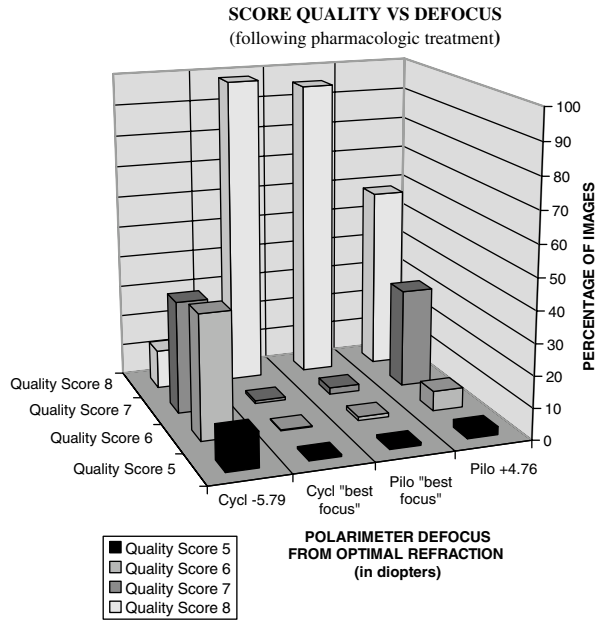

Figure 4 The three-dimensional graph shows the effect of defocusing the refraction in the GDx from its optimal level on the 'quality score' in 25 eyes following pharmacologic treatment with either phenylephrine and cyclopentolate in the right eye or phenylephrine and pilocarpine in the left eye The baseline 'cyclo' and 'pilo' conditions were obtained by setting the refractive setting of the GDx to the best-corrected focus after the application of either cyclopentolate (cyclo) in the right eyes or pilocarpine (pilo) in the left eyes. Defocusing was obtained by subtracting 5.79 D from this refractive setting in the right eyes (myopic defocus) or adding 4.76 D to this refractive setting of the left eyes (hyperopic defocus). Defocusing the GDx causes a reduction in the 'quality' of the scores. This effect is most apparent with myopic defocus in a widely dilated pupil.

database.[20] Using different methodology, Knighton and Huang[21] report that corneal birefringence was well correlated between the two eyes of a subject. Therefore, rather than reflecting any anatomic difference between paired corneas, it is likely that this interocular difference is a GDx-based artefact associated with the eye alignment, the axial pathway angles, and the testing algorithm. A small, but consistent disparity in the intereye light pathways may be sufficient to consistently alter the retardation measurement.

The VCC measurement is based upon proper positioning of the corneal measurement ellipse on the macula and the assumption that the Henle fibre layer is radially and anatomically symmetrical. Thus, any polarization due to the Henle fibre layer would be fully neutralized, if this assumption were true, and if the corneal measurement ellipse was placed perfectly at the centre of the macula. Our hypothesis to explain the consistently greater retardance in the left eyes of our subjects is that neither of the above conditions was fulfilled under the conditions of this study.

Optical coherent tomography (OCT) has documented that the inner retina of the nasal macula is approximately 15% thicker than the temporal macula.[22] Since the nasal Henle's fibre layer is thicker in this OCT measurement and also appears to be thicker histologically,[23] we propose that the GDx measurements from the left eyes demonstrate a greater retardance because of this asymmetry in the thickness of the Henle fibre layer. Our GDx retardance measurements were 13% greater in left eyes than right.

We suspect that this difference was identifiable by the GDx VCC measurement because the physiologic location of the pupil is not symmetrically positioned in the two eyes of the same individual, nor is it centred with respect to the limbus.[14–16] The GDx is physically aligned by centring the crosshairs of the device within the image of the patient's pupil and then adjusting the focus by positioning the peripupillary 'focus dot' in the centre of the horizontal red line.[24] The peripupillary 'focus dot' always is positioned on the iris and to the left of the pupil margin. For right eyes, the focus dot is always located at

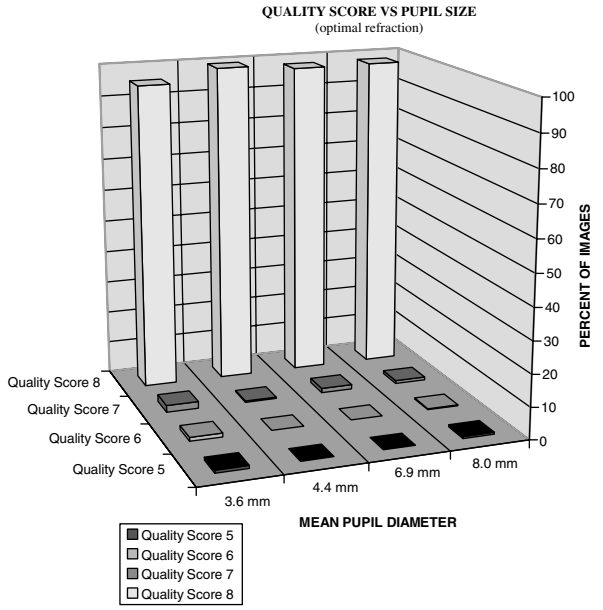

Figure 5 The three-dimensional graph shows the effect of pupil size on the distribution of the 'quality scores'. The mean pupil size following treatment with phenylephrine and pilocarpine was 3.6 mm, at baseline (without any topical medication) was 4.4 mm, following phenylephrine alone was 6.9 mm, and following phenylephrine and cyclopentolate was 8.0 mm. The distribution of the 'quality scores' of the images obtained under these conditions is plotted. Note that there is little shift in the distribution of the 'quality score' due to the effect of these treatments on pupil size.

the temporal margin of the pupil, and for left eyes, the focus dot is always located at the nasal margin of the pupil. This procedure, along with the asymmetry of pupil location, may be responsible for the consistent finding of a difference in the retardance between the right and left eyes.

In this study, the system software automatically placed the corneal measurement ellipse at the centre of the macula to provide the VCC measurement. The positioning of the 'focus dot' at the temporal margin of the right pupil, when aligning the right eye, may cause the GDx to include more of the temporal macula in the corneal measurement ellipse. While, conversely, the positioning of the 'focus dot' at the nasal margin of the left pupil may result in the GDx, including more of the nasal macula within the corneal measurement ellipse, it is likely that the nasal malalignment of corneal measurement ellipse at the macula in the left eyes results in emphasizing the difference in thickness and retardance between the nasal and temporal horizontal segments of the macula.

The disparity between right and left eye GDx VCC measurements is clinically important because it increases the variability in normal databases, which are not eye specific. Moreover, it can potentially result in spurious conclusions during interocular peripapillary RNFL comparisons. Since the difference between right and left eyes was 5.26 ± 9 nm, to be at least 99% confident that there is a true difference in peripapillary RNFL between right and left eyes, the retardance difference should be >27 nm (3 SD).

Change in pupil size does not appear to alter the quality score (Figure 5), although it does cause a statistically significant change in the polarization retardation (Table 3, rows 2–4). Defocus of the GDx polarimeter from the best-corrected refraction is associated with much larger reductions in VCC retardation (Table 3, rows 7–9), while only occasionally associated with lower-quality image scores (Figure 3). It is only when both the pupil size is altered and the GDx polarimeter is defocused that quality scores fall substantially (Figure 4). Although defocus will always be associated with a highly significant reduction in VCC retardation (Table 3, rows 7–9), the fall in the 'quality score' may not identify the presence of this defocus of the instrument. Defocus and to a lesser degree pupillary size changes can increase the variability of the VCC measurement and, thereby, may affect its accuracy for individualized corneal calibration.

In summary, the VCC was introduced as a method to reduce variability and enhance intereye precision of the peripapillary measurement. Reducing the error associated with this corrected corneal component could further assist in obtaining more accurate peripapillary measurements. The examiner can optimize the reproducibility of the VCC GDx polarimetric measurement by careful attention to optimizing focus and avoiding the use of the GDx when the pupils have been dilated. The examiner should be cautious when comparing peripapillary RNFL measurements of right and left eyes and only accept as significant, a retardance difference between eyes that is >27 nm. In order to reduce variability in the normative database associated with the pooling of retardance data from the right and left eyes of the same patients, a redesign of the method by which the GDx instrument is aligned and then acquires data from each eye may be desirable.

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