

Reproducibility of peripapillary retinal nerve fiber layer thickness measurements with Cirrus HD-OCT in glaucomatous eyes

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Abstract

• **AIM:** To assess the reproducibility of Cirrus high-definition optical coherence tomography (HD-OCT; Carl Zeiss Meditec, Dublin, CA, USA) for analysis of peripapillary retinal nerve fiber layer (RNFL) thickness in glaucomatous eyes

• **METHODS:** Forty -five eyes (one eye from each glaucomatous patient) were imaged with Cirrus HD-OCT. Each eye was imaged three times by two separate operators. Intraclass correlation coefficient (ICC), coefficient of variation (CV), and test-retest variability were evaluated for both intraobserver and interobserver measurements

• **RESULTS:** In intraobserver measurements, the average RNFL thickness ICC was 0.983. CV and test-retest variability were 2.3% and 4.4 μm respectively. In quadrants ICC ranged from 0.886 to 0.956, the lowest associated with nasal quadrant and CV ranged from 3.6% to 7.7%. In interobserver measurements, the average RNFL thickness ICC was 0.979. CV and test-retest variability were 2.4% and 4.5 μm respectively. In quadrants ICC ranged from 0.886 to 0.957, the lowest associated with nasal quadrant and CV ranged from 3.8% to 8.6%.

• **CONCLUSION:** The reproducibility of Cirrus OCT for RNFL thickness is sufficiently good to be useful clinically as a measure of glaucoma progression.

• **KEYWORDS:** optical coherence tomography; reproducibility; glaucoma; retinal nerve fiber layer

INTRODUCTION

Quantitative assessment of retinal nerve fiber layer is considered to be a valuable method for early detection of glaucoma and its progression. Introduced in 1991, optical coherence tomography (OCT) is a high-resolution imaging technique that allows measurements of the retinal nerve fiber layer (RNFL) thickness^[1]. The Cirrus HD-OCT (Carl Zeiss Meditec, Inc.) is a spectral-domain OCT device which in contrast to time-domain Stratus OCT (Carl Zeiss Meditec, Dublin, CA, USA) has faster scan speed and higher axial resolution^[2-4]. The built-in algorithm of Cirrus HD-OCT identifies the optic disc center and places the calculation circle automatically around the disc center^[5]. It is postulated that the fast scan speed and this algorithm for automated placement of the scan circle can reduce RNFL measurement variability secondary to movement artifact and scan displacement.

Reproducibility is always one of the most important considerations, regardless of the imaging instrument used. Reproducibility data are specially important in the monitoring of a glaucoma patient undergoing progressive RNFL thinning^[3,6]. Detectable RNFL thinning requires a change greater than that expected for measurement reproducibility.

The purpose of this study was to evaluate the reproducibility of the peripapillary RNFL thickness measurements obtained by Cirrus HD-OCT in glaucomatous eyes.

SUBJECTS AND METHODS

In this prospective study 45 glaucoma patients referred to Amiralmomenin Eye and Ear Hospital, Guilan University of Medical Sciences, were enrolled from December 2011 to September 2012. The study was performed in accordance with the Declaration of Helsinki, and all patients provided informed consent.

Reproducibility of RNFL thickness measurements

A complete ophthalmologic examination was performed for each study participant. The examination included assessment of visual acuity (VA), slit-lamp examination, intraocular pressure (IOP) measurement with Goldman tonometer (Haag Streit, AT 900), visual field (VF) examination with the Humphrey Visual Field Analyzer (Carl Zeiss Meditec), and dilated fundus examination.

Subjects included those with diagnoses of any form of chronic glaucoma, defined as optic disc abnormalities consistent with glaucomatous optic neuropathy with corresponding VF loss. The VF was considered abnormal if 3 or more non-edge contiguous test locations in the pattern deviation plot were depressed significantly at the $P < 0.05$ level with at least 1 at the $P < 0.01$ level on the same side of the horizontal meridian, or was classified as outside normal limits by the glaucoma hemifield test [7]. The other inclusion criteria were 1) 18y or older; 2) best-corrected VA of 20/40 or better; 3) lower than 5 diopters (D) of spherical and 3 D of cylindrical refractive error; 4) pupil diameter of ≥ 2 mm. Patients with any anterior segment dysgenesis, corneal scarring or opacities, severe lens opacity, proliferative or nonproliferative diabetic retinopathy or any history of ocular or neurologic disease or surgery that might produce test results or vision changes that confound recognition of a test result due solely to glaucoma were excluded from study. If both eyes of a participant fitted the criteria only one eye from each subject was selected randomly.

All eyes were imaged with Cirrus HD-OCT (Carl Zeiss Meditec, Inc, software version 4.0) for RNFL thickness measurements. The Cirrus HD-OCT is a spectral-domain OCT device with the acquisition rate of 27 000 A-scans per second. Optic disc cube 200×200 was the scan acquisition protocol used. The optic disc cube is a glaucoma scan protocol that images the optic disc and the parapapillary retinal region covering an area of 6×6-mm² (200×200 data points). The RNFL thickness at each scan point is analyzed and an RNFL map is constructed. The built-in algorithm identifies the optic disc center, and a circle of diameter 3.46 mm is positioned automatically evenly around the disc center to generate average and clock-hour parapapillary RNFL measurements. For each eye, imaging was performed by two separate experienced operators in one day. Each eye was imaged 3 times by each operator (with 15min interval for intraobserver measurements). The operators did the procedure in a random order to prevent any effect of fatigue bias (with 30min interval between interobserver measurements). Images with movement artifact or signal strength of less than 7 were repeated once, if the second scan was also unusable, that eye was excluded from the analysis. The average, quadrant, and clock-hour parapapillary RNFL thickness were recorded.

Table 1 ICC, CV and test-retest variability for intraobserver measurements

Parameters	ICC (95%CI)	CV (%)	Test-retest variability (μm)
Average	0.984 (0.977-0.989)	2.3	4.4
S	0.936 (0.910-0.954)	5.4	7.3
T	0.955 (0.935-0.975)	3.6	5.7
I	0.956 (0.938-0.968)	4.8	6.6
N	0.883 (0.795-0.945)	7.7	9.2
H1	0.896 (0.854-0.926)	5.2	7.1
H2	0.938 (0.912-0.956)	4.6	6.4
H3	0.795 (0.791-0.841)	12.8	14.8
H4	0.902 (0.862-0.930)	6.2	8.7
H5	0.968 (0.956-0.977)	4.9	6.6
H6	0.951 (0.931-0.965)	4.8	6.4
H7	0.930 (0.902-0.950)	6.6	9.1
H8	0.873 (0.822-0.910)	9.2	12.1
H9	0.854 (0.795-0.896)	8.3	10.9
H10	0.831 (0.823-0.909)	9.6	12.7
H11	0.934 (0.907-0.953)	8.1	10.6
H12	0.963 (0.948-0.974)	4.9	6.6

ICC: Intraclass correlation coefficient; CV: Coefficient of variation.

Data analysis was performed with SPSS version 18 (Chicago, Illinois, USA). To determine the reproducibility of peripapillary RNFL thickness measurements, the intraclass correlation coefficient (ICC) and 95% confidence interval (CI), the coefficient of variation (CV), and test-retest variability were computed for both intraobserver and interobserver measurements. Bland-Altman plots were also used to evaluate the agreement between RNFL thickness measurements^[8].

RESULTS

After exclusion of 7 eyes (2 for severe lens opacity and 5 because of low signal strength), a total of 45 subjects were studied. There were 18 females and 27 males with a mean age of 65.17y (SD, 7.33; range 47-80). The mean deviation of VF was -9.64 ± 2.24 .

Table 1 shows the ICCs, CVs, and test-retest variability for intraobserver measurements. For average RNFL thickness measurements, ICC was 0.984, CV was 2.3%, and test-retest variability was 4.4 μm . For quadrants, ICC ranged from 0.883 (nasal) to 0.956 (inferior) and CV ranged from 3.6% (temporal) to 7.7% (nasal) and test-retest variability were between 5.7 to 9.2 μm .

ICCs, CVs, and test-retest variability for interobserver measurements are shown in Table 2. The average thickness ICC was 0.979. CV and test-retest variability were 2.4% and 4.5 μm respectively. For quadrants, ICC ranged from 0.886 (nasal) to 0.957 (temporal) and CV ranged from 3.8% (temporal) to 8.6% (nasal) and test-retest variability were between 5.1 to 11.2 μm .

Table 2 ICC, CV and test-retest variability for interobserver measurements

Parameters	ICC (95%CI)	CV (%)	Test-retest variability (μm)
Average	0.979 (0.971-0.988)	2.4	4.5
S	0.935 (0.913-0.962)	5.3	7.2
T	0.957 (0.938-0.977)	3.8	5.1
I	0.952 (0.937-0.966)	5.4	7.5
N	0.886 (0.806-0.954)	8.6	11.2
H1	0.894 (0.844-0.928)	6.6	8.8
H2	0.929 (0.908-0.947)	5.4	7.3
H3	0.781 (0.765-0.824)	13.2	16.6
H4	0.905 (0.887-0.932)	7.9	10.4
H5	0.944 (0.929-0.961)	7.3	9.8
H6	0.948 (0.933-0.959)	4.8	6.6
H7	0.921 (0.898-0.942)	8.4	10.9
H8	0.865 (0.831-0.897)	11.2	13.8
H9	0.834 (0.790-0.877)	8.1	10.6
H10	0.811 (0.784-0.838)	11.8	14.2
H11	0.933 (0.904-0.959)	9.1	11.7
H12	0.958 (0.941-0.972)	7.4	9.9

ICC: Intraclass correlation coefficient; CV: Coefficient of variation.

Figures 1 and 2 show the Bland-Altman plots of the agreement between the average RNFL thickness for intraobserver and interobserver measurements, respectively. Figure 3 shows the OCT images of a glaucomatous eye with time interval of 15min.

DISCUSSION

Reproducibility of a diagnostic test is important not only for diagnostic accuracy of the test but also for monitoring of changes in disease status. Reproducibility has a particular importance in evaluation of progressive RNFL thinning occurring in glaucoma and monitoring glaucoma progression^[3,6,9].

Many studies have evaluated the reproducibility of RNFL thickness measurements with time-domain OCT in normal and glaucomatous eyes^[10-13]. Although many studies evaluating the reproducibility of time-domain OCT measurements have found it to have more variability in glaucomatous eyes, Budenz *et al*^[12] concluded that it has acceptable reproducibility. They performed RNFL measurements using Stratus OCT in glaucomatous eyes. The mean RNFL thickness intersession ICC for the Standard and Fast scans was both 0.96. For mean RNFL thickness CV was 5.2% and 5.1% for the Standard and Fast scans respectively and test-retest variability was between 6.6 and 6.7 μm . For quadrants, the ICC was 0.9 or higher and the CV was under 10% except nasally. Test-retest variability for quadrant measurements ranged from 6 to 16 μm . For clock hours, test-retest variability approached 20 μm between sessions in some sectors. In general, the ICC was lower in the nasal region than elsewhere. Our results shows even less variability

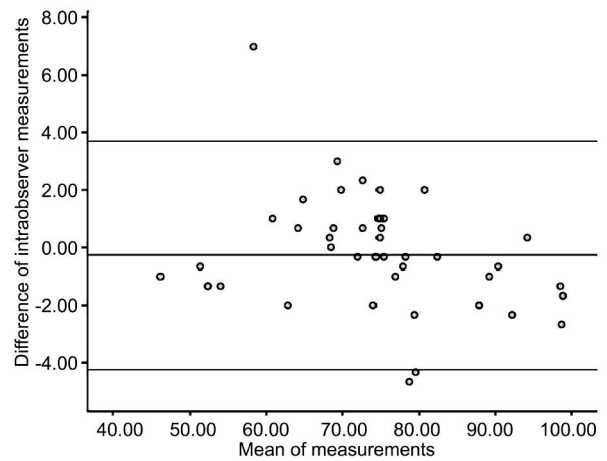


Figure 1 Bland-Altman plot showing the difference between the average RNFL thicknesses for intraobserver measurements
 The 95% agreement limit is - 4.25 μm to 3.70 μm . The dash lines enclose difference from -1.96 SD to +1.96 SD.

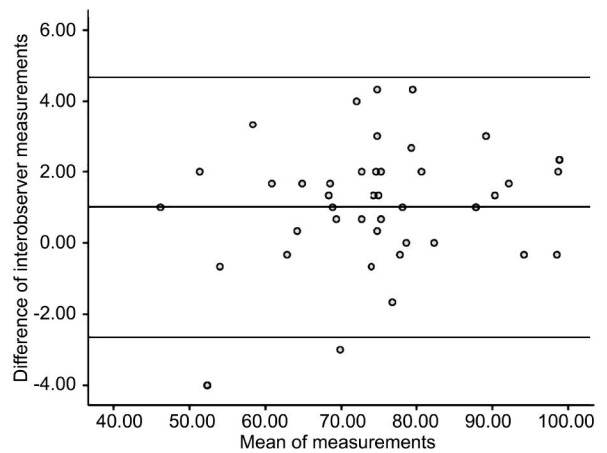


Figure 2 Bland-Altman plot showing the difference between the average RNFL thicknesses for interobserver measurements
 The 95% agreement limit was -2.65 to 4.68 μm . The dash lines enclose difference from -1.96 SD to +1.96 SD.

as test-retest variability ranged between 5.7 to 9.2 μm in quadrants and CV between 3.6% to 7.7% (intraobserver measurements).

Leung *et al*^[3] evaluated RNFL measurement variability of normal and glaucomatous eyes as measured by Stratus time-domain OCT and Cirrus HD spectral- domain OCT and compared the results. Cirrus HD-OCT demonstrated lower measurement variability compared with Stratus OCT in this study. For Cirrus HD-OCT the mean RNFL thickness CV was 1.89% and ICC was 0.975 (intravisit measurements) which is nearly the same as our findings. ICC was more than 0.9 in all quadrants (the same as our results except nasally) and CV ranged from 2.54% (inferior) to 3.64% (nasal) for intravisit measurements. It is postulated that the built-in algorithm with its ability to place the calculation circle automatically around the disc center and the faster scan speed of spectral-domain OCTs leads to lower measurement variability as compared with time-domain OCTs.

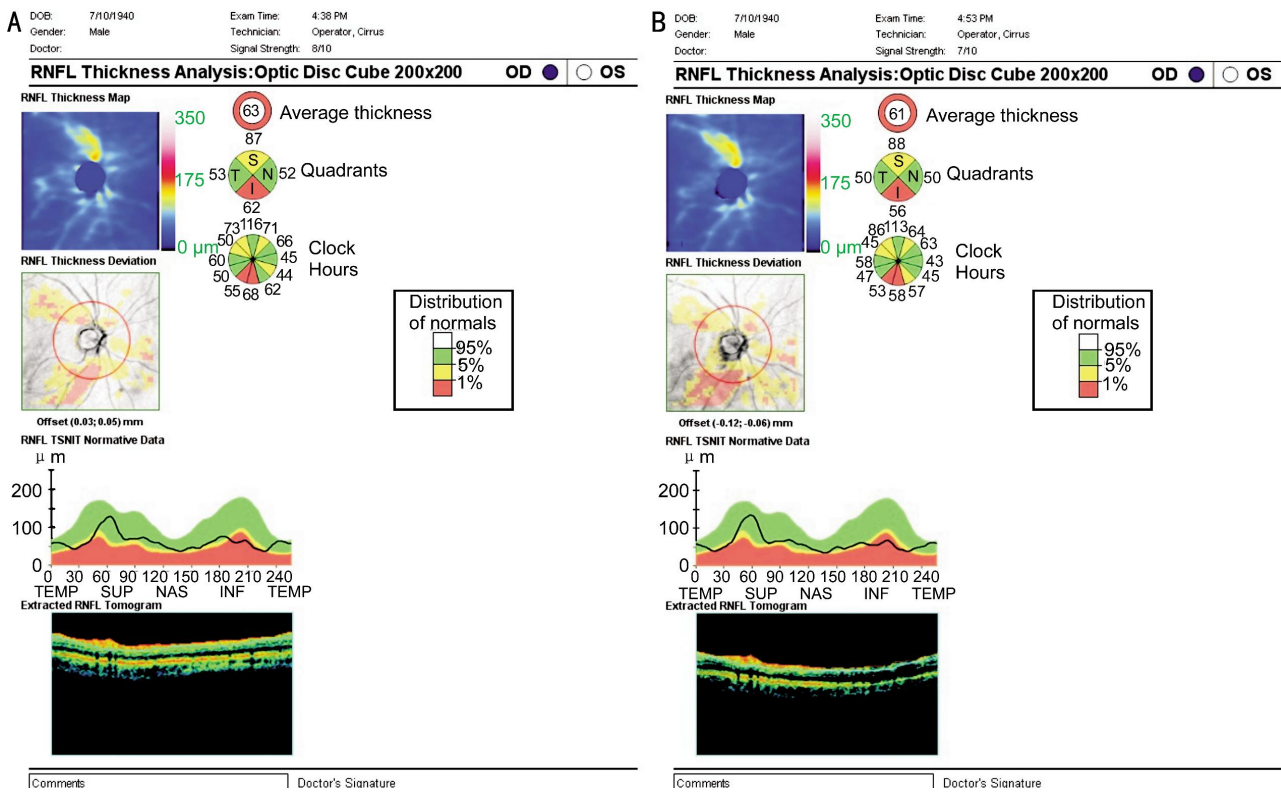


Figure 3 Cirrus OCT images A: OCT image of a glaucomatous eye; B: OCT image of the same eye captured 15min later by the same operator.

Mwanza *et al*^[14] assessed the reproducibility of peripapillary retinal nerve fiber layer thickness and optic nerve head parameters measured with cirrus HD-OCT in glaucomatous eyes. All ICCs were excellent, ranging from 83.9% to 99.2% for intravisit measurements and from 80.8% to 99.1% for intervisit measurements. Nasal clock hours and quadrants showed the poorest reproducibility. There were some differences between this study and ours: all scans were acquired by the same operator in their study so they did not evaluate the interobserver measurements. They assessed the reproducibility of optic nerve head parameters but we did not.

Toscano *et al*^[15] evaluated the reproducibility of peripapillary retinal nerve fiber layer thickness measurements using Spectralis spectral domain OCT in normal and glaucomatous eyes. The mean ICC was 0.937 and in quadrants, the ICC ranged between 0.827 to 0.964. CV was 4.65% for mean RNFL thickness and ranged between 8.44 (temporal) to 11.44 (nasal) in quadrants. Test-retest variability for quadrant measurements ranged from 9.95 to 14.24 μm and it was 6.61 μm for mean RNFL thickness. Their results showed a little more variability than ours. Wu *et al*^[16] also evaluated the reproducibility of Spectralis in normal and glaucomatous eyes. Their ICCs ranged from 0.983 (temporal) to 0.997 (inferior quadrant) in glaucomatous eyes. CVs ranged from 1.74% (mean RNFL thickness) to 3.22% (temporal quadrant)

for glaucoma patients. Their results showed even less variability than ours but the number of glaucomatous participants was smaller than our study.

Although nasal quadrant showed more measurement variability in our study and some previous studies^[10,12] this merits little clinical significance as nasal RNFL thickness has less performance for both glaucoma detection and glaucoma progression than other quadrants^[17-19].

In conclusion, this study demonstrated that the reproducibility of Cirrus HD-OCT for RNFL thickness is sufficiently good to be useful clinically as a measure of glaucoma progression.

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