Morphometric Analysis of Epiretinal Membranes Using SD-OCT

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BACKGROUND AND OBJECTIVE: To determine whether the volumes of macular layers before and after epiretinal membrane (ERM) peeling as measured by spectral-domain optical coherence tomography (SD-OCT) correlated with best-corrected visual acuity (BCVA) or ERM location.

PATIENTS AND METHODS: Thirty-six eyes with idiopathic ERM and 12 control eyes were imaged preoperatively and postoperatively using SD-OCT. The inner, middle, and outer retinal layers were measured in the temporal and nasal half of the central 1,500 µm of the macula for each of the SD-OCT five raster scans and used to estimate the volumes for each group.

RESULTS: The inner layer volumes were larger in cases compared with control eyes. The nasal inner and temporal inner layer volumes decreased after ERM removal in the nasal dominant, macular dominant, and temporal dominant groups. The inner layer volume decreased more temporally than nasally in the macular dominant and temporal dominant groups but not in the nasal dominant group. The volume decreased more in the temporal middle than the nasal middle layer for the temporal dominant group. The BCVA improvement correlated with nasal inner layer volume decrease and nasal outer and temporal outer layer volume increase.

CONCLUSION: The volume of the inner perifoveal retinal sections decreases after ERM peeling, possibly representing resolution of edema or reorganization of the nerve fiber layer on release of mechanical traction. Visual improvement correlated with volume increase of the outer retinal layers and may represent photoreceptor cell recovery after ERM peeling.

INTRODUCTION

Idiopathic epiretinal membrane (ERM) is a common macular surface abnormality,¹ and consists of fibrous astrocytes, retinal pigment epithelial cells, fibrocytes, and macrophages.²⁻⁵ Many of the cell types have myoblastic properties, which may affect surface traction that may impinge deeper retinal layers. The epicenter...
of the ERM may be located at various positions around the fovea and cause clinically visible foveal distortion and thickening. Management is usually governed by the degree to which this traction seems to impact visual acuity. Surgically peeling the ERM to relieve traction-induced visual loss partially restores visual function by reducing metamorphopsia and improving visual acuity in approximately 80% of patients. Although beneficial anatomic effects are generally credited with postoperative visual improvement, little is known regarding the specific components of the pathophysiologic effects of ERMs. For example, is it changes of certain retinal layers that impact visual acuity, are some more affected than others, and could surgical peeling impact these changes? It follows that ERM surface effects or volume might extend to deeper retinal layers variably, from both an anatomic and functional perspective, because each layer might be influenced by primary or secondary effects of mechanical traction (shear) to different degrees. It seems reasonable to assert that these effects probably determine the degree of visual loss, but such anatomic effects could not be measured until the availability of spectral-domain optical coherence tomography (SD-OCT). SD-OCT has allowed unprecedented capabilities to resolve layers and to quantitate areas of retinal elements, and has yielded potentially valuable information for evaluating retinal diseases such as retinal detachment, age-related macular degeneration, and macular hole.

The purpose of this study was to measure the volumes of retinal layers before and after idiopathic ERM peeling using SD-OCT and to determine whether these anatomic parameters correlate with best-corrected visual acuity (BCVA) or improvement.

**PATIENTS AND METHODS**

The study protocol was approved by the Human Subjects Committee of the University of Miami Miller School of Medicine and was conducted according to the tenets of the Declaration of Helsinki. Patients with idiopathic ERM who underwent surgery by one surgeon (WES) between 2008 and 2010 in a university setting were consecutively selected if preoperative and postoperative SD-OCT scans were available. Five patients who had potentially confounding conditions, including branch retinal vein occlusion, previous retinal detachment repair, giant retinal tear, dry age-related macular degeneration, or secondary ERM, were excluded. Surgery consisted of 20-gauge pars plana vitrectomy with ERM peeling in all eyes. Internal limiting membrane peeling was performed at the discretion of the surgeon on a case-by-case basis.

The patients underwent complete ophthalmologic examination including refraction and BCVA using Snellen charts preoperatively and approximately 3 months postoperatively. Patients were included if preoperative and postoperative SD-OCT examinations were available from the same date as the BCVA testing was performed.

All eyes were scanned with an SD-OCT system (Cirrus SD-OCT; Carl Zeiss Meditec, Inc., Dublin, CA). The scanning format included five high-resolution horizontal 6-mm and axial 2-mm B-scans (4,096 A-scans per B-scan) spaced at 250-µm separations (raster). Macular cube (200 × 200 or 512 × 128) scans covering a retinal area of 6 × 6 mm² were performed, yielding retinal three-dimensional surfaces and thickness maps, but only the central 1.5 × 1.0 mm² area was used for volume measurements (Figure 1).

The three-dimensional retinal thickness map, the internal limiting membrane surface map, and the central five-line B-scan raster images were used to categorize each case as nasal dominant (ND), macular dominant (MD), or temporal dominant (TD) based on the epicenter of the directional lines (Figure 2). Cases with components that were located or extended superiorly or inferiorly were characterized by their horizontal location relative to the fovea.

The macula was defined as the central area cube measuring 1,500 (horizontal) × 1,000 (vertical) × 2,000 (axial) µm for calculations in the current study (Figure 1A). Each raw image of the five horizontal B-scan raster was exported as a JPEG file and covered a 6,000 × 2,000 µm area in 750 × 500 pixels. Therefore, the pixel lengths of each side from the fovea by Image J software (NIH image J; National Institutes of Health, Bethesda, MD) were (1,500 × 750 µm/6,000 µm) = 187.5 pixel lengths in the raw image; thus, 94 pixel lengths constituted each side (nasal and temporal) (Figure 1B). Similarly, calculations yielded a fixed conversion factor between real retinal area and pixel area [the conversion factor per pixel was (6,000 × 2,000) / (750 × 500) = 32 µm² or 12,000,000 µm² / 375,000 pixels] (Figure 1B).

The location of the fovea, defined from the raster, was identified as the center of the foveal pit when pre-
Figure 1. Illustration of the area of different layers (inner, middle, and outer) of different sides (nasal and temporal) measured. (A) Macula selection (1,500 × 1,000 µm²) from spectral-domain optical coherence tomography (SD-OCT) fundus image with five 6-mm horizontal B-scans. (B) Each SD-OCT B-scan covered an area of 6,000 × 2,000 µm. Exported raw image of B-scan from commercial SD-OCT covered an area of 750 × 500 pixels. The macula was bisected nasally and temporally and further segmented into inner (1 and 4), middle (2 and 5), and outer (3 and 6) layers. The area of each section was measured in pixels automatically by the software. (C) A three-dimensional prism whose face was the image of each SD-OCT raster section was constructed to calculate the volumes. (D) The depth of each volume prism was set equal to the 250-µm separation of each of the five-line rasters.

Figure 2. Location group categorization defined from the retinal thickness map, three-dimensional retinal thickness map, retinal surface map, and the central B-scan in the five-line raster image obtained from spectral-domain optical coherence tomography. (A) Nasal dominant group. (B) Macular dominant group. (C) Temporal dominant group.
sentenced. If the foveal pit was not well defined due to surface distortion, the center of the zone of photoreceptor thickening was chosen as the foveal center. When the foveal pit was absent and the zone of photoreceptor thickening was not distinct, the center of the scan was defined as the fovea.

The central foveal thickness was measured from the central five-line raster image from the vitreous/ERM or vitreous/nerve fiber layer to the Bruch’s membrane/choroid. The average foveal thickness was calculated by averaging the foveal thickness of the five raster images. The pixel length of thickness was measured automatically by Image J software and was converted to the real retinal thickness by the fixed conversion factor (2,000 μm/500 pixels).

The macular portion of each raster scan was bisected into nasal and temporal segments at the center of the fovea, each measuring 94 pixels (750 μm) horizontally. The nasal and temporal segments were magnified 200% and straightened using Image J software edit-selection-straighten functions (Figure 1B).

Three layers of the retina were defined as follows: inner (from vitreous/ERM or vitreous/nerve fiber layer to outer plexiform layer/outer nuclear layer), middle (from outer plexiform layer/outer nuclear layer to inner/outer segment junction), and outer (from inner/outer segment junction to Bruch’s membrane/choroid). These landmarks were used due to their reproducibly distinct appearances as boundaries. The distinct boundaries of each layer were marked by manually tracing, and the pixel areas of each layer for both the nasal and temporal segments were measured automatically by Image J software (analyze-measure functions) (Figure 1B). Measurements were repeated at an independent sitting. In this manner, six areas were measured for each raster scan. Areas of hyporeflective, black spaces representing macular edema were subtracted. Each area was measured twice, at different sittings, for reliability.

Software to calculate the volumes of each layer for each segment was not available. Hence, volumes were approximated using the Riemann sum of the areas on each raster image multiplied by the 250-μm separation between each raster. For example, the nasal inner layer (NIL) volumes were $\left( \frac{1 \text{ area}_{\text{NIL}} + 2 \text{ area}_{\text{NIL}}}{2} + \frac{2 \text{ area}_{\text{NIL}} + 3 \text{ area}_{\text{NIL}}}{2} + \frac{3 \text{ area}_{\text{NIL}} + 4 \text{ area}_{\text{NIL}}}{2} + \frac{4 \text{ area}_{\text{NIL}} + 5 \text{ area}_{\text{NIL}}}{2} \right) \times 250 \, \mu\text{m}^3$ (1 area$_{\text{NIL}}$, 2 area$_{\text{NIL}}$, 3 area$_{\text{NIL}}$, 4 area$_{\text{NIL}}$, and 5 area$_{\text{NIL}}$ represent the NIL areas in each image of the five-line raster scan). The average volume was calculated using measurements from each of the two independent sittings.

All statistical calculations were performed using SPSS software version 17.0 (SPSS, Inc., Chicago, IL). Intraclass correlation coefficients were used to test the reliability of the two sets of area measurements. Paired t tests were used to compare the preoperative and postoperative central foveal thickness and average foveal

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<th>No. of patients</th>
<th>No. of eyes</th>
<th>Age (y) (mean ± SD)</th>
<th>Gender</th>
<th>Symptoms (%)</th>
<th>Duration (mo) (mean ± SD)</th>
<th>Lens status (%)</th>
<th>BCVA, LogMAR (mean ± SD)</th>
<th>SD-OCT examination</th>
<th>Postoperative follow-up (mo), mean ± SD</th>
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<td>No. of patients</td>
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<td>36</td>
<td>72.19 ± 8.24 (range: 57–89)</td>
<td>16 females/18 males</td>
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<td>8.73 ± 7.60 (range: 25–36)</td>
<td>Phakic = 14 (38.89%)</td>
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SD = standard deviation; VA = visual acuity; PVD = posterior vitreous detachment; ILM = internal limiting membrane; BCVA = best-corrected visual acuity; LogMAR = logarithm of the minimum angle of resolution; SD-OCT = spectral-domain optical coherence tomography.
thickness and the volume differences of the nasal versus the temporal side. Independent t tests were used to compare the volumes of different layers in control and study eyes. BCVA was converted to logarithm of the minimum angle of resolution (LogMAR) for all calculations. The Pearson correlation test was used to analyze the correlations between the LogMAR difference and central foveal thickness difference and average foveal thickness difference and correlations between the LogMAR difference and the volume difference in different layers. P values of less than .05 were considered statistically significant.

### RESULTS

The distribution of categorized cases was ND (10 eyes), MD (13 eyes), and TD (13 eyes). The demographic and clinical characteristics of the 34 patients in the study were similar to other representative clinical series (Table 1). Preoperative BCVA (LogMAR) was 0.50 ± 0.25 and postoperative BCVA (LogMAR) was 0.37 ± 0.20; the BCVA improved postoperatively (P = .007). In addition, the central foveal thickness and average foveal thickness decreased after surgery (P < .001 for both) but did not correlate with LogMAR im-
The volume of the nasal inner layer (NIL) was greater than that of controls both preoperatively and decreased after surgery (3 days before surgery), and postoperative best-corrected visual acuity of 20/80 (4.5 months after surgery). Comparing preoperative and postoperative values, the volume of the nasal inner layer (NIL) decreased from 0.222 to 0.121 mm³, the nasal middle layer (NML) decreased from 0.071 to 0.062 mm³, and the temporal middle layer (TML) decreased from 0.083 to 0.076 mm³. The volume of the nasal outer layer (NOL) increased from 0.055 to 0.059 mm³ and the temporal outer layer (TOL) increased from 0.051 to 0.055 mm³.

The larger volume of the combined middle layers (nasal and temporal) was greater than that of controls both preoperatively and postoperatively (Pr < .001 for both) and decreased after surgery (P = .043). The larger volume of the nasal middle layer (NML) versus controls both preoperatively and postoperatively bordered on statistical significance (P = .090 and .101, respectively) and its decrease after surgery bordered on statistical significance (P = .073). The volume of the temporal middle layer (TML) was greater than that of controls both preoperatively and postoperatively (P = .036 and .302, respectively) and decreased after surgery (P = .003). The volumes of the nasal outer layer (NOL) and temporal outer layer (TOL) were similar in both cases and controls; NOL did not change significantly compared with the control eyes but TOL increased significantly after surgery (P = .046).

The volume of the inner layers taken together (nasal and temporal) was greater than that of controls both preoperatively and postoperatively (P = .001 and .003, respectively) and decreased after surgery (P = .030). The larger volume of the combined middle layers (nasal and temporal) compared to controls both preoperatively and postoperatively was almost statistically significant (P = .059 and .073, respectively) and decreased significantly after surgery (P = .023). The volume of the combined outer layers (nasal and temporal) was not different between cases and controls and did not change after surgery.

In each of the three location groups, the volumes of the NIL and TIL were greater than the corresponding control level both preoperatively and postoperatively, but the other layers including NML, TML,
NOL, and TOL did not change significantly compared with the corresponding control level. The volume of preoperative NML and TML and postoperative TOL was greater than that of controls only in the TD group (\(P = .011, < .001, \) and .048, respectively).

For the ND group, the volume of the NIL and TIL decreased after ERM peeling (\(P = .004\) and .002, respectively) and the decrease of the TIL volume was not significantly different from the NIL volume (\(P = .380\)). The changes in volume of the NML, NOL, TML, and TOL were not significant (Figure 3).

For the MD group, the volume of the NIL and TIL decreased postoperatively (\(P < .001\) for both) and the volume of the TIL decreased more than that of the NIL (\(P = .004\)). The volume of the middle and outer layers in the nasal and temporal segments did not change significantly (Figure 3).

For the TD group, the volume of the NIL and TIL decreased postoperatively (\(P < .001\) for both) and the volume of the TIL decreased more than that of the NIL (\(P = .003\)). In addition, the volume of the TML decreased postoperatively (\(P = .010\)) and more than that of the NML (\(P = .029\)). The volume of the TOL increased significantly after ERM peeling (\(P = .049\)). As in the other location categories, the volume of the NML did not change significantly (Figure 5).

To summarize, the inner segment volumes decreased significantly after surgery collectively and for all three location categories of ERM, and reflected local ERM effects in that the decrease was more on the temporal side for the TD and MD groups than for the ND group; the outer segment volumes increased after ERM peeling, but the increase was significant only for TOL in the TD group.

Improved LogMAR visual acuity correlated with an increase in NOL (\(P = .002\)) and TOL (\(P < .001\)) volumes postoperatively and a decrease in NIL volume postoperatively (\(P = .028\)) (Figure 6). Changes in TIL, NML, and TML volumes did not correlate with improved LogMAR visual acuity.

**DISCUSSION**

It would seem intuitive that the impact of traction secondary to an ERM would likely be better understood by considering it in a three-dimensional context. This would include position and morphologic effects relative to the fovea and on deeper retinal layers where the initial visual event occurs. This study examined volume changes of retinal layers and their possible relationships to anatomic and visual acuity for subgroups of the ERM locations relative to the fovea. The principal findings were that the inner retinal layer volumes decreased postoperatively regardless of the location of the ERM and that the decrease generally correlated to more visual improvement, but more so when the ERM overlaid the same side. Second, an increase in the thickness of the outer layers correlated to better postoperative vision and the increase postoperatively correlated to more visual gain.

Previous investigations have principally studied two-dimensional features such as central retinal thickness or disruptions in external limiting membrane or inner/outer segment junction, finding these most consistently correlate with poor preoperative or postoperative visual acuity. Our study showed that although the central foveal thickness and average foveal thickness decreased
postoperatively, this did not correlate with improvement of BCVA. External limiting membrane and inner/outer segment junction defects in eyes with ERM are not as discrete and quantifiable as for eyes with macular holes, where definite discontinuities have yielded convincing correlations with postoperative vision. 12-15

Previous studies in eyes with ERMs have not evaluated macular volume changes that might be provided by OCT and have not considered the impact of different ERM locations on the retinal layers or for different locations of the ERM focus. Treumer et al. studied the foveal structure and the thickness of individual retinal layers after ERM peeling, but preoperative SD-OCT data to confirm changes in thickness were lacking. 8 Aso et al. found that early postoperative changes in retinal thickness were relatively static with longer follow-up examinations. 3 Michalewski et al. found central retinal thickness, but not cystic changes, to correlate with visual acuity. 3 Faulkner-Radler et al. did not find central retinal thickness and visual acuity to correlate, but baseline distance and near BCVA did correlate with decrease in central retinal thickness postoperatively at 3 months. 10 Kim et al. found central retinal thickness correlated with BCVA and that most changed by 3 months, but some up to 12 months. 21 Oster et al. found central retinal thickness correlated with visual acuity. 16 Mitamura et al. did not find a correlation between central foveal thickness and BCVA. 18 Watanabe et al. found a correlation between inner nuclear layer thickening and metamorphopsia and maximal thickness of the inner and outer nuclear layers and visual acuity loss. 22

The mechanical traction and shear effects from an ERM are commonly a prominent ophthalmoscopic feature, sometimes more prominent than the appearance of the ERM itself. The three-dimensional retinal surface and thickness maps depict effects on retinal architecture more globally (and also more sensitively) than clinical examination and allow better estimates of volumes of various retinal layers. These parameters may be important in understanding the pathophysiology of the ERM’s effects on BCVA and its improvement with surgical removal. Surface traction effects are apparent by OCT imaging as distortion of the inner retinal surface and disappearance of the normal foveal depression. The current study found enlarged inner layer volumes with ERMs and that a postoperative decrease correlated with more vision improvement. The decreased thickness in the current study was not simply attributable to the removal of the space-occupying ERM because the membrane was excluded from measurements. The inner layer thickening decreased even on the opposite side of the fovea from the principal location of the ERM, indicating further reaching shear effects and their partial reversibility. However, it may also hint at adjacent and subadjacent anatomic effects of the ERM on visual function.

Additionally, the current study found that a thickening of the outer retinal layer postoperatively correlated with improved vision. The outer retinal changes are less likely to be due to transmitted mechanical shear forces, and may be more of an indirect physiologic effect because there was a surprising lack of correlation with volume changes in the middle layer. The increased volume might correlate with regeneration or reorganization/restoration of visually important elements, especially photoreceptor outer segments. Outer retinal elements have been the focus of many investigations because of their apparent effect on visual acuity and postoperative improvements. Photoreceptor inner/outer segment junction defects generally correlate with postoperative visual impairment in cases with macular hole, 12-15 and probably to some degree in ERM, 6,10,16-18 and retinal detachment. 19,20 These findings of reconstitution of external limiting membrane or inner/outer segment junction attenuation after ERM removal possibly represent a two-dimensional observation of the same feature the current study demonstrates volumetrically. However, the inner/outer segment junction and the external limiting membrane are not as prominently disrupted with ERMs, even when examined with SD-OCT imaging. Consequently, the volume measurements might be a more detectable surrogate.

A limitation of the current study is that, as with reported two-dimensional metrics, the volume measurements might still be changing even at 3 months postoperatively. However, because visual acuity improvements are usually stabilizing by 6 weeks, the spread from an exact 3-month follow-up time point would not seem to be a serious flaw of the current study. The study was retrospective and as such depended on the availability of imaging studies both preoperatively and postoperatively. The current study evaluated only the central 1.5 \( \times \) 1.0 mm² area because that is the most important determinant of visual acuity and the locus of the most exact SD-OCT data. It is plausible that examining a broader area might yield additional insights. Although
this study represents a larger one than in the previous literature, a larger data set might allow more conclusive correlations.

This study has demonstrated that although the most prominent changes induced by the directional traction from an ERM are measurable in the inner retina, visual acuity results were more tightly correlated with changes in the volumes of the outer retina and nasal inner retina. The inner retina decreased in volume regardless of the dominant location of the ERM or visual acuity improvement, probably reflecting improvement in the mechanical deformation, whereas the visual acuity improvement was more correlated with the restoration of outer retinal volume. These results support the paradigm that the normalization of the appearance of the macula is most determined by the anatomy of the inner retina and the functional qualities of the macula are more dependent on the integrity of the outer retinal elements.

REFERENCES