Repeatability of Choroidal Thickness Measurements in Healthy Subjects using RTVue XR Optical Coherence Tomography

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Abstract

Purpose: To determine the intrasession, intraobserver, interobserver, and repeatability of choroidal thickness measurements in the healthy subjects imaged on enhanced depth imaging system of RTVue XR spectral domain optical coherence tomography (OCT).

Methods: In this prospective, cross-sectional study, seventy eyes of 70 healthy volunteers with no known ocular disease were imaged using high-density scanning protocol of RTVue XR OCT. In a single imaging session, three sequential 12 mm macular-enhanced depth horizontal line scans were obtained through the fovea. Two experienced examiners measured the subfoveal choroidal thickness (SFCT), choroidal thickness at 500 μm nasally and temporally from the fovea in all the eyes, using the manual calipers provided in the software. The graders were masked to each other's measurement readings. The coefficient of repeatability (CR) and intraclass correlation coefficient (ICC) were used to measure the reliability within graders. Intergrader variability was assessed using Bland-Altman method and 95% limits of agreement (LoA).

Results: Intragrader CR for grader one was 4.11 μm (95% confidence interval [CI], −2.84–11.06) for SFCT and 5.73 μm (95% CI, −3.71–15.16) for the grader two. Intragrader ICC of grader one ranged from 0.996 for SFCT to 0.994 for temporal choroidal thickness. Intragrader ICC of grader two ranged from 0.993 for temporal choroidal thickness to 0.991 for SFCT. Intergrader CR ranged from 5.24 μm (95% CI, −4.66–15.15) for SFCT to 5.89 μm (95% CI, −7.27–19.04) for temporal choroidal thickness. Intergrader 95% LoA for SFCT, nasal and temporal choroidal thickness were, −15.84–12.15 μm, −15.99–17.7 μm, and − 19.12–15.57 μm, respectively.

Conclusion: Choroidal thickness measurements can be quantified with good repeatability using RTVue XR OCT, which would be useful in patients with chorioretinal diseases.

Keywords: Choroidal thickness measurements, Repeatability, RTVue XR optical coherence tomography

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INTRODUCTION

Spectral domain optical coherence tomography (SD-OCT) has become a valuable tool for *in vivo* choroidal imaging and is useful in understanding the pathophysiology of chorioretinal diseases.[1] It gives high resolution, cross-sectional images of the choroid, and allows enhanced visualization of the pathology. It also provides reliable, quantitative measurement of choroidal thickness at various locations within the macular region.

Knowledge of the repeatability of OCT-derived choroidal thickness measurements is crucial, as it is used in both clinical practice and research domains to identify chorioretinal disease progression or improvement and also as an outcome measures in the clinical trials. It is imperative to understand the repeatability of OCT-derived choroidal thickness measurements in healthy subjects to distinguish true clinical change from measurement error or variability. Choroidal thickness repeatability has

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been reported in normal subjects using different SD-OCT or enhanced depth OCT.[2-9] To our knowledge, repeatability of choroidal thickness measurements using enhanced depth imaging (EDI) protocol of high-density (HD) RTVue XR SD-OCT in healthy subjects has not been studied in detail. To differentiate true clinical change from measurement variability with a given device, it is important to validate the repeatability of measurements so that it will help clinicians to interpret the results.

The aim of this study was to investigate the repeatability measurements of subfoveal choroidal thickness (SFCT), choroidal thickness at 500 μm nasally and temporally in the horizontal line scans, within and between observers in the healthy Asian Indian subjects using EDI protocol of HD RTVue XR OCT.

METHODS

In this prospective study, choroidal imaging in healthy, adult volunteers with no known ocular disease was carried out using OCT. The study was approved by the internal institutional review board and was conducted in adherence with the tenets of the Declaration of Helsinki.

Seventy healthy participants gave informed consent to participate in the study, which was conducted in January 2022. Exclusion criteria included significant media opacity precluding an adequate fundus view, prior ocular surgery (refractive, anterior, or posterior segment), and any ocular disease.

After informed consent, the best-corrected visual acuity, medical, ocular history, and complete ophthalmic evaluation were carried out for each subject. All the participants underwent three consecutive HD angio retina scans in a single imaging session, between 2 pm and 4 pm, after pupillary dilatation with 2.5% phenylephrine hydrochloride and 1% tropicamide eye drops, which were performed by a retina fellow in training. In each session, three single line-enhanced HD scan was performed consecutively, centered at the fovea, using a the AngioVue HD software (version: A2018,0,0,18) of the Avanti RTVue XR SD-OCT device (OptoVue, Inc., Fremont, California). The subject was allowed to sit back in between the scans sets for a minute.

The optical coherence tomography angiography imaging utilizes proprietary split-spectrum amplitude-decorrelation angiography algorithm to minimize the scan acquisition time and reduce the signal-to-noise ratio of the obtained blood flow information.[10] Motion correction technology reduces motion artifacts. We obtained 6 mm × 6 mm HD Angio Retina scans, centered on the fovea, obtained with a rate of 70,000 A-scans per second. Each volume contains 304 × 304 A-scans with 2 consecutive B-scans captured at each fixed position, before proceeding to the next sampling location. The current software uses eye tracking technology, for controlling the motion artifacts and HD scanning mode, to improve the resolution of the scans.

Two experienced graders performed manual SFCT thickness, nasal and temporal choroidal thickness measurements at 500 μm from the center of fovea. Measurements were made using calipers, provided within the proprietary software by measuring the distance between the hyper-reflective outer surface of the retinal pigment epithelium (RPE)/Bruch's membrane complex to the outer hyporeflective choroidal surface, which marks the chorioscleral interface. Both the graders were masked to each other's measurement readings. All images were checked for sufficient image quality and segmentation. Any scan showing motion or projection artifacts and/or segmentation errors and signal strength <60 were discarded and repeated.

Statistical analysis was performed using the SPSS software version 17 (IBM Corp., Chicago, IL, USA). The Shapiro−Wilk test was used to assess the normality of distribution. Descriptive statistics included mean and standard deviation (SD) for normally distributed variables and median and interquartile range (IQR: first quartile, third quartile) for nonnormally distributed variables.

The coefficient of repeatability (CR) was used as a measure of repeatability within the graders. The repeatability coefficient is a precision measure which represents the value below which the absolute difference between two repeated test results may be expected to lie with a probability of 95%. In addition, the 95% confidence intervals (CIs) for the estimated CR were also calculated. The intraobserver repeatability was determined by calculating the CR of the SFCT, nasal and temporal choroidal thickness measurements for the three repeated images on all the 70 eyes. Agreement between the intraobserver measurements was assessed using intraclass correlation coefficient (ICC). Reproducibility or interobserver variability was assessed using Bland-Altman plots, and 95% limits of agreement (LoA) were calculated.

RESULTS

Seventy eyes of 70 healthy subjects were included in the analysis. Median age of the patients was 37 (IQR: 27, 44.5) years. There were 20 males and 50 females. Overall median signal strength for all the scans was 65.67 (IQR: 62.75, 69.83). Demographics and clinical characteristics of the study participants are summarized in Table 1.

For the grader 1 and grader 2, median (IQR) of SFCT, choroidal thickness measurements at nasal and temporal 500 μm from the fovea are shown in Table 2.

The intragrader CR of the SFCT measurements was 4.11 (95% CI: −2.84–11.06 μm) for grader 1 and 5.73 (−3.71–15.16 μm) for grader 2. CR of the nasal choroidal thickness measurements at 500 μm from fovea was 4.44 (95% CI: −3.16–12.05 μm) for grader 1 and 6.36 (95% CI: −5.05–17.76 μm) for grader 2. CR of the temporal choroidal thickness measurements at 500 μm from fovea was 4.21 (95% CI: −1.93–10.36 μm) for grader 1 and 5.67 (95% CI: −3.07–14.42 μm) for grader 2.

Table 1: Demographic and clinical characteristics of the study participants

Parameters measured	Values
Total cohort (*n*=70)	
Age (years)	37 (27-44.5)
Gender (male/female)	20/50
Intraocular pressure (mmHg)	12 (12-14)
Systolic blood pressure (mmHg)	110 (110-120)
Diastolic blood pressure (mmHg)	70 (70-80)
Spherical equivalent (diopters)*	0.11±1.24
Axial length (mm)*	22.74±0.76
Signal strength	
Scan 1	67 (64-72)
Scan 2	65 (63-70)
Scan 3	65 (62-69)
Overall SFCT (μm)	
Grader 1	249 (226.83-268)
Grader 2	254.33 (234.17-267.92)
Overall nasal choroidal thickness at 0.5 mm from fovea (μm)	
Grader 1	245.67 (224.25-262.33)
Grader 2	242.33 (221.42-262)
Overall temporal choroidal thickness at 0.5 mm from fovea (μm)	
Grader 1	245.67 (226.75-264)
Grader 2	248.5 (229.67-263.75)

*Values are mean±Standard deviation. All values are median with interquartile range in parentheses (first quartile, third quartile) unless otherwise specified. SFCT: Subfoveal choroidal thickness

Intragrader ICC of grader 1 for SFCT, nasal, and temporal choroidal thickness was 0.996 (0.993–0.997), 0.995 (95% CI: 0.993–0.997), and 0.994 (95% CI: 0.991–0.996), respectively. Intragrader ICC of grader 2 was to 0.991 (95% CI: 0.987–0.994) for SFCT and nasal choroidal thickness and 0.993 (95% CI: 0.990–0.996) for temporal choroidal thickness.

Intragrader 95% LoA for SFCT, nasal and temporal choroidal thickness for grader 1 were −10.82–10.36 μm, −11.03–11.92 μm, and −10.05–10.48 μm, respectively. Intragrader 95% LoA for SFCT, nasal and temporal choroidal thickness for grader 2 were −15.89–12.6 μm, −15.95–17.52 μm, and −14.17–14.03 μm, respectively.

The intergrader CR of SFCT was 5.24 μm (95% CI: −4.66–15.15 μm), CR of the nasal choroidal thickness measurements at 500 μm from fovea was 5.64 (95% CI: −6.92–18.2 μm), and CR of the temporal choroidal thickness measurements at 500 μm from fovea was 5.89 (95% CI: −7.27–19.04 μm). The intergrader CR is shown in Table 3.

The mean ± SD difference between the two observers was 1.84 ± 7 μm, 0.86 ± 8.42, and 1.77 ± 8.67 for SFCT, nasal, and temporal choroidal thickness, respectively. Intergrader 95% LoA for SFCT, nasal, and temporal choroidal thickness was −15.84–12.15 μm, −15.99–17.7 μm, and −19.12–15.57 μm, respectively.

Table 2: Summary of intrasession intragrader repeatability of choroidal thickness measurements in three successive scans

	Choroidal thickness (μm)			Mean difference ±SD (μm) (95% limits of agreement)	ICC (95% CI)	Intrasession coefficient of repeatability (95% CI) (μm)
	Scan 1*	Scan 2*	Scan 3*			
Grader 1 (μm)						
SFCT	250.00 (229.25-267.50)	250.00 (226.75-266.75)	249.50 (229.00-266.00)	−0.23±5.4 (−10.82-10.36)	0.996 (0.993-0.997)	4.11±3.47 (−2.84-11.06)
Nasal choroidal thickness at 0.5 mm from fovea	247.00 (225.25-260.00)	242.00 (222.25-262.25)	244.00 (224.25-263.00)	0.44±5.85 (−11.03-11.92)	0.995 (0.993-0.997)	4.44±3.8 (−3.16-12.05)
Temporal choroidal thickness at 0.5 mm from fovea	247.00 (227.00-264.00)	245.00 (226.00-263.00)	245.00 (226.00-263.00)	0.21±5.24 (−10.05-10.48)	0.994 (0.991-0.996)	4.21±3.07 (−1.93-10.36)
Grader 2 (μm)						
SFCT	252.00 (234.50-266.00)	254.00 (231.00-266.75)	253.00 (234.00-267.00)	−1.64±7.27 (−15.89-12.6)	0.991 (0.987-0.994)	5.73±4.72 (−3.71-15.16)
Nasal choroidal thickness at 0.5 mm from fovea	244.00 (223.00-258.75)	242.00 (220.75-262.00)	242.00 (222.00-263.75)	0.79±8.54 (−15.95-17.52)	0.991 (0.987-0.994)	6.36±5.7 (−5.05-17.76)
Temporal choroidal thickness at 0.5 mm from fovea	248.00 (232.25-263.00)	247.50 (227.00-264.00)	248.00 (229.00-263.00)	−0.07±7.19 (−14.17-14.03)	0.993 (0.990-0.996)	5.67±4.37 (−3.07-14.42)

*Values are median with interquartile range in parentheses (first quartile, third quartile). SD: Standard deviation, CI: Confidence interval, ICC: Intraclass correlation coefficient, SFCT: Subfoveal choroidal thickness

Table 3: Summary of intergrader repeatability of choroidal thickness measurements

	Mean difference±SD	95% limits of agreement	Coefficient of repeatability (95% CI) (µm)
SFCT (µm)	−1.84±7	−15.84-12.15	5.24±4.95 (−4.66-15.15)
Nasal choroidal thickness at 0.5 mm from fovea (µm)	0.86±8.42	−15.99-17.7	5.64±6.28 (−6.92-18.2)
Temporal choroidal thickness at 0.5 mm from fovea (µm)	−1.77±8.67	−19.12-15.57	5.89±6.58 (−7.27-19.04)

SD: Standard deviation, CI: Confidence interval, SFCT: Subfoveal choroidal thickness

Bland-Altman plot shows the difference between mean SFCT [Figure 1a], nasal at 500 µm from fovea [Figure 1b], and temporal at 500 µm from fovea [Figure 1c] choroidal thickness measurements between the two graders.

DISCUSSION

We are not aware of any studies that have reported on the repeatability measurements of SFCT using EDI RTVue Avanti XR OCT in the healthy subjects. Previous study on comparison of different SD-OCT platforms suggests that there is the potential for differences in the repeatability of OCT-derived choroidal thickness measurements.[9] A software algorithm for choroidal segmentation does not yet exist for RTVue XR OCT, so the choroidal thickness measurements were taken manually, which is a tedious process and can account for measurement variability. Our study suggests that RTVue XR SD-OCT-derived choroidal thickness measurements show good intrasession, intraobserver, and interobserver repeatability.

Variability in the choroidal measurements could be related to the image quality, and if the scans are taken at different point locations, the exact topographic location of the second line scan relative to the first line scan can also affect the measurement made by the grader. One may anticipate less variability in measurements if the same grader measures the same scan twice, even if masked to the previous results. Hence, in our study, we included only good quality image scans (signal strength >60) and measured the choroidal thickness variability among two experienced graders in the same session and also the variability between the observers at SFCT and 2 points at nasal and temporal 500 µm from the fovea.

Studies evaluating the repeatability and reproducibility of choroidal measurements with different OCT in healthy subjects have used different image acquisition protocols and manual segmentation techniques, which may explain notable disparities between choroidal thickness measurements.[2-9] Our study showed that the overall median SFCT in healthy subjects was 249 µm (grader 1) and 254 µm (grader 2). Branchini *et al.*[9] imaged 28 eyes, using RTVue retina cross

scan with chorioretinal imaging mode by adjusting the zero delay position, relative to the patient's eye. They reported a mean (SD) of 337.46 (89.01) µm in healthy subjects. The mean age of their study participants was 35.2 years compared with a median age of 37 years in our study. The previous study[9] had used retina cross scan for imaging, which uses 16 B-scans averaging in nasal temporal orientation, which was used to analyze the data. Hence, a direct comparison between the studies cannot be made as the current EDI OCT imaging software of RTVue XR OCT uses averaged 72 B-scan images. The line scan averaging technology and variation in segmentation software, different ethnicity, and OCT software used may account for the difference in the SFCT measurements between the two studies.

Branchini *et al.*[9] measured interobserver repeatability of SFCT, nasal and temporal choroidal thickness measurements at 0.75 µm from fovea as a part of their study, and the results showed that the Pearson correlations were 0.93, 0.95, and 0.94, respectively (all $P < 0.0001$). They compared the measurements with Cirrus (Carl Zeiss Meditec, Inc., Dublin, CA) and Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany) and found that there was a trend towards RTVue system measurements being smaller by 10 µm than the other systems.

We found excellent intrasession reproducibility in choroidal thickness measurements for the 3 studied choroidal points. The mean difference between intergrader measurements was approximately 1.84 µm for SFCT and 0.86 µm for nasal and 1.77 µm for temporal choroidal thickness. The low variability was thought to be due to the eye-tracking features during scanning, use of HD scanning protocol, improved resolution and imaging speed of the current software, and inclusion of good image quality scans.

Increased variability in the measurement could be also predicted if different observers measured the same scan. In our study, we found the intrasession, intergrader CR of SFCT measurements as 5.24 µm. This suggests that in healthy eyes, a change of > 5.24 µm in SFCT is possibly a cut-off to distinguish true clinical change from measurement variability. Clinicians need to be aware of the degree of measurement variation of their preferred OCT device when managing patients with choroidal diseases, in order to facilitate the management protocol and follow-up decision. We found a intragrader CR of 4.11 µm for grader 1 and 5.73 µm for grader 2 compared with 5.24 µm for intergrader variability. These contributions to both the intragrader and intergrader measurement variability may be further minimized if there is reliable segmentation software to detect choroidal boundaries as some choroidal scans have a distinct hyporeflective chorioscleral interface line. However, sometimes, the line can be indistinct, and manual demarcation of the interface can lead to the measurement variability.

We report a good intrasession, intergrader, and intragrader measurements for nasal and temporal CT at 500 µm from the center of fovea. This may allow better understanding and
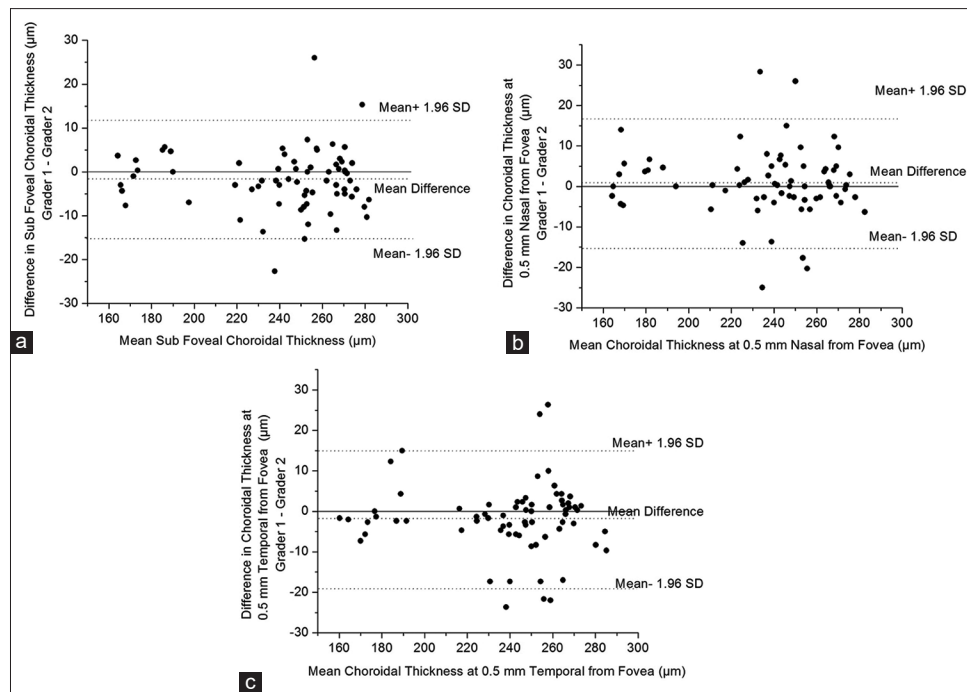
Figure 1: (a) Bland-Altman plots showing the intergrader agreement between subfoveal choroidal thickness (SFCT) measurements. The ordinate axis represents the difference between measurements, the abscissa axis shows the mean of the measurements. The mean line presents the mean difference, and the dotted lines are the limits of agreement, corresponding ±1.96 SD from the mean difference. (b) Bland-Altman plots showing the intergrader agreement between SFCT 0.5 mm nasal to fovea choroidal thickness measurements. (c) Bland-Altman plots showing the intergrader agreement between SFCT 0.5 mm temporal to fovea choroidal thickness measurements

facilitate studies on the diseases with an underlying pathology in the choroid or with associated choroidal changes, using the current software of RTVue XR OCT.

The strengths of the study include its sample size and prospective design, thereby reducing inclusion/recruitment and reporting biases. This study included three repeated measurements with a wide range of choroidal thicknesses at three point locations. Scans for the subjects were acquired consecutively in the same session, which minimized the possibility of true change in the computed tomography measurements caused by diurnal fluctuation in the choroidal thickness.[11]

A limitation of this study was that scans were acquired from healthy subjects with no ocular pathology, and it does not reflect on the patients in an outpatient setting, as the clarity of scan images could be hindered by ocular pathology such as significant media opacity and in eyes with posterior segment pathology, where disruption of the normal retinal morphology hinders accurate determination of the fovea or if the choroidal reflectance is masked by the choroidal hyper-reflective lesions. Patients with poor fixation may lead to poor quality scans and hinder the accurate measurement of choroidal thickness difficult. However, given the lack of intrasession intraobserver repeatability or interobserver reproducibility studies on RTVue XR OCT, we chose to study healthy subjects. Manual measurements of choroidal thickness require identification of the RPE/Bruch's complex and chorioscleral interface and accurate application of callipers for the measurement,

which is a tedious process and can affect measurement variability. Nevertheless, the results of this study using manual measurements may help to improve our understanding of the repeatability of choroidal thickness measurements until automated choroidal segmentation software is made available.

In summary, we report the repeatability of RTVue XR SD-OCT-derived measurements of choroidal thickness in the normal Asian Indian eyes. The choroidal thickness measurements can be quantified with good reliability, repeatability, and reproducibility. Accurate quantitative assessment of these measurements may provide new insights into the role of the choroid in the patients with chorioretinal disease such as neovascular age-related macular degeneration, central serous chorioretinopathy, and idiopathic polypoidal choroidal vasculopathy. Additional studies are warranted to test the repeatability of choroidal thickness measurements in patients with aforementioned pathology and in separate scanning sessions using this protocol.

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Conflicts of interest
There are no conflicts of interest.

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