

Reproducibility of Macular Thickness Measurements Using Cirrus SD-OCT in Neovascular Age-Related Macular Degeneration

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PURPOSE. To assess the test-retest variability of central and sectorial macular thickness measurements obtained by Cirrus HD-OCT (Carl Zeiss Meditec, Dublin, CA) in neovascular age-related macular degeneration (nAMD).

METHODS. Macular thickness measurements of nine standard ETDRS subfields were obtained and analyzed. The repeatability of macular thickness measurements by Cirrus HD-OCT was assessed by examining the intrasession within subject standard deviation (Sw), coefficient of repeatability (CR), and coefficient of variation (CV), before and after eyes with retinal segmentation errors were excluded.

RESULTS. Forty-nine nAMD eyes of 49 consecutive patients were included in the study. The CR for the central macular subfield was 42.4 μm (10.5%) and ranged from 12.1 μm (3.7%) for the outer nasal to 41.8 μm (11.4%) for the inner nasal subfields. In a secondary analysis, eyes affected by erroneous detection of inner and outer retinal boundaries (6/49, 12.24%) were excluded. The revised coefficient of repeatability for the central macular subfield was 26.1 μm (8.1%) and ranged from 10.3 μm (3.8%) for the outer superior to 30.2 μm (8.3%) for the inner nasal subfields.

CONCLUSIONS. Overall, the test-retest variability of Cirrus HD-OCT is good for the central and sectorial macular subfields, with a low incidence of scan artifacts. (*Invest Ophthalmol Vis Sci.* 2010;51:4788–4791) DOI:10.1167/iovs.09-4976

Optical coherence tomography (OCT) is a noninvasive technique that provides detailed cross-sectional images of the retina.¹

OCT has progressively become an important tool in the management of patients with neovascular age-related macular degeneration (nAMD), because of its high resolution and ability to quantify changes in retinal thickness, either spontaneous or in response to different treatments. These capabilities are particularly important in the new era of anti-vascular endothelial growth factor (VEGF) therapies, in which qualitative and quantitative information provided by OCT are integral parts of retreatment criteria.² Despite the advantages provided by OCT

over other imaging techniques, interpretation of OCT outcomes in patients with nAMD has been prone to frequent significant errors in the identification of retinal boundaries by the automated image-analysis software.³

To date, time-domain OCT (Stratus; Carl Zeiss Meditec, Inc., Dublin, CA) has been the most commonly used technique for obtaining macular thickness measurements^{3–7} and has been shown to generate measurements with high repeatability.^{8–13}

Recent advantages in OCT technology have led to the development of faster and more accurate OCT scanning systems, known as *spectral* or *Fourier domain* OCT (SD-OCT), which is capable of acquiring large, volumetric data sets in a short time frame, giving more detailed information on nAMD.^{14–18}

Cirrus HD-OCT (Carl Zeiss Meditec, Inc.) is an SD-OCT that has an axial resolution of 5 μm and a scan velocity of 27,000 axial scans per second. These features improve the ability to visualize smaller and thinner structures that are difficult to visualize with time-domain OCT.^{14,15,19,20}

Cirrus HD-OCT has been demonstrated to have high intrasession repeatability in healthy subjects^{21,22} and provides retinal thickness measurements approximately 43 μm higher than does Stratus OCT (Carl Zeiss Meditec, Inc.), which is likely to be attributable to the difference in the detection of the outer retinal boundary by the two instruments: the retinal pigment epithelium and the inner-outer segment photoreceptor junction for Cirrus and Stratus, respectively.²³

OCT-derived retinal thickness measurements with Stratus are subject to considerable measurement variability in patients with nAMD, with changes of more than 50 μm .³

The difficulty in estimating the repeatability of automated retinal thickness measurements in retinal diseases characterized by marked alteration in the retinal morphology, as in nAMD, arises from the higher incidences of scanning artifacts and automated segmentation algorithm errors that affect these eyes.^{24–26}

The purpose of this study was to assess the test-retest variability of central and sectorial macular thickness measurements obtained by Cirrus HD-OCT in nAMD and to determine the incidence of scanning artifacts and their influence on test-retest variability.

METHODS

Forty-nine consecutive subjects with active neovascular age-related macular degeneration after at least one treatment session with anti-VEGF drugs and with different degrees of disease activity were included in the study. Only one eye of each patient was included. If both eyes met the inclusion criteria, the eye with the best distance acuity was selected. According to biomicroscopy and fluorescein angiography, staging of the lesion was performed: stage 1 represented lesions without signs of classic, occult, or minimally classic fibrosis; stage 2 included lesions containing fibrotic parts.²⁵ The study was performed

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in accordance with the ethical standards stated in the Declaration of Helsinki and was approved by the institutional review board. Each patient signed an informed consent before the enrollment in the study.

Exclusion criteria were poor OCT image quality (signal strength, ≤ 5), the presence of a refractive error $> \pm 5$ D, astigmatism > 2 D, media opacities, the presence of epiretinal membrane or vitreomacular traction, and a history of ocular trauma or ocular diseases other than nAMD. All subjects received a complete ophthalmic evaluation, including noncontact IOP measurement (Ocular Response Analyzer [ORA]; Reichert, Depew, NY) and indirect ophthalmoscopy.

Each subject underwent three OCT scanning sessions within 3 hours on the same day, with the 512×128 Cirrus OCT scanning protocol. Retinal scans were performed by the same operator (MS), who has been certified by image-reading centers for OCT imaging in multicenter clinical trials. All image sets were analyzed to rule out segmentation algorithm errors by two graders (MP, FM), both experienced in management and treatment of nAMD and certified as OCT operators in several multicenter clinical trials.

All scans were used for the primary analysis (low-quality [LQ] analysis). In a secondary analysis, only images without segmentation errors were included (high-quality [HQ] analysis).

Retinal thickness measurements of each of the nine subfields corresponding to the Early Treatment of Diabetic Retinopathy Study (ETDRS) areas were examined in the analysis.²⁷ ETDRS areas are defined by three concentric rings centered into the fovea with diameters of 1, 3, and 6 mm, respectively, and with the two outer rings divided into quadrants by two intersecting orthogonal lines. All imaging sessions were performed after pupil dilation with 1 drop of 1% tropicamide in the selected eye.

Scanning with the Cirrus HD-OCT was performed with the 512×128 -scan pattern, in which a 6.6-mm area on the retina is scanned with 128 horizontal lines, each consisting of 512 A-scans per line within a scan time of 2.4 seconds.

The primary objective was to assess the test-retest variability of macular thickness measurements performed by Cirrus HD-OCT in nAMD. Secondary objectives included assessment of the incidence of scanning artifacts and their influence on test-retest variability of macular thickness measurements.

Mean and 95% confidence interval (95% CI) were used to describe continuous variables. The coefficient of repeatability (CR) was calculated according to the methods outlined by Bland and Altman^{28,29} for each of the automated retinal thickness measurements in the nine ETDRS subfields ($1.96 \times$ square root of the within-subject variance from repeated measurements). The CR was also expressed as a percentage of the mean measurement.³

RESULTS

Fifty-three nAMD eyes of 53 consecutive patients were screened for enrollment in the study. Four eyes were excluded because of poor-quality scans (signal strength < 5 , according to the inclusion and exclusion criteria).

Forty-nine eyes of 49 consecutive subjects (mean age, 74.1 ± 1.2 years; 29 men and 20 women) with active nAMD were included in the study and considered for the statistical analysis.

nAMD was classified according to the presence of fibrosis within the lesions.²⁵ Of the 49 patients, 35 (71.4%) had lesions without signs of fibrosis (classic, occult or minimally classic) and were defined as stage 1. The remaining 14 (28.6%) presented lesions containing fibrosis (stage 2). The mean visual acuity was 0.32 ± 0.15 logMAR.

The CR for the central macular subfield was $42.4 \mu\text{m}$ (10.5%), ranging from $12.1 \mu\text{m}$ (3.7%) for the outer nasal to $41.8 \mu\text{m}$ (11.4%) for the inner nasal subfields (LQ analysis). Full details are presented in Table 1. Erroneous detection of inner and outer retinal boundaries by the automated software was present in six sets of scans. After exclusion of the 6 macular scans with significant segmentation errors, 43 scans were left for the subanalysis (HQ analysis). The revised coefficient of repeatability for the central macular subfield was $26.1 \mu\text{m}$ (8.1%) and ranged from $10.3 \mu\text{m}$ (3.8%) for the outer superior to $30.2 \mu\text{m}$ (8.3%) for the inner nasal subfields. The CR change from LQ analysis for the central macular subfield was 38.4%. Full details are presented in Table 2.

DISCUSSION

This study provides an estimate of the reproducibility of Cirrus HD-OCT-derived retinal thickness measurements in patients with nAMD.

Overall, retinal thickness measurements obtained with Cirrus HD-OCT were found to be highly reproducible, with CR values for the central macular subfield of $42.4 \mu\text{m}$ (10.5%), ranging across different macular subfields from $12.1 \mu\text{m}$ (3.7%) for the outer nasal to $41.8 \mu\text{m}$ (11.4%) for the inner nasal subfields (LQ analysis). The reproducibility of retinal thickness measurements increased after scans were excluded with errors in retinal boundary identification, with CR values for the central macular subfield of $26.1 \mu\text{m}$ (8.1%), ranging across macular subfields from $10.3 \mu\text{m}$ (3.8%) for the outer superior to $30.2 \mu\text{m}$ (8.3%) for the inner nasal subfields (HQ analysis). The CR change from LQ analysis for the central macular subfield was 38.4%.

Wolf-Schnurrbusch et al.²² recently compared the repeatability of central retinal thickness measurements by different OCT systems and reported a coefficient of variation of 3.09% for the Cirrus SD-OCT in normal eyes. More recently, Menke et al.³⁰ tested the reproducibility of retinal thickness measurements performed by the Fourier-domain Topcon 3D-OCT 1000 (Topcon Corp.) in patients with dry and exudative AMD and showed good reproducibility in both groups, with better results in dry than in exudative lesions (coefficient of variation, 1.8% vs. 3.7%). The results of our study showed similar results,

TABLE 1. Results of Low-Quality Analysis of ETDRS Subfields in All Patients

Macular Field	CV (%)	CR ($1.96 \times$ SD) (μm)	Mean of Three Scan Measurements (μm)	CR Expressed As Percentage of Mean (%)
Central	5.37	42.4	340.79 ± 12.91	10.5
Outer superior	2.65	14	265.07 ± 4.57	5.2
Inner superior	3.54	25.9	333.33 ± 8.92	6.9
Outer temporal	4.24	19.9	257.86 ± 5.61	8.3
Inner temporal	4.32	29.2	320.01 ± 9.21	8.5
Outer inferior	4.86	28.3	271.67 ± 8.88	9.5
Inner inferior	6.25	43.2	336.56 ± 12.37	12.2
Outer nasal	1.88	12.1	293.97 ± 3.82	3.7
Inner nasal	5.81	41.8	335.66 ± 12.04	11.4

Scans with segmentation errors were not excluded.

TABLE 2. Results of High-Quality Analysis of ETDRS Subfields in All Patients

Macular Field	CV (%)	CR (1.96 × SD) (μm)	Mean of Three Scan Set Measurements (μm)	CR Expressed As Percentage of Mean (%)	CR % Change From IQ Set (%)
Central	4.15	26.1	335.38 ± 9.21	8.1	-38.4
Outer superior	1.95	10.3	265.58 ± 3.59	3.8	-26.4
Inner superior	3.04	20.5	329.77 ± 7.23	5.9	-20.8
Outer temporal	4.23	19.9	259.80 ± 5.11	8.3	-0.0
Inner temporal	2.58	16.4	318.72 ± 6.30	5.1	-43.8
Outer inferior	4.68	27.8	272.36 ± 8.05	9.2	-1.76
Inner inferior	4.62	29.6	336.15 ± 8.59	9.1	-31.5
Outer nasal	1.80	12	296.62 ± 5.56	3.5	-0.8
Inner nasal	4.23	30.2	355.89 ± 9.54	8.3	-27.7

Scans with segmentation errors were excluded.

despite a slightly higher variability of measurements of central retinal thickness (coefficient of variation, 5.37% in the central macular subfield in the LQ analysis and 4.15% in the HQ analysis) compared with their data from the exudative AMD group. However, any comparisons of reproducibility between studies have to be interpreted with caution, because they may be influenced by several factors, including type and software version of the imaging device, within-study-group variance, the scan protocol, and the method applied for statistical analysis.

Variability of retinal thickness measurements was found to be inconsistent across sectorial subfields, with CR ranging from 3.7% to 11.4% in the LQ analysis and from 3.5% to 9.2% in the HQ analysis. No clear trend of increasing or decreasing variability was identified according to either the eccentricity or position of the subfields. Explanations for these observations may be the presence of eccentric fixation, different location, and extension of retinal changes induced by choroidal neovascularization, or out-of-register error leading to segmentation errors.

Six (12.24%) of 49 pairs of scan sets were affected by retinal boundary segmentation errors and therefore excluded from statistical analysis.

The percentage of failing segmentation artifacts found in our study was lower than that reported by Krebs et al.²⁵ (25% vs. 12.4%) in a study specifically designed to assess the accuracy of OCT segmentation algorithms in nAMD eyes. Even though the sample populations of the two studies share several characteristics, such as mean age (74 vs. 78 years) and type of nAMD lesion (prevalence of lesions with signs of fibrosis, 28.6% vs. 31.1%), they differ in treatment status (lesions under treatment 100% vs. 70.2%) and distance visual acuity (0.32 vs. 0.64 logMar). Specifically, distance visual acuity differences, as an expression of differences in disease severity, may account for the lower incidence of segmentation artifacts found in our study.

The repeatability of Cirrus HD-OCT measurements found in our population of nAMD patients improved after all the scan sets with retinal segmentation errors were excluded. In fact, the CR for central macular subfield improved by 38.4%, changing from 42.4 (10.5%) to 26.1 (8.1%) μm. Although this change is likely to have an impact in clinical practice, it also indicates that software algorithms must be improved and become more reliable in cases of severe morphologic changes associated with neovascular AMD, making clinical assessment easier.

Compared with previously published results on repeatability of retinal thickness measurements with Stratus OCT in nAMD patients, Cirrus HD OCT offered a better performance, with a lower degree of variability of retinal measurements, before and after the exclusion of scans affected by segmentation errors (26 vs. 50 μm for the Cirrus and Stratus, respectively).³

The lower Cirrus HD-OCT variability is most likely attributable to better-quality images, faster scan acquisition, and higher resolution and to the particular software segmentation algorithm (detection of the outer band of the retinal pigment epithelium versus Stratus OCT detection of the inner-outer segment photoreceptor junction). Nevertheless, it must be emphasized that the severity of nAMD is likely to have an impact on the variability of test-retest OCT retinal thickness measurements, challenging the OCT retinal segmentation algorithms. In fact, in our sample population, 71.4% of the study subjects showed lesions—classic, occult, or minimally classic—without signs of fibrosis, thus potentially leading to an overestimation of the reproducibility of retinal thickness evaluation compared with the daily clinical routine when more advanced lesions are imaged.

The diagnostic accuracy of a test is usually characterized by its sensitivity and specificity. The quantitative accuracy of OCT retinal thickness measurements, high in normal eyes and in patients with diabetic macular edema, has been demonstrated to be reduced in subjects with nAMD. In clinical settings, retinal specialists often base their retreatment decision on qualitative OCT analysis, which is less prone to error, whereas quantitative automatic analysis is cautiously interpreted, because of the reduced reproducibility of quantitative OCT measures. A higher CR has been found for measurements acquired in patients with nAMD, perhaps for several reasons, including fixation instability and extensive anatomic disruption of the macular structure, accounting for the inability of the OCT automatic intrinsic segmentation algorithm to correctively detect neuroretinal boundaries and to precisely localize the foveal area. Therefore, high measurement accuracy is crucial when assessing the efficacy of anti-VEGF therapy concerning only the quantitative OCT measurements. High accuracy is important to distinguish between measurement variability and small changes in retinal morphology induced by treatment or evidence of an early increase recurrence.

Changes of more than 26 μm in central macular thickness, according to our data, may better reflect true clinical change in the scan without significant segmentation errors and may be used to guide retreatment of patients with nAMD in clinical trials and clinical practice.

In conclusion, the test-retest variability of Cirrus HD-OCT is good for central and sectorial macular subfields, with a low incidence of scan artifacts. The continuous implementation of the OCT technique, with the recent shift from time- to spectral-domain technology, has led to an increased level of reproducibility of OCT retinal measurements in subjects with nAMD, and this improvement should be considered when planning clinical trials.

References

- Huang D, Swanson EA, Lin CP, et al. Optical coherence tomography. *Science*. 1991;254(5035):1178-1181.
- Fung AE, Lalwani GA, Rosenfeld PJ, et al. An optical coherence tomography-guided, variable dosing regimen with intravitreal ranibizumab (Lucentis) for neovascular age-related macular degeneration. *Am J Ophthalmol*. 2007;143:566-583.
- Patel PJ, Chen FK, Ikeji F, et al. Repeatability of stratus optical coherence tomography measures in neovascular age-related macular degeneration. *Invest Ophthalmol Vis Sci*. 2008;49:1084-1088.
- Jaffe GJ, Caprioli J. Optical coherence tomography to detect and manage retinal disease and glaucoma. *Am J Ophthalmol*. 2004;137:156-169.
- Otani T, Kishi S, Maruyama Y. Patterns of diabetic macular edema with optical coherence tomography. *Am J Ophthalmol*. 1999;127:688-693.
- Haouchine B, Massin P, Tadayoni R, et al. Diagnosis of macular pseudoholes and lamellar macular holes by optical coherence tomography. *Am J Ophthalmol*. 2004;138:732-739.
- Sanchez-Tocino H, Alvarez-Vidal A, Maldonado MJ, et al. Retinal thickness study with optical coherence tomography in patients with diabetes. *Invest Ophthalmol Vis Sci*. 2002;43:1588-1594.
- Polito A, Napolitano MC, Bandello F, et al. The role of optical coherence tomography (OCT) in the diagnosis and management of retinal angiomatous proliferation (RAP) in patients with age-related macular de generation. *Ann Acad Med Singapore*. 2006;35:420-424.
- Massin P, Vicaud E, Haouchine B, et al. Reproducibility of retinal mapping using optical coherence tomography. *Arch Ophthalmol*. 2001;119:1135-1142.
- Polito A, Del Borrello M, Isola M, et al. Repeatability and reproducibility of fast macular thickness mapping with Stratus optical coherence tomography. *Arch Ophthalmol*. 2005;123:1330-1337.
- Danis RP, Fisher MR, Lambert E, et al. Results and repeatability of retinal thickness measurements from certification submissions. *Arch Ophthalmol*. 2008;126:45-50.
- Krzystolik MG, Strauber SF, Aiello LP, et al. Reproducibility of macular thickness and volume using Zeiss optical coherence tomography in patients with diabetic macular edema. *Ophthalmology*. 2007;114:1520-1525.
- Ho J, Sull AC, Vuong LN, et al. Assessment of artefacts and reproducibility across spectral- and time-domain optical coherence tomography devices. *Ophthalmology*. 2009;116(10):1960-1970.
- Wojtkowski M, Srinivasan V, Ko T, et al. Ultrahigh-resolution, high-speed, Fourier domain optical coherence tomography and methods for dispersion compensation. *Opt Express*. 2004;12:2404-2422.
- Leitgeb R, Drexler W, Unterhuber A, et al. Ultrahigh resolution Fourier domain optical coherence tomography. *Opt Express*. 2004;12:2156-2165.
- Menke MN, Dabov S, Sturm V. Features of age-related macular degeneration assessed with three-dimensional Fourier-domain optical coherence tomography. *Br J Ophthalmol*. 2008;92(11):1492-1497.
- Witkin AJ, Vuong LN, Srinivasan VJ, et al. High-speed ultrahigh resolution optical coherence tomography before and after ranibizumab for age-related macular degeneration. *Ophthalmology*. 2009;116(5):956-963.
- Chen Y, Vuong LN, Liu J, et al. Three-dimensional ultrahigh resolution optical coherence tomography imaging of age-related macular degeneration. *Opt Express*. 2009;17(5):4046-4060.
- Ko TH, Fujimoto JG, Duker JS, et al. Comparison of ultra-high- and standard resolution optical coherence tomography for imaging macular hole pathology and repair. *Ophthalmology*. 2004;111:2033-2043.
- Ko TH, Fujimoto JG, Schuman JS, et al. Comparison of ultra-high- and standard resolution optical coherence tomography for imaging of macular pathology. *Ophthalmology*. 2005;112:1922.e1-e15.
- Legarreta JE, Gregori G, Punjabi OS, et al. Macular thickness measurements in normal eyes using spectral domain optical coherence tomography. *Ophthalmic Surg Lasers Imaging*. 2008;39(4 suppl):S43-S49.
- Wolf-Schnurrbusch UE, Ceklic L, Brinkmann CK, et al. Macular thickness measurements in healthy eyes using six different optical coherence tomography instruments. *Invest Ophthalmol Vis Sci*. 2009;50:3432-3437.
- Kiernan DF, Hariprasad SM, Chin EK, Kiernan CL, Rago J, Mieler WF. Prospective comparison of cirrus and stratus optical coherence tomography for quantifying retinal thickness. *Am J Ophthalmol*. 2009;147(2):267-275.e2.
- Keane PA, Mand PS, Liakopoulos S, Walsh AC, Sadda SR. Accuracy of retinal thickness measurements obtained with Cirrus optical coherence tomography. *Br J Ophthalmol*. 2009;93(11):1461-1467.
- Krebs I, Falkner-Radler C, Hagen S, et al. Quality of the threshold algorithm in age-related macular degeneration: Stratus versus Cirrus OCT. *Invest Ophthalmol Vis Sci*. 2009;50(3):995-1000.
- Ghazi NG, Kirk T, Allam S, Yan G. Quantification of error in optical coherence tomography central macular thickness measurement in wet age-related macular degeneration. *Am J Ophthalmol*. 2009;148(1):90-96.e2.
- Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema, Early Treatment Diabetic Retinopathy Study Report No 1. *Arch Ophthalmol*. 1985;103:1796-1806.
- Bland JM, Altman DG. Statistical methods for assessing agreement between two methods for clinical measurement. *Lancet*. 1986;1:307-310.
- Bland MJ. How should I calculate a within-subject coefficient of variation? <http://www-users.york.ac.uk/~mb55/meas/cv.htm>.
- Menke NM, Dabov S, Knecht P, Sturm V. Reproducibility of retinal thickness measurements in patients with age-related macular degeneration using 3D Fourier-domain optical coherence tomography (OCT) (Topcon 3D-OCT 1000). *Acta Ophthalmol*. Published online December 21, 2009.