Reproducibility of peripapillary retinal nerve fibre layer thickness measurements with spectral domain optical coherence tomography in normal and glaucomatous eyes

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ABSTRACT

Aim To determine reproducibility of peripapillary retinal nerve fibre layer thickness (RNFLT) measurements by spectral optical coherence tomography scanning laser ophthalmoscope (Spectral OCT/SLO) in normal and glaucomatous eyes.

Methods 61 normal subjects and 41 glaucoma patients underwent three RNFLT measurement by Spectral OCT/SLO in one of the eyes with a rest of 1 h between each scan. The series was repeated on three different days within 1-month period. Intrasession, intersession reproducibility of average, quadrant and clock hour RNFLT measurements were calculated for both groups. All scans were acquired by a single operator after dilation.

Results The intrasession intraclass coefficient correlations for mean RNFLT in normal and glaucomatous eyes were 0.994 and 0.998, respectively. The intrasession test coefficient of variation (CV) ranged from 1.2% for mean RNFLT to 5.1% for temporal clock hour in normal eyes and 1.3% for mean RNFLT to 3.6% for nasal quadrant in glaucomatous eyes. The intersession intraclass coefficient correlation for mean RNFLT in normal and glaucomatous eyes was 0.988. Intersession CV ranged from 3.96% for mean RNFLT to 9.56% for temporal clock hour in normal eyes and 3.28% for mean RNFLT to 13.39% for temporal clock hour in glaucoma patients.

Conclusion The RNFLT measurement showed increased variability for narrower peripapillary areas, nasal and temporal quadrants showed higher variability than superior and inferior quadrants in normal and glaucomatous eyes. Spectral OCT/SLO demonstrated excellent intrasession and intersession reproducible measurements of peripapillary RNFLT in both groups. This finding may be useful for diagnosis and monitoring the progression of glaucoma and other optic neuropathies with spectral OCT/SLO.

INTRODUCTION

Optical coherence tomography (OCT) is a non-contact, non-invasive in vivo imaging device that produces high resolution, cross-sectional images of optic nerve head (ONH) and retinal nerve fibre layer thickness (RNFLT). It provides objective and quantitative estimation of RNFLT by measuring echo time delay and intensity of backscattered light from different retinal layers, using an optical correlation technique known as Michelson low coherence interferometry.[1]

Previous studies have shown that OCT provides reproducible measurements of RNFLT obtained with first prototype OCT, second generation OCT and third generation time domain Stratus OCT.[2–8]

Spectral domain OCT provides improved visualisation of retinal morphological and pathological features.[9] Spectral OCT/SLO (OPKO/OTI; Miami, Florida, USA) is a combination of OCT and scanning laser ophthalmoscope (SLO), designed to image retina for accurate, point-to-point registration and orientation. It has higher axial resolution of <6 μm, transverse resolution of 20 μm and a scan velocity of 27 000 axial scans/s compared with Stratus OCT (axial resolution 8–10 μm, scan speed 400 axial scans/s).

Spectral OCT/SLO uses low coherence interferometry to detect light echoes, relying on a spectrometer and high-speed camera, and is based on the mathematical formula of fast Fourier transformation. This results in the measurement of echoes of light simultaneously, which causes significant reduction of motion artefact and an increase in signal-to-noise ratio.[10]

A critical test for any technology for clinical use is its measurement reproducibility. With the development in OCT technology and software, an improvement in reproducibility of RNFLT measurements is expected.

The purpose of this study was to determine the reproducibility of peripapillary RNFLT measurements obtained with Spectral OCT/SLO in normal and glaucomatous eyes on the same day (intrasession) and on different days (intersession) by a single operator.

MATERIALS AND METHODS

For the study, normal volunteers were recruited from staff and glaucoma patients from glaucoma clinic of the Institute. All participants were Asian Indians.

Each subject underwent complete ophthalmic evaluation, including, best corrected visual acuity (BCVA), refraction, slit lamp biomicroscopy, intraocular pressure (IOP) measurement by Goldmann applanation tonometer, gonioscopy by Volk four-mirror Sussman goniolens, optic disc and fundus evaluation with +78 Diopter (D) lens, and achromatic automated perimetry using Swedish Interactive Threshold Algorithm Standard, 24-2 program with Humphrey visual field analyzer (Carl Zeiss Meditec, Dublin, California, USA).

For inclusion in the study the subjects had to have BCVA ≥20/30, sphere within ±3 D, cylinder within ±1.5 D, clear ocular media (nuclear opalescence,

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nuclear colour and cortical changes up to grade 3 on Lens Opacities Classification System III)[11] and open angles on gonioscopy.

Subjects with intraocular surgery, ocular trauma, neurological disease, corneal, retinal or macular pathology, uveitis, tilted discs with peripapillary atrophy were excluded from the study. Normal subjects had IOP <21 mm Hg, normal optic disc appearance (that is, absence of glaucomatous optic neuropathy), normal and reliable visual field. Normal visual field indices were defined as mean deviation and pattern standard deviation (PSD) within 95% confidence limits and glaucoma hemifield test "within normal limits".

Patients with glaucoma had IOP >22 mm Hg on more than three occasions, characteristic glaucomatous optic disc changes (vertical cup-disc asymmetry >0.2 between two eyes, neuroretinal rim thinning, notching or excavation, localised pallor or RNFL defect), corresponding and reliable visual field defect (which satisfied >2 of Anderson and Patella[12] criteria). Based on Hodapp and Anderson[13] criteria, nine patients had early glaucoma, 12 patients had moderate glaucoma and 20 patients had advanced glaucoma.

OCT technique

After dilation with 1% tropicamide eye drop, images were obtained by single operator (T M) using Spectral OCT/SLO with RNFL scanning mode. Using internal fixation target, a circular scan of 3.4 mm diameter was centred around ONH and the location was observed on the SLO image to ensure proper positioning of scan in relation to the ONH. The RNFL analysis uses an automated OCT software algorithm to identify anterior and posterior margins of RNFL and averages three measurements around the circular scan to obtain average, four quadrants and eight clock hour RNFLT. The sectors were defined in clockwise order for the right eye and counter clockwise order for the left eye.

Three RNFL scans were taken in each session with 1 h rest between each scan to obtain intrasession variability and the procedure was repeated on three different days within 1 month period to determine intersession variability. To be acceptable for inclusion, quality of scan image was subjectively assessed to look for dense and even colour saturation across the entire scan, signal strength of >7, good centration of scan around ONH and no RNFL discontinuity.

Statistical analysis

Statistical analysis was performed using SPSS program version 15 (SPSS Inc., Chicago, IL, USA). Reproducibility for RNFLT measurements was calculated using intraclass correlation coefficient (ICC), coefficient of variation (CV) and test–retest variability (TRV). ICC represents concordance where 1 is perfect agreement and 0 is no agreement at all. The CV was calculated as the ratio of the root mean square error and mean of dependent variable. TRV was calculated as two times the standard deviation (SD) of three repeated measurements.

RESULTS

Sixty-one normal subjects and 41 glaucoma patients were enrolled in the study. Statistically significant differences were observed in mean age, mean deviation and pattern standard deviation (PSD) between healthy and glaucomatous eyes ($p<0.001$) (table 1).

Intrasession ICCs were excellent in normal (0.974 for temporal clock hour to 0.994 for mean RNFLT) and glaucoma subjects (0.984 for temporal and superior temporal clock hour to 0.998 for mean RNFLT) (tables 2 and 3). The intersession ICC for mean RNFL thickness in normal and glaucomatous eyes was 0.988 (tables 4 and 5).

Table 1 Demographic and ocular characteristics of study participants

	Normal eyes	Glaucoma patients
n	61	41
Age (years)*	38.26±14.11 (19–79)	57.24±9.2 (40–70)
Male (n (%))	31 (50.8)	22 (53.7)
Female (n (%))	30 (49.2)	19 (46.3)
Mean deviation (dB)*	−1.55±0.73	−14.19±7.89
Pattern standard deviation (dB)*	1.44±0.39	8.74±2.9

*Values are mean±SD (range).
dB, decibel.

Of the peripapillary quadrant measurements in the normal eyes, nasal and temporal quadrant had a lower ICC (0.983) than superior and inferior quadrant. In glaucomatous eyes, nasal quadrant had the lowest ICC (0.995) (tables 2 and 3).

For intrasession visit, temporal quadrants had the highest CV of 3.8% in normal eyes and 3.6% in nasal quadrant in glaucomatous eyes (tables 2 and 3). For intersession visit, temporal quadrants has the highest CV of 7.6% in normal eyes and 10.47% in glaucomatous eyes (tables 4 and 5). Temporal and nasal quadrants were more variable than superior and inferior quadrants in both groups.

For the peripapillary clock hour measurements, intrasession CV ranged from 1.8% for inferior clock hour to 3.7% for nasal clock hour in normal eyes and 2.6% in inferior clock hour to 5.1% in temporal clock hour in glaucomatous eyes (tables 2 and 3).

Intersession CV ranged from 5.41% for inferior clock hour to 9.56% for inferior temporal clock hour in normal eyes and 6.8% in inferior clock hour to 13.39% in temporal clock hour in glaucomatous eyes (tables 4 and 5).

Intrasession variability for RNFLT was less than intersession variability in both groups. For both intrasession and intersession visits, the quadrants had larger variance than the overall mean RNFLT and clock hours had larger variance than the quadrants RNFLT.

DISCUSSION

Factors that influence reproducibility of RNFLT measurements are pupil dilation,[6] variations of signal strength,[14] sampling density,[15] media opacity and the quadrants measured.[8] Wu *et al*[14] showed that the impact of low signal strength scores can

Table 2 Intrasession intraclass correlation coefficient (ICC) and 95% lower CI (confidence interval), coefficient of variation (CV) and test-retest variability (TRV) of retinal nerve fiber layer thickness (RNFLT) in normal subjects

RNFL parameters	ICC (95% lower CI)	CV (%)	TRV (μm)
Average	0.994 (0.97)	1.2	1.46
Quadrants			
Superior	0.987 (0.979)	2.2	2.96
Temporal	0.983 (0.974)	3.8	1.89
Inferior	0.992 (0.987)	1.6	2.18
Nasal	0.983 (0.975)	2.9	2.78
Clock hour			
Superior	0.989 (0.982)	2.7	3.64
Superior temporal	0.987 (0.980)	3.1	3.28
Temporal	0.974 (0.960)	3.2	1.83
Inferior temporal	0.979 (0.968)	3.6	3.62
Inferior	0.992 (0.988)	1.8	2.77
Inferior nasal	0.986 (0.979)	2.9	3.27
Nasal	0.987 (0.980)	3.7	3.28
Superior nasal	0.975 (0.962)	2.8	3.47

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Table 3 Intrasession intraclass correlation coefficient (ICC) and 95% lower CI (confidence interval), coefficient of variation (CV) and test–retest variability (TRV) of retinal nerve fibre layer thickness (RNFLT) in glaucoma patients

RNFL parameters	ICC (95% lower CI)	CV (%)	TRV (μm)
Average	0.998 (0.997)	1.3	1.20
Quadrants			
Superior	0.997 (0.995)	2.4	2.54
Temporal	0.991 (0.984)	3.4	2.21
Inferior	0.997 (0.995)	1.8	1.86
Nasal	0.995 (0.991)	3.6	2.94
Clock hour			
Superior	0.995 (0.992)	3.0	3.27
Superior temporal	0.984 (0.973)	4.8	4.14
Temporal	0.984 (0.972)	5.1	2.88
Inferior temporal	0.988 (0.981)	3.9	3.39
Inferior	0.995 (0.992)	2.6	2.74
Inferior nasal	0.994 (0.990)	3.4	3.27
Nasal	0.995 (0.992)	3.6	2.77
Superior nasal	0.995 (0.991)	3.4	3.40

be relevant and the larger signal strength changes (>1 unit) may lead to a greater RNFLT from baseline. In our study, scans were obtained after pupillary dilation using internal fixation target and only scans with signal strength of >7 were included for analysis. Similarly to a previous study, we found that the narrower the peripapillary area measured, the higher the variability. As the area measured gets larger, more individual measurements are added into the mean for that area: this sort of signal averaging results in more reliable measurements.[8]

Schuman *et al*[2] used first generation OCT to measure RNFLT five times on five separate occasion within 1 month period. They found ICC of 0.56 in 11 normal subjects and 0.52 in 10 glaucoma subjects, respectively, and concluded that RNFLT measurements were reproducible using internal fixation compared with external fixation.

Carpineto *et al*[3] used first generation OCT to test reliability of RNFLT measurements in 24 glaucoma and 24 normal subjects by five repetitions of a series of scans on five separate occasions within a 0.5 month period. For normal eyes, ICCs were close to 0.5 for mean and all quadrants except for temporal quadrant (ICC −0.33); for glaucomatous eyes the mean, superior and inferior quadrants had ICCs close to 0.5.

Table 4 Intersession intraclass correlation coefficient (ICC) and 95% lower CI (confidence interval), coefficient of variation (CV) and test–retest variability (TRV) of retinal nerve fibre layer thickness (RNFLT) in normal subjects

RNFL parameters	ICC (95% lower CI)	CV (%)	TRV (μm)
Average	0.988 (0.90)	3.96	1.4
Quadrants			
Superior	0.916 (0.892)	5.06	6.76
Temporal	0.743 (0.671)	7.6	5.20
Inferior	0.907 (0.880)	4.3	6.02
Nasal	0.858 (0.819)	7.39	7.08
Clock hour			
Superior	0.921 (0.899)	6.2	8.56
Superior temporal	0.891 (0.860)	7.07	7.52
Temporal	0.714 (0.633)	7.86	4.44
Inferior temporal	0.678 (0.588)	9.56	9.65
Inferior	0.892 (0.861)	5.41	8.28
Inferior nasal	0.847 (0.805)	8.15	8.99
Nasal	0.868 (0.831)	9.34	8.07
Superior nasal	0.79 (0.731)	6.59	8.09

Table 5 Intersession intraclass correlation coefficient (ICC) and 95% lower CI (confidence interval), coefficient of variation (CV) and test–retest variability of retinal nerve fibre layer thickness (RNFLT) in glaucoma patients

RNFL parameters	ICC (95% lower CI)	CV (%)	TRV (μm)
Average	0.988 (0.984)	3.28	2.96
Quadrants			
Superior	0.984 (0.978)	4.7	5.05
Temporal	0.864 (0.817)	10.47	6.86
Inferior	0.968 (0.956)	5.31	5.48
Nasal	0.951 (0.934)	9.5	8.00
Clock hour			
Superior	0.966 (0.954	6.95	7.69
Superior temporal	0.913 (0.883)	9.92	8.47
Temporal	0.835 (0.777)	13.39	7.65
Inferior temporal	0.92 (0.892)	8.8	7.66
Inferior	0.957 (0.943)	6.8	7.25
Inferior nasal	0.953 (0.936)	9.0	8.66
Nasal	0.948 (0.929)	10.5	8.15
Superior nasal	0.971 (0.961)	6.9	6.99

Blumenthal *et al*[4] used second generation OCT to measure RNFLT in 10 normal and 10 glaucomatous eyes in eight scanning sessions during two visits. They reported CVs for mean RNFLT of 7% in normal and 13% in glaucomatous eyes.

Jones *et al*[5] used second generation OCT on two separate sessions in 15 normal patients and found CV for mean RNFLT of 5% in normal subjects. Measurements in nasal quadrant were more variable with a CV of 20%.

Paunescu *et al*[6] scanned RNFLT in 10 normal subjects six times per day on three different days over a 5 month period using Stratus OCT before and after dilation and found that for most of the RNFL parameters, reproducibility was better with dilated standard density scanning.

Budenz *et al*[7] used Stratus OCT to measure intrasession variability of RNFLT in 88 normal and 59 subjects with glaucoma. In normal eyes, ICCs ranged from 0.84 to 0.97 and CVs from 1.7% for mean RNFLT to 8.2% in nasal quadrant. In glaucomatous eyes the ICC ranged from 0.79 to 0.98 and CVs from 3.7% for mean RNFLT to 11.9% in nasal quadrant.

In another study by the same author[8] in 59 subjects with glaucoma, RNFLT measurements were made three times in a day and on five different days within a 2 month period. ICC, CV and TRV were virtually identical to those in a previous study[7] despite measurements being taken by different operators on different group of subjects. The measurements are more reproducible when scans are obtained within the same session rather than on separate visits, similar to our results.

Gurses-Ozden *et al*[15] with second generation OCT reported that increasing the sampling density or number of A-scans can increase reproducibility of RNFL measurements. Our study showed higher ICCs and lower CVs, which might indicate an improvement in the reproducibility of RNFLT measurements. confirming this hypothesis, as spectral domain OCT acquires a greater number of A-scans than previous generation OCT. However, ICCs between studies cannot be compared since measurements were performed in different groups of subjects with different OCT models. Gonzalez-Garcia *et al*[16] obtained RNFLT measurements in 60 healthy and 76 glaucomatous eyes (61 eyes with early glaucoma and 15 eyes with moderate glaucoma) without pupil dilation and showed an average ICC of 0.97 with RTVue (Fourier domain OCT) (Optovue Inc, Fremont, California, USA). Bland–Altman plots showed good agreement

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between RTVue and Stratus OCT for average RNFLT measurements.

Using RTVue-100 OCT, Garas *et al*[17] measured RNFLT in 14 normal and ocular hypertension eyes, 11 eyes with moderate glaucoma and 12 eyes with severe glaucoma, five times per day, and the measurement series were performed again 3 months later. Intrasession CV of peripapillary RNFLT sectors varied between 4.9% and 11.66%. Patients' age and experience in imaging examinations did not influence reproducibility in clinically significant manner.

There was significant trend for increasingly higher CV with increasing glaucoma severity. However, the disease severity had no influence on the average and quadrant RNFLT values that were used for comparison with the normative database for statistical classification.

As advanced glaucomatous damage may result in decrease in measurement reproducibility, study design, which has potential to influence results, should be considered when comparing studies. In our study 20 patients had advanced glaucoma and although we did not compare variability between grades of glaucoma severity, the reproducibility for RNFLT in glaucoma group was found to be good for most of the parameters.

Most of the previous studies have measured RNFLT after pupil dilation.[2–5 7 8 15 17] For Stratus OCT pupil dilation has shown to improve image quality and reproducibility.[6] RNFLT measured with Stratus OCT showed better reproducibility in healthy eyes than in glaucomatous eyes.[7] A study with RTVue[16] found good reproducibility of RNFLT measurements that were obtained without pupil dilation in healthy and glaucoma patients.

Another study on spectral domain OCT[17] found no clinically significant change in RNFLT after dilation except for average and sector 9. In our study, all images were acquired after dilation for better image quality as recommended by the manufacturer.[7]

Our study demonstrated good reproducibility of RNFLT measurement in both normal and glaucomatous eyes on same visit and different visits. In addition, intrasession CV values for RNFLT in normal and glaucoma subjects was found to be better than the values reported in studies on Stratus OCT[7 8] and are similar to those reported by using RTVue.[16 17]

Our study showed less variability for superior and inferior quadrants than for nasal and temporal quadrants. Jones *et al*[5] hypothesised that using a circular scan in the presence of elliptical ONH, the nasal and temporal areas would be farther from disc margin than vertical meridian, resulting in lower RNFLT measurement in nasal and temporal quadrants.

The effect of IOP reduction on RNFLT measurement variability is unclear.[18 19] In our study, only patients whose IOP were controlled and stable were included and hence IOP fluctuation is unlikely to play a role in RNFL measurement variability between visits.

A limitation of this study is that the healthy participants were of younger age than glaucoma patients. However, the age range of healthy participants was wide (table 1). The current OCT system does not offer ONH tracking during the acquisition of the RNFLT scan. Variability in scan position over time may be a possible component in affecting intervisit reproducibility.

Gabriele *et al*[20] reported that any shift in the location of the scan circle that brings a sector closer to the disc margin causes a increase in thickness in that region and a decrease in the opposite region. Although we had taken care to include images without obvious motion artefacts, there could be small eye movements within the scan which were undetected.

In conclusion, the present study demonstrates that reproducible measurements of peripapillary RNFLT can be obtained with Spectral OCT/SLO by the same operator on same day and on different days in normal and glaucomatous eyes. This is important as RNFLT measurements for the same patient may be compared with each other to assess progression of RNFL thinning in longitudinal study.

However, it is also important to remember that improved reproducibility does not always lead to improved accuracy. Further studies evaluating reproducibility of RNFLT measurements on same and different days by different operators can provide useful information on operator induced variability component.

Competing interests None to declare.

Patient consent Obtained.

Ethics approval This study was conducted with the approval of the Pushpagiri Eye Institute. The study protocol conformed the Declaration of Helsinki.

Provenance and peer review Not commissioned; externally peer reviewed.

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