Comparison of Geographic Atrophy Measurements from the OCT Fundus Image and the Sub-RPE Slab Image

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PURPOSE: To compare two different approaches to measuring areas of geographic atrophy (GA) using spectral-domain optical coherence tomography (SD-OCT).

METHODS: Fifty eyes with GA were imaged with an SD-OCT instrument. OCT fundus images and sub-retinal pigment epithelium (RPE) slab images were generated. Three graders manually drew the GA boundaries on both en face images. An automated algorithm was used to segment the GA boundaries from the sub-RPE slabs.

RESULTS: The agreement between the three manual measurements on both OCT fundus images (ICC = .998) and sub-RPE slabs (ICC = .999) was excellent. Area measurements from OCT fundus images and sub-RPE slabs were highly correlated. The agreement between manual and automated measurements on the sub-RPE slabs was very good (ICC = .795).

CONCLUSION: Both OCT fundus images and sub-RPE slab images proved useful for measuring GA in age-related macular degeneration. The automated algorithm typically provided useful measurements of GA area from the sub-RPE slabs.

segment layer, and the RPE–Bruch’s membrane complex. Schmitz-Valckenberg et al compared the fundus autofluorescence and SD-OCT appearance of eyes with GA and showed that the mean length of an atrophic lesion measured on the fundus autofluorescence image had the closest agreement with the appearance of choroidal hyperreflectivity on the SD-OCT B-scan, and the reduction of the fundus autofluorescence signal seen from GA was spatially correlated with the abrupt transition on the SD-OCT B-scan from a hypo-reflective choroid to a hyperreflective choroid. This increased penetration of light below Bruch’s membrane is presumably due to the loss of the RPE and choriocapillaris. Sayegh et al also showed that the area of choroidal signal enhancement on the SD-OCT B-scans correlated well with the hypofluorescent area measured on fundus autofluorescence.

OCT imaging can also provide an en face image of GA that complements the B-scan cross-sectional images. This OCT fundus image (OFI) is generated by summing the signal of each of the A-scans and viewing their relative values en face. It is this en face OFI that results in the visualization of GA as a bright area on the image due to the increased penetration of light into the choroid where atrophy has occurred in the macula. The increased OCT choroidal signal associated with GA results in the GA appearing brighter on the en face OFI compared with the surrounding areas because the absence of the RPE and choriocapillaris in GA results in more light penetrating the choroid and being reflected back to the detector compared with the light scattering that occurs with an intact RPE in the surrounding areas. This OFI correlates well with the GA observed on clinical examination, fundus photography, and autofluorescence imaging.

The current study introduces a new approach for imaging GA, recently introduced in the Cirrus HD-OCT (Carl Zeiss Meditec, Dublin, CA) advanced RPE analysis, known as the sub-RPE slab, which creates the en face image only from the light reflected from beneath the RPE. By only using the light that penetrates into the choroid, we found the sub-RPE slab had higher contrast at the borders of GA, and the GA appeared more distinct. To validate this new approach, we compared the same datasets and measured the areas of GA observed using the standard OFI and the areas measured using the sub-RPE slab. We then tested the performance of an automatic algorithm (available on the Cirrus HD-OCT) used to detect and quantitate GA areas on the sub-RPE slab, and we compared these automated measurements with measurements obtained manually.

**SUBJECTS AND METHODS**

**Subjects**

Patients were recruited from an outpatient clinic at the Bascom Palmer Eye Institute. Approval for the collection and analysis of SD-OCT images was obtained from the institutional review board at the University of Miami Miller School of Medicine, and all patients signed informed consent documents. The study was performed in accordance with HIPAA regulations.

Patients enrolled in the study were older than 50 years with a diagnosis of atrophic AMD in at least one eye. The GA could be unifocal or multifocal. Patients were excluded from the study if the study eye demonstrated areas of peripapillary atrophy communicating with the central area of GA. Patients were also excluded if the GA extended outside the central scanning area, which was a square centered on the fovea with dimensions of 6 × 6 mm. Additional exclusion criteria for the study eye included evidence of neovascular AMD, a history of retinal surgery (including laser treatment), any sign of diabetic retinopathy, a history of retinal vascular occlusion, and a history or evidence of an inherited retinal degeneration.

**OCT Fundus Image**

SD-OCT images were obtained using the Cirrus HD-OCT. This SD-OCT device has an axial resolution of 5
µm and a scanning rate of 27,000 A-scans per second. The central macula of each study eye was imaged using a 200 × 200 raster scan pattern. The first number in the 200 × 200 scan pattern refers to the number of A-scans used to form each horizontal B-scan, whereas the second number is the total number of horizontal B-scans. The SD-OCT was calibrated so that the horizontal and vertical dimensions of the OFI generated from all 40,000 A-scans measured 6 × 6 mm on the retina. A single research technician performed all scans. All scans were performed between January 1, 2007, and June 1, 2010, using a single Cirrus SD-OCT instrument and performed after dilation of the pupil with one drop of 2.5% phenylephrine hydrochloride and 1% tropicamide. Attempts were made to perform five scans on each patient; however, low-quality scans with signal strength less than 7 and scans with motion artifacts were discarded in the analysis.

The SD-OCT en face fundus image and the sub-RPE slab were obtained for each three-dimensional dataset using the commercially available software on the Cirrus HD-OCT (version 6.0). The OFI is created by summing all pixel intensity values along individual A-scans, while the sub-RPE slab is an en face visualization using only the light penetrating below the RPE into the choroid and sclera. In the healthy regions of RPE, the pigment in the RPE will block most of the light penetrating into the choroid, while in areas of GA, the underlying choroid will be illuminated. The sub-RPE slab is formed by axially projecting only the OCT image data from a region below the contour of a robust polynomial fit to the RPE segmentation. The region extends from 65 µm to 400 µm below the robust RPE fit. Image processing was used to reduce noise and suppress the appearance of the choroidal vasculature. These en face fundus images were then used to measure the area of GA. A proprietary algorithm included in the Cirrus OCT software was used to automatically quantitate the area of GA from the sub-RPE slab.

**Measurement of GA**

The OFI and the sub-RPE slab for each patient were exported as a bitmap file measuring 200 × 200 pixels. The area of GA was quantified by using a Cintiq WACOM digitizing tablet (WACOM, Vancouver, WA) and image analysis software (Adobe Photoshop CS2; Adobe Systems, San Jose, CA). Three graders outlined the areas of GA identified on the OFI and the sub-RPE slab. In the cases in which the precise limits of GA were ambiguous, all three graders discussed and reached an agreement on the areas to be included before drawing the final outline. The encircled area was then quantified using software written as a MATLAB (MathWorks, Natick, MA) R2006a routine, which would convert the number of pixels into the area of GA. The pixel area was converted to square millimeters using the same fixed ratio established by the calibrated SD-OCT; the conversion factor per pixel was 0.0009 (36 mm²/40,000 pixels).

**Statistical Methods**

Multiple scans (more than three) were performed on each patient. Each scan was reviewed for quality, and low-quality scans with signal strength less than 7, as well as scans with motion artifacts, were discarded. The best quality scan was chosen to generate the OFI and the sub-RPE slab. In cases in which several scans had the same good quality, the scan to be used was chosen randomly. Analysis was performed to assess inter-grader agreement of area measurements made from each image. In addition to intraclass correlation coefficient calculations, Bland-Altman plots were constructed to determine limits of agreement.
between measurements made on the sub-RPE slabs by two graders and between the manual segmentation and the automatic segmentation algorithm.\textsuperscript{24}

Statistical analysis to test the correlation between OFI and sub-RPE slab was done using the Pearson correlation coefficient. All statistical calculations were carried out with SPSS V17.0 software (SPSS, Chicago, IL). Statistical significance was defined as $P < .05$.

**RESULTS**

Fifty eyes of 37 patients with GA were analyzed. The mean total area measured manually on the OFI by the three graders was 6.43 mm$^2$ (SD: 4.78), with a range from 0.16 to 18.62 mm$^2$. The mean total area measured manually on the sub-RPE slab was 6.41 mm$^2$ (SD: 4.88), with a range from 0.17 to 18.79 mm$^2$. The agreement between the three graders on measurements made from the OFIs and sub-RPE slabs was assessed by intraclass correlation coefficients were 0.998 and 0.999, respectively. The agreement between the two en face SD-OCT imaging strategies using the Bland-Altman test are shown in Figure 1. Bland-Altman graphs relate the measurement differences between two SD-OCT en face images versus the average measurement from two images, and overall there was little difference between the measurements. The mean difference of OFI and the sub-RPE slab was 0.06 (SD: 0.23), with a range of –0.5 to 0.89 ($P = .062$). Figure 2 shows the correlation between the measurements from the two en face SD-OCT images, showing a good correlation between these two strategies.

To assess the ability of the automatic algorithm to detect and segment the area of GA, we compared the average measurements made by the three graders on the sub-RPE slabs with the measurements made by the automatic segmentation algorithm. Overall, there was a good correlation between the average manual grader measurements and the automatic segmentation algorithm made on the sub-RPE slab. The ICC for the automatic algorithm and the averaged graders was 0.795 (ICC for automated algorithm and graders 1, 2, and 3 were 0.794, 0.791, and 0.798, respectively). As shown in Figure 3, a Bland-Altman graph relates the difference between the automatic segmentations made on the sub-RPE slab and the average manual segmentation performed by the three graders. The mean (SD [range]) of the averaged grader slab measurements was 6.41 (4.88 [0.17 to 18.79]), and the automated algorithm mean was 5.27 (3.68 [0.1 to 13.42]). The mean difference was $-1.13$ (2.60) $[2.02$ to $-12.81]$ with a 95% confidence interval between $-1.9$ and $-0.4$ ($P = .003$). Plots of the data suggest that there is a moderately strong, statistically significant negative correlation ($r = 0.48$, $P < .001$), which demonstrated larger differences with increasing lesion size. The automated algorithm tended to underestimate the size of the large lesions when compared with the manual grading. Figures 4 and 5 show examples of unifocal and multifocal GA with comparisons between two SD-OCT en face images and the results of the manual and automatic segmentation made on the sub-RPE slab images.

**DISCUSSION**

Both the OFI and sub-RPE slab images can be used to quantify areas of GA. The measurements obtained from the OFIs and sub-RPE slabs were highly reproducible, and there was excellent agreement between graders for both types of fundus images. There was excellent correlation between the manual measurements of atrophy on the OFI and the sub-RPE slab with a Pearson correlation of 0.999.

Up until recently, there has not been an automatic algorithm capable of detecting and measuring the area of GA imaged using SD-OCT. Schutze et al\textsuperscript{25} reported on the use of the retinal thickness map as a way of detecting GA, but there was not a good topographic cor-
relation between areas of retinal thinning and actual GA identified using scanning laser ophthalmoscopy and fundus photography. Our study is, to the best of our knowledge, the first to report the use of an automatic algorithm for measuring GA on SD-OCT images. While we have demonstrated a good correlation with measurements made manually, the automated algorithm for measuring the area of GA tends to un-
derestimate the size of larger lesions. One explanation for this discrepancy in size between automated and manual measurements may be the result of the degenerating RPE along the border of the GA. The amount of light at the borders may vary depending on the amount of melanin present and the integrity of the choriocapillaris. As a result, the algorithm may miss some parts of the lesion with irregular brightness and/or poor contrast. Even with this caveat in mind, the sub-RPE slab algorithm and an automated algorithm for area detection equipped with an editor tool for modifying the boundaries of GA should prove very useful for the detection and measurement of GA in clinical practice and in clinical trials. These algorithms and the editing software are now available in version 6.0 of the Cirrus operating system. For larger areas of GA that extend beyond the borders of the 6 × 6 mm scan area, algorithms have been developed that are capable of assembling multiple overlapping SD-OCT fundus images into a larger montage of the macula so that any area of GA can be imaged and measured using this SD-OCT approach.

The limitations to this study include the use of lesions in which the area of the GA was wholly contained within the raster scan area measuring 6 × 6 mm. In addition, we used SD-OCT as the sole imaging modality and did not compare the SD-OCT images to other modalities such as fundus autofluorescence or color fundus images.

In this study, we have shown that GA can be reproducibly identified and measured using the two types of en face SD-OCT fundus images. Advantages of using the SD-OCT fundus images compared with other imaging strategies for GA include the convenience and assurance of using only one type of imaging technique for documenting both en face and cross-sectional images of the macula and following patients with both wet and dry AMD. This imaging approach ensures that the area of perceived GA actually corresponds to the loss of photoreceptors and retinal pigment epithelium, which correlates with the loss of visual function.

REFERENCES


