Segmentation error and macular thickness measurements obtained with spectral-domain optical coherence tomography devices in neovascular age-related macular degeneration

Moosang Kim, Seung Jun Lee, Jisang Han1, Seung-Young Yu1, Hyung Woo Kwak1

Purpose: To evaluate frequency and severity of segmentation errors of two spectral-domain optical coherence tomography (SD-OCT) devices and error effect on central macular thickness (CMT) measurements. Materials and Methods: Twenty-seven eyes of 25 patients with neovascular age-related macular degeneration, examined using the Cirrus HD-OCT and Spectralis HRA + OCT, were retrospectively reviewed. Macular cube 512 × 128 and 5-line raster scans were performed with the Cirrus and 512 × 256 volume scans with the Spectralis. Frequency and severity of segmentation errors were compared between scans. Results: Segmentation error frequency was 47.4% (baseline), 40.7% (1 month), 40.7% (2 months), and 48.1% (6 months) for the Cirrus, and 59.3%, 62.2%, 57.8%, and 63.7%, respectively, for the Spectralis, differing significantly between devices at all examinations (P < 0.05), except at baseline. Average error score was 1.21 ± 1.65 (baseline), 0.79 ± 1.18 (1 month), 0.74 ± 1.12 (2 months), and 0.96 ± 1.11 (6 months) for the Cirrus, and 1.73 ± 1.50, 1.54 ± 1.35, 1.38 ± 1.40, and 1.49 ± 1.30, respectively, for the Spectralis, differing significantly at 1 month and 2 months (P < 0.02). Automated and manual CMT measurements by the Spectralis were larger than those by the Cirrus. Conclusions: The Cirrus HD-OCT had a lower frequency and severity of segmentation error than the Spectralis HRA + OCT. SD-OCT error should be considered when evaluating retinal thickness.

Key words: Central macular thickness, neovascular age-related macular degeneration, segmentation error, spectral-domain optical coherence tomography

Macular thickness is an important index for determining macular disease severity and progression. Due to the widespread use of intravitreal anti-vascular endothelial growth factor (VEGF) injections to treat neovascular age-related macular degeneration (AMD), accurate macular thickness measurements are required for follow-up and large-scale clinical studies. Fung et al.[1] defined a ≥100 μm increase in retinal thickness as a criterion for retreatment of neovascular AMD in an OCT-guided treatment regimen and stressed the importance of central macular thickness (CMT) measurement in follow-up examinations.

The retinal thickness analyzer, confocal scanning laser ophthalmoscope, and optical coherence tomography (OCT) are used to obtain images of the macula and measure its thickness. Of these, OCT is an important noninvasive diagnostic tool for evaluating retinal diseases and the Stratus OCT (Carl Zeiss Meditec, Dublin, California) is one of the most commonly used OCTs. As a time-domain OCT (TD-OCT), the Stratus OCT can perform 400 A-scans per second and has an axial resolution of approximately 10 μm. Using an image processing technique, the Stratus OCT can automatically detect the inner and outer retinal boundaries and measure retinal thickness in B-scans.[2] Analyzing images from the Stratus OCT, Keane et al.[3] reported 92% of eyes had retinal thickness measurement errors, 13% of which were severe. The recently introduced Spectral-domain OCT (SD-OCT) has a high axial resolution (5–8 μm) and a speed of over 20,000 A-scans per second, and shows the retinal image in more detail at a faster rate than the TD-OCT.[4-7] In addition, while the TD-OCT defines the boundary between the inner and outer segments of the photoreceptor layer as the outer retinal boundary, the SD-OCT has different boundary ranges depending on the machine type. With its high resolution, fast image acquisition, and elaborate image processing software, the SD-OCT was expected to have much fewer errors than the TD-OCT. Recent reports, however, indicate that the SD-OCT also has frequent errors.[8,9]

Previous studies reported only the frequency with which retinal thickness was measured inaccurately due to OCT error. There are no data available regarding the extent to which such an error affects the retinal thickness measurement outcome. Because segmentation errors are thought to have the greatest impact on CMT measurements in patients with neovascular AMD, we examined the frequency and severity of these errors in two SD-OCT devices, and evaluated the extent to which OCT segmentation error affects CMT measurement outcome.

Materials and Methods

The Institutional Review Board approved the data collection and analysis. Medical records of patients who received intravitreal anti-VEGF (bevacizumab or ranibizumab) injection therapy between September 2008 and January 2010, after diagnosis of choroidal neovascularization (CNV) secondary to neovascular AMD, were retrospectively analyzed. Only patients who received three consecutive intravitreal anti-VEGF...
injections and were followed up for 6 months or more were included in the study, and the lesion type or size of CNV was not considered. Patients with an ophthalmic disease that could lead to visual loss other than neovascular AMD or those who received cataract surgery and vitrectomy were excluded. The best-corrected visual acuity and OCT records at baseline, 1 month, 2 months and 6 months were analyzed.

OCT images were obtained by one experienced examiner and were read by two retinal ophthalmologists (MSK, SYY) in a blinded manner. Patients were examined 30 minutes after administration of three drops of intraocular mydriatics (Mydrin-P®, Santen, Osaka, Japan) applied with a 5-minute interval. The two OCT devices used in this study were as follows:

The Cirrus HD-OCT (Carl Zeiss Meditec, Dublin, CA) has an axial resolution of approximately 5 μm and a speed of 27,000 A-scans per second. Macular cube 512 × 128 and 5-line raster scans were performed. The macular cube 512 × 128 scan uses a raster scan mode that scans a 6 × 6-mm macular area into 512 × 128 (length by width) points. The 5-line raster scan comprises five 6-mm long lines at 250-μm intervals. In both scans, only those cases with signal intensity greater than or equal to 7 were included in the study results.

The Spectralis HRA + OCT (Heidelberg Engineering GmbH, Heidelberg, Germany) is a high-resolution SD-OCT that can simultaneously perform scanning laser ophthalmoscopy. A 6 × 6-mm macular area was examined in the fast scanning mode comprising 25 B-scans of 512 pixels. Measurements were performed with the automatic real-time function of eye tracking and volume scans including concentric circles of 1 mm, 3 mm, and 6 mm. Only those cases whose concentric circles were all inside the scan area were included in this study and five B-scans within 1 mm of the central fovea were analyzed separately from 25 B-scans.

This study analyzed inner and outer retinal boundary misidentifications, which are thought to have a greater influence on macular thickness measurements than any other type of error. The scope of analysis was the central fovea of 1 mm in size, not the entire macular area. The Cirrus HD-OCT can measure a 1 mm of fovea because its 5-line raster scan comprises five 6-mm long lines at 250-μm intervals. In the Spectralis HRA + OCT, the 5 B-scans including the 1 mm of fovea were analyzed on the 512 × 25 scan. Frequencies of segmentation errors were assessed by reading each of the five images taken in 5-line raster scan of the Cirrus HD-OCT and each of the five images of the fovea taken with Spectralis HRA + OCT and by dividing the number of images with a segmentation error by the total number of images taken.

To determine segmentation error severity, we modified the error scoring method described by Sadda et al.[10] to obtain the average error score (AES).[10] Sadda et al.[5,10] method gives a weight of 1 point to an error found in the center of the macula irrespective of the error type; however, we did not apply such a weight because we only analyzed a 1-mm diameter circle at the fovea (inside a 1-mm diameter circle from the center of the macula). Two retinal specialists analyzed images, gave scores, and calculated the mean values. Zero to five points were allocated to each image; one point if there was a segmentation error, another point for a segmentation error greater than or equal to 1/3 and less than 2/3 of the entire range in horizontal or vertical direction, and two additional points for segmentation errors greater than or equal to 2/3 of the range. Each of the five images obtained in the 5-line raster scan of Cirrus HD-OCT and each of the five images of the fovea taken with the Spectralis HRA + OCT were analyzed and scored and the mean value was calculated as the final error score [Fig. 1].

Retinal thickness in a 1-mm diameter circle at the fovea was used for automated CMT measurements in a macular cube of 512 × 128 scan for the Cirrus HD-OCT. Manual CMT was determined by calculating the mean value of three thicknesses measured with calipers at three points at the central 1 mm of the 6-mm long 5-line raster scan (the central foveal point and two other points 500 μm away from the central foveal point in either direction). In the Cirrus HD-OCT, the retinal thickness in a 1-mm diameter circle at the fovea was also determined as the automated CMT in Spectralis HRA + OCT and the manual CMT was determined based on the mean value of three manual thickness measurements in the segmentation line edit mode on three points at the central 1 mm among the five B-scans at the fovea (the central foveal point and two other points 500 μm away from the central foveal point in either direction).

Data were summed up using Microsoft Excel. The Mann-Whitney U test was used to examine the frequency and AES of segmentation errors of the two OCT and to compare automated and manual CMT measurements. Pearson correlation test was used to determine whether a CMT reduction in either device correlated with an improvement in visual acuity. Statistical analysis was performed with SPSS 12.0 for Windows (SPSS INC). P values <0.05 were considered statistically significant.

**Results**

This study included 27 eyes of 25 patients (19 men, 6 women; mean age = 68.74 ± 8.52 years). Of the 27 eyes, 7 were treated...
with bevacizumab (Avastin®, Genentech Inc., San Francisco, CA), 10 with ranibizumab (Lucentis®, Genentech Inc), and 10 switched from bevacizumab to ranibizumab.

During follow-up, the segmentation error frequency was 47.4% (baseline), 40.7% (1 month), 40.7% (2 months), and 48.1% (6 months) in the Cirrus HD-OCT, and 59.3%, 62.2%, 57.8%, and 63.7%, respectively, in the Spectralis HRA + OCT [Table 1], differing significantly different between the two devices at all examinations \((P < 0.05)\), except at baseline. AES was 1.21 ± 1.65 (baseline), 0.79 ± 1.18 (1 month), 0.74 ± 1.12 (2 months), and 0.96 ± 1.11 (6 months) for the Cirrus HD-OCT, and 1.73 ± 1.50, 1.54 ± 1.35, 1.38 ± 1.40, and 1.49 ± 1.30, respectively, for the Spectralis HRA + OCT [Fig. 2], differing significantly between the two devices at 1 month \((P = 0.011)\) and 2 months \((P = 0.018)\).

Automated and manual CMT measurements of the Cirrus HD-OCT and Spectralis HRA + OCT are compared in Fig. 3. During the follow-up, automated CMT values measured with the Spectralis HRA + OCT averaged 79.13 ± 19.2 μm larger than those measured with the Cirrus HD-OCT. Manual CMT values measured with Spectralis HRA + OCT averaged 128.7 ± 5.8 μm larger than those measured with the Cirrus HD-OCT. With the Cirrus HD-OCT, the automated CMT measurement was larger than the manual CMT measurement by a mean of 12.5%, whereas with the Spectralis HRA + OCT, the automated CMT measurement was smaller than that of the manual CMT by a mean of 6.8%.

Fig. 4 shows the correlations between the decrease in CMT and improvement in visual acuity. Manual CMT measurements were used to exclude segmentation errors. With the Cirrus HD-OCT, a decrease in the manual CMT did not correlate significantly with visual acuity improvement \((P = 0.090, \text{ correlation coefficient 0.492})\), but manual CMT measured with the Spectralis HRA + OCT correlated significantly with visual acuity \((P = 0.022, \text{ Correlation coefficient 0.438})\).

**Discussion**

Previous studies demonstrated that the frequency of OCT errors differs depending on the OCT type, analysis method, and retinal disease studied. Ray et al.\(^{[1]}\) measured the retinal thickness map using the Stratus OCT, a TD-OCT, analyzed 6 radial scan images, and reported an error frequency of approximately 42%. Sadda et al.\(^{[10]}\) also used the Stratus OCT, analyzed errors found in all images taken by 6 radial lines or a fast macular thickness protocol, and found one or more errors in approximately 92% of all images, irrespective of a retinal thickness map. Ho et al.\(^{[8]}\) compared the errors of recently introduced SD-OCTs (Cirrus HD-OCT, RTVue-100, and Topcon 3D-OCT 1000) and the TD-OCT (Stratus OCT) and reported an error frequency of 73.8% in the Stratus OCT.

**Table 1: Frequency of segmentation error**

|                     | Baseline | 1 month | 2 months | 6 months |
|---------------------|----------|---------|----------|----------|
| Cirrus HD-OCT       | 47.4%    | 40.7%   | 40.7%    | 48.1%    |
| Spectralis HRA + OCT| 59.3%    | 62.2%   | 57.8%    | 63.7%    |

\(P\) values obtained using the Chi-square test.
68.5% in the Cirrus HD-OCT, 83.3–88.9% in the RTVue-100, and 73.6–90.6% in the Topcon 3D-OCT 1000. Compared to the TD-OCT, SD-OCT has a higher resolution, greater speed, and more elaborate software using the raster scanning method, but the error frequency remains high.

Previous studies examined the frequency with which the retinal thickness was inaccurately measured, but failed to evaluate the extent to which OCT errors affected retinal thickness measurements. Using SD-OCT, we examined the frequency and severity of segmentation errors, which are considered to have the largest impact on CMT measurements and evaluated the extent of the effect on CMT measurements.

We used a modified method of the approach used by Sadda et al. [10] to score the degree of OCT segmentation error. In Sadda et al. [10] and the present study, AES of the Cirrus HD-OCT and Spectralis HRA + OCT was less than 50% of the full score of five points, indicating that although the error frequency was high, the severity of error was unremarkable. When retinal lesions improved with intravitreal anti-VEGF therapy, the AES severity also decreased [Figs. 2 and 5]. Though also SD-OCTs, the Cirrus HD-OCT and Spectralis HRA + OCT produced different segmentation error and AES frequencies because the two devices use different approaches to determine the boundaries based on which retinal thickness is measured. The segmentation algorithm of each machine determined the boundaries. When measuring CMT, the Cirrus HD-OCT measured from the internal limiting membrane to the retinal pigment epithelium (RPE), [12,13] while the Spectralis HRA + OCT measured from the internal limiting membrane to Bruch’s membrane by distinguishing the RPE from Bruch’s membrane. [14,15] The frequency and severity of segmentation errors were higher in the Spectralis HRA + OCT than in the Cirrus HD-OCT, mainly because the RPE remains more or less intact compared to Bruch’s membrane, which is invaded and destroyed by CNV.

The difference in the retinal thicknesses measured by the two OCT machines is derived from the difference in the RPE layer height. The RPE layer height is approximately 9 μm histologically [16] and the fovea in normal eyes is approximately 20 μm thicker in the Spectralis HRA + OCT than in the other OCT machines. In patients with neovascular AMD in this study, automated CMT measurements were thicker by a mean of 80 μm in the Spectralis HRA + OCT than in the Cirrus HD-OCT, possibly due to the fact that the Spectralis HRA + OCT includes the CNV or sub-RPE fluid accumulation when measuring CMT thickness. Because CNV affects the thickness or location of the RPE with a high reflectivity on OCT, the machine cannot accurately detect such changes, which results in frequent outer retinal boundary misidentification. Thus, the Cirrus-HD-OCT tended to overestimate the automated CMT relative to the manual CMT. In the Spectralis HRA + OCT, however, the boundary is determined along the RPE instead of the usually used Bruch’s membrane in the presence of large pigment epithelial detachment around the fovea [Fig. 6]. This seemed to have resulted in an underestimation of the automated CMT by approximately 6.8% compared to the manual CMT.

The correlation with the visual acuity improvement was evaluated with manual CMT measurements to exclude the effect of segmentation error. A decline in manual CMT measured with the Cirrus HD-OCT did not significantly correlate with improved visual acuity; however, manual CMT measured with the Spectralis HRA + OCT showed a significant correlation. The trends of the CMT and visual acuity changes were similar in both machines, however, during the overall treatment process.

This study has limitations in that it was a retrospective study, a small number of eyes was investigated, and a subjective scoring system was used to estimate the severity of errors as described by Sadda et al. [10] Thus, we cannot claim that the error score was linearly proportional to the severity of error.

In conclusion, the findings of the present study confirmed that the SD-OCT error was not infrequent in neovascular AMD patients. The frequency of segmentation error and AES was less in the Cirrus HD-OCT than in the Spectralis

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**Figure 5:** Changes in the segmentation error following intravitreal anti-VEGF injections in the same patient. In both devices, segmentation error decreased as the macular lesion improved. (a–d), Cirrus HD-OCT. (a). Baseline. (b). 1 month. (c). 2 months. (d). 6 months. (e–h), Spectralis HRA + OCT. (e). Baseline. (f). 1 month. (g). 2 months. (h). 6 months

**Figure 6:** Examples of poorly measured macular thickness. (a). Normal segmentation line (b). Underestimation of macular thickness due to outer retina boundary misidentification. There were some cases in which the boundary was indented along the retinal pigment epithelium when there was a large pigment epithelial detachment, not at the usual Bruch’s membrane (dotted line)
An optical coherence tomography-guided, variable dosing. Example of a correct style

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