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·Clinical Research·

Reflectivity and thickness analysis of epiretinal membranes using spectral-domain optical coherence tomography

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Abstract

• AIM: To compare thickness and reflectivity spectral domain optical coherence tomography (SD-OCT) findings in patients with idiopathic epiretinal membranes (ERMs), before and after ERM peeling surgery, with normal controls.

• METHODS: A retrospective study analyzing SD-OCTs of eyes with ERMs undergoing ERM peeling surgery by one surgeon from 2008 to 2010 and normal control eyes. SD-OCTs were analyzed using a customized algorithm to measure reflectivity and thickness. The relationship between the SD-OCT findings and best corrected visual acuity (BCVA) outcomes was also studied.

• RESULTS: Thirty-four ERM eyes and 12 normal eyes were identified. Preoperative eyes had high reflectivity and thickness of the group of layers from the internal limiting membrane (ILM) to the retinal pigment epithelium (RPE) and the group of layers from the ILM to the external limiting membrane (ELM). The values of reflectivity of these two groups of layers decreased postoperatively, but were still higher than normal eyes. In contrast, preoperative eyes had lower reflectivity of two 10×15 pixel regions of interest (ROIs) incorporating: 1) ELM + outer nuclear layer (ONL) and 2) photoreceptor layer (PRL) + RPE, compared to controls. The values of reflectivity of these ROIs increased postoperatively, but were still lower than normal controls. A larger improvement in BCVA postoperatively was correlated with a greater degree of abnormal preoperative reflectivity and thickness findings.

• CONCLUSION: Quantitative differences in reflectivity and thickness between preoperative, postoperative, and normal SD-OCTs allow assessment of changes in the retina secondary to ERM. Our study identified hyperreflective inner retina changes and hyporeflective outer retina changes in patients with ERMs. SD-OCT quantitative measures of reflectivity and/or thickness of specific groups of retinal layers and/or ROIs correlate with improvement in BCVA.

• KEYWORDS: epiretinal membranes; optical coherence tomography; reflectivity; retina; imaging; vitrectomy

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INTRODUCTION

Idiopathic epiretinal membranes (ERMs) are found in approximately 6% of the population, although the majority do not cause substantial visual loss [1]. ERMs are comprised of several different cell types, some of which have myofibroblastic properties, which can result in traction on the retina [2-4]. ERM-induced traction may cause symptoms of metamorphopsia, monocular diplopia, and decreased visual acuity [5]. Surgical ERM peeling relieves the retinal traction and often alleviates symptoms in selected patients[5-9].

Spectral-domain optical coherence tomography (SD-OCT) demonstrates the ERM-induced tractional effect on the retina, and changes in these effects consequent to ERM peeling[10-13]. Previous SD-OCT studies of ERMs have focused on morphological features of the outer retina, especially those that depict photoreceptor cell integrity such as the external limiting membrane (ELM), ellipsoid zone (EZ), or changes in the thickness/volume of various retinal layers[10-18].

In addition to the providing high resolution images of the retina and thickness data, optical coherence tomography (OCT) can be used to analyze the optical properties of the retina, by quantitatively measuring reflectivity[19]. Reflectivity, the basis for generating the OCT image itself, is the quantitation of the backreflection of the incident light source and likely provides information inherent in the structural arrangement of the tissues. Studying the effects of diseases on the reflectivity of the retina can provide additional information about cellular damage which are not captured by morphologic or thickness parameters[19-20]. Such analysis of retinal reflectivity allowed a better discriminating power than thickness analysis between mild diabetic retinopathy and normal eyes[20].

The purpose of this study was to compare thickness, and reflectivity SD-OCT findings in patients with idiopathic ERMs (before and after ERM peeling surgery) with normal controls. Additionally, the relationship of these SD-OCT findings and visual acuity was assessed.

SUBJECTS AND METHODS

The study protocol to review retrospectively medical records and SD-OCTs of patients with ERMs was approved by the Medical Sciences Subcommittee for the Protection of Human Subjects of the Institutional Review Board of the University of Miami Miller School of Medicine. Consecutive patients with ERMs with no other retinal disease who underwent surgery by one surgeon (Smiddy WE) at the Bascom Palmer Eye Institute between 2008 and 2010 with preoperative and approximately three month (10 to 14wk) postoperative SD-OCT scans were identified [13]. All patients underwent 20-gauge pars plana vitrectomy with ERM peeling; internal limiting membrane (ILM) peeling was performed at the discretion of the surgeon. Twelve normal SD-OCTs were identified among the study subjects' fellow eye for comparison.

All patients had ophthalmologic examinations, including best corrected visual acuity (BCVA) using Snellen charts preoperatively and approximately three months postoperatively (the same date the postoperative SD-OCT was performed)[13]. Patients who underwent cataract extraction between the preoperative and postoperative SD-OCT were excluded. All eyes were scanned with the Cirrus SD-OCT system (Carl Zeiss Meditec, Inc., Dublin, CA, USA). The scanning format included five high- resolution horizontal 6-mm and axial 2-mm B-scans (4096 A-scans per B-scan) spaced at 250-µm separations (raster).

A customized algorithm written in Matlab (Mathworks, Inc., Natick, MA, USA) was used to assess average reflectivity (decibels, dB) and thickness (µm) of the central 1500 µm of the five horizontal raster SD-OCT scans of the group of layers from the ILM to the outer border of the retinal pigment epithelium (RPE; Figure 1A) and the group of layers from the ILM to the outer border of the ELM (Figure 1B). Hyporeflective findings of the photoreceptor layer (PRL) and ELM were not able to be discerned by analyzing the reflectivity of the group of layers from the ILM to RPE, because hyperreflectivity of inner retinal structures dominated measurements, outweighing outer retinal hyporeflectivity findings. Therefore, two regions of interest (ROIs) were selected to allow focal analysis of outer layers. The ROIs were selected as central 10×15 pixel areas to encompass 1) the ELM + outer nuclear layer (ONL) and 2) the PRL + RPE for focal reflectivity analysis (Figure 1).

Reflectivity measurements were calculated across 5 raster scans after blood vessel shadows were identified and digitally subtracted, as previously described [21-22]. The reflectivities of the group of retinal layers and ROIs described above were calculated using a ratio of measured reflectivity per A-scan to the saturation reflectivity of each image (B-scan) and then normalized to the RPE reflectivity [20-21,23]. Normalized reflectivity values were then converted to decibels [dB=10×log (reflectivity)] [20]. The image processing and diagnostic parameter calculations were programmed in Matlab 7.0 (The Mathworks, Natick, Massachusetts, USA).

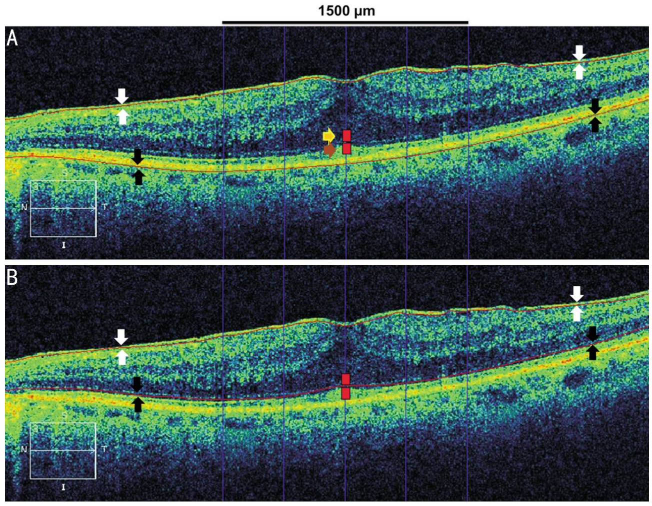

Figure 1 Image of customized OCT analysis algorithm software The five raster images of the SD-OCT of preoperative patients with ERMs, postoperative patients with ERMs, and normal patients were analyzed using a customized algorithm. A: The segmentation of the ILM (red line) is marked by the white arrows. The segmentation of the RPE (red line) is marked by the black arrows. The 10×15 pixel ROI encompassing the central outer nuclear layer and ELM (top red rectangle) is marked by the yellow arrow. The 10×15 pixel ROI encompassing the central photoreceptor layer RPE (bottom red rectangle) is marked by the orange arrow. B: The segmentation of the ILM (red line) is marked by the white arrows. The segmentation of the ELM (red line) is marked by the black arrows.

Statistical analyses were performed using Statistical Package for the Social Sciences software version 17.0 (SPSS Inc., Chicago, Illinois, USA). Snellen VA was converted to logarithm of minimal angle of resolution (logMAR) equivalents. The mean SD-OCT reflectivity and thickness parameters were compared between preoperative, postoperative, and normal eyes using ANOVA. The Pearson correlation test was used to analyze the relationship between the SD-OCT thickness and reflectivity parameters and postoperative BCVA and change in preoperative and postoperative BCVA. Intraclass correlation analysis was performed to assess reproducibility. P values less than 0.05 were considered statistically significant.

RESULTS

Patient Demographics The study cohort consisted of 34 consecutive eyes with idiopathic ERMs (32 patients, Table 1). The mean logMAR BCVA improved from 0.54±0.31 (Snellen VA equivalent approximately 20/69) preoperatively to

Table 1 Demographic and visual acuity data of patients with epiretinal membranes and control patients

Demographic/visual acuity	ERM	Control
Number of Eyes	34 (32 patients)	12
Age (a, $\bar{x}\pm s$)[a]	71.5±8.2	66.8±10.7
Gender	16 F/16 M	7 F/5 M
Preoperative BCVA (mean logMAR±SD)	0.54±0.31	0.05±0.07
Postoperative BCVA (mean logMAR±SD)	0.40±0.25[b]	

BCVA: Best corrected visual acuity; ERM: Epiretinal membrane; logMAR: Logarithm of minimal angle of resolution; SD: Standard deviation. [a]No difference in age between normal and patients with ERM (*P*=0.123, independent *t*-test); [b]Improvement of postoperative BCVA from preoperative BCVA (*P*=0.030, paired *t*-test).

0.40 ±0.25 (Snellen VA equivalent approximately 20/50) postoperatively (*P* =0.021). The mean logMAR BCVA of the 12 normal fellow eyes was 0.05 ±0.07 (Snellen VA equivalent approximately 20/22). The gender and age distributions were similar between study and control eyes.

Reproducibility of the Customized Spectral -Domain Optical Coherence Tomography Analysis Algorithm All SD-OCT scans of preoperative, postoperative and normal eyes were analyzed twice using the customized algorithm. The intraclass correlation was >95% for all analyzed parameters.

Changes in Spectral -Domain Optical Coherence Tomography Retinal Thickness and Retinal Reflectivity in the Group of Layers The thickness and reflectivities of the group of layers from ILM to RPE and group of layers from ILM to ELM were determined for all SD-OCTs and compared between preoperative, postoperative and normal eyes (Table 2). The mean thickness of the group of layers from ILM to RPE was larger in preoperative eyes (246.55±40.64 μm) than in postoperative eyes (203.28±28.39 μm, *P*<0.001) and normal eyes (162.95 ±9.46 μm, *P* <0.001). The mean thickness of the group of layers from ILM to RPE in postoperative eyes was also larger than in normal eyes (*P*= 0.005). The mean thickness of the group of layers from ILM to ELM was larger in preoperative eyes (202.09±39.73 μm) than in postoperative eyes (158.00±28.85 μm, *P*<0.001) and normal eyes (122.83±9.93 μm, *P*<0.001). The mean thickness of the group of layers from ILM to ELM in postoperative eyes was also larger than in normal eyes (*P*=0.004).

The mean reflectivities of the group of layers from ILM to RPE was higher in preoperative eyes (79.17±4.66 dB) than in postoperative eyes (76.13±4.91 dB, *P* =0.024) and normal eyes (74.67±3.74 dB, *P* =0.014). The mean reflectivity of the group of layers from ILM to RPE in postoperative eyes was not different than in normal eyes (*P* =0.617). The mean reflectivity of the group of layers from ILM to ELM was higher in preoperative eyes (41.06 ±11.53 dB) than in postoperative eyes (33.67±11.16 dB, *P* =0.021) and normal eyes (30.99±8.23 dB, *P* =0.018). The mean reflectivity of the group of layers from ILM to ELM in postoperative ERM eyes was not different than in normal eyes (*P* =0.748).

Changes in Spectral -Domain Optical Coherence Tomography Retinal Reflectivity in Outer Retinal Regions of Interest The reflectivities of central 10×15 pixel ROIs encompassing the ELM+ONL and encompassing the PRL + RPE were determined for all SD-OCTs and compared between preoperative, postoperative and normal eyes (Table 2). The mean reflectivity in the ROIs encompassing the ONL+ELM in preoperative eyes (3.88 ±1.51 dB) and postoperative eyes (4.49±1.45 dB) were lower than in normal eyes (5.96±1.87 dB, *P* <0.001 and *P* =0.016, respectively). The mean reflectivity in the ROI encompassing the ONL+ELM in preoperative eyes was not different than in postoperative eyes (*P* =0.238).

The mean reflectivity in the ROI encompassing the PRL + RPE in preoperative eyes (7.55±1.76 dB) was lower than in normal eyes (9.12±0.95 dB, *P* =0.008).The mean reflectivity in the ROI encompassing the PRL + RPE in postoperative eyes (8.16±1.43 dB) was not different than in preoperative or normal eyes (*P* =0.229 and 0.155, respectively).

Correlation of Preoperative Spectral -Domain Optical Coherence Tomography Retinal Reflectivity and Thickness Parameters with Postoperative Best Corrected Visual Acuity and Improvement in Best Corrected Visual Acuity Higher reflectivity of the group of layers from ILM to ELM on preoperative SD-OCT scans was correlated with better postoperative BCVA (*r* =-0.369, *P*=0.032; Table 3). A larger improvement in postoperative BCVA from preoperative BCVA was correlated with thicker measurements of the preoperative group of layers from ILM to RPE (*r* =0.449, *P* =0.008; Table 4) and the group of layers from ILM to ELM(*r* =0.484, *P* =0.004; Table 4). Additionally, a larger improvement in BCVA was correlated with higher preoperative reflectivity of the group of layers from ILM to ELM (*r*=0.439, *P*=0.009), and a lower reflectivity in the ROI encompassing the PRL + RPE (*r*=-0.342, *P* =0.048; Table 4).

DISCUSSION

This study demonstrates that reflectivity analysis using SD-OCT provides a quantitative method to assess changes in the retina due to ERMs preoperatively and postoperatively. The reflectivity and thickness of the group of layers from ILM to RPE and from ILM to ELM are high in preoperative eyes, and decrease postoperatively, but remain higher than in normal eyes (Table 2). In contrast, the ROIs in the outer retina (ELM + ONL and PRL + RPE) have lower reflectivity in preoperative eyes compared to the postoperative eyes, but retain lower reflectivity than in normal eyes (Table 2).

OCT uses low coherence optical interferometry to produce an image based on backreflection from tissue microstructures[24-25]. Normal retina OCTs have reproducible and predictable hypo-

Table 2 Comparison between optical coherence tomography parameters for preoperative patients with epiretinal membranes, postoperative patients with epiretinal membranes, and normal patients $\bar{x} \pm s$

OCT parameters	Preop.	Postop.	Control	P^a	Interpretation
Thickness ILM to RPE (μm)	246.55±40.64	203.28±28.39	162.95±9.46	^1P<0.001, ^2P<0.001, ^3P=0.005	Preop. ERM>postop. ERM>normal
Total reflectivity ILM to RPE (dB)	79.17±4.66	76.13±4.91	74.67±3.74	^1P=0.024, ^2P=0.014, ^3P=0.617	Preop. ERM>postop. ERM>normal
Thickness ILM to ELM (μm)	202.09±39.73	158.00±28.85	122.83±9.93	^1P<0.001, ^2P<0.001, ^3P=0.004	Preop. ERM>postop. ERM>normal
Total reflectivity ILM to ELM (dB)	41.06±11.53	33.67±11.16	30.99±8.23	^1P=0.021, ^2P=0.018, ^3P=0.748	Preop. ERM>postop. ERM>normal
Region of interest ELM+ONL (dB)	3.88±1.51	4.49±1.45	5.96±1.87	^1P=0.238, ^2P<0.001, ^3P=0.016	Preop. ERM<postop. ERM<normal
Region of interest PRL+RPE (dB)	7.55±1.76	8.16±1.43	9.12±0.95	^1P=0.229, ^2P=0.008, ^3P=0.155	Preop. ERM<postop. ERM<normal
Thickness ILM to RPE (μm)	246.55±40.64	203.28±28.39	162.95±9.46	^1P=0.000, ^2P<0.001, ^3P=0.005	Preop. ERM>postop. ERM>normal

dB: Decibel; ELM: External limiting membrane; ERM: Epiretinal membrane; ILM: Internal limiting membrane; ONL: Outer nuclear layer; Preop: Preoperative; Postop: Postoperative; PRL: Photoreceptor layer; SD-OCT: Spectral-domain optical coherence tomography; RPE: Retinal pigment epithelium. [a]ANOVA test; [1]Comparison between preoperative values of patients with ERMs and postoperative values of patients with ERMs; [2]Comparison between preoperative values of patients with ERMs and values of control patients; [3]Comparison between values of postoperative patients with ERMs and values of control patients.

Table 3 Correlation between optical coherence tomography parameters of preoperative patients with epiretinal membranes and postoperative visual acuity

Preoperative ERM OCT parameters	Correlation with postoperative BCVA (logMAR)	P^a	SD-OCT parameter	Postoperative BCVA
Thickness ILM to RPE (μm)	-0.170	0.335	NS	NS
Total reflectivity ILM to RPE (dB)	-0.276	0.114	NS	NS
Thickness ILM to ELM (μm)	-0.162	0.359	NS	NS
Total reflectivity ILM to ELM (dB)	-0.369	0.032	Higher reflectivity	Better postoperative BCVA
Region of interest ELM+ONL (dB)	-0.144	0.416	NS	NS
Region of interest PRL+RPE (dB)	-0.013	0.941	NS	NS

BCVA: Best corrected visual acuity; dB: Decibel; ELM: External limiting membrane; ERM: Epiretinal membrane; ILM: Internal limiting membrane; logMAR: Logarithm of minimal angle of resolution; NS: Non-significant; SD-OCT: Spectral-domain optical coherence tomography; ONL: Outer nuclear layer; PRL: Photoreceptor layer; RPE: Retinal pigment epithelium. [a]Pearson correlation test.

Table 4 Correlation between optical coherence tomography parameters of preoperative patients with epiretinal membranes and change in visual acuity

Preoperative ERM OCT parameters	Correlation with BCVA improvement (logMAR)	P^a	SD-OCT parameter	Improvement in BCVA
Thickness ILM to RPE (μm)	0.449	0.008	Increased thickness	Larger improvement in postoperative BCVA
Total reflectivity ILM to RPE (dB)	0.209	0.236	NS	NS
Thickness ILM to ELM (μm)	0.484	0.004	Increased thickness	Larger improvement in postoperative BCVA
Total reflectivity ILM to ELM (dB)	0.439	0.009	Higher reflectivity	Larger improvement in postoperative BCVA
Region of interest ELM+ONL (dB)	-0.028	0.877	NS	NS
Region of interest PRL+RPE (dB)	-0.342	0.048	Lower reflectivity	Larger improvement in postoperative BCVA

BCVA: Best corrected visual acuity; dB: Decibel; ELM: External limiting membrane; ERM: Epiretinal membrane; ILM: Internal limiting membrane; logMAR: Logarithm of minimal angle of resolution; NS: Non-significant; SD-OCT: Spectral-domain optical coherence tomography; ONL: Outer nuclear layer; PRL: Photoreceptor layer; RPE: Retinal pigment epithelium. [a]Pearson correlation test.

and hyperreflective layers corresponding to the cellular makeup and boundaries of the different retinal layers. Since the optical properties of the tissue can change due to disease, studying reflectivity may allow insights into disease or therapeutic effects. Changes in the reflectivity of the retina have been described in several disease states, including diabetic retinopathy, macular edema, and multiple sclerosis[20,26-28].

The findings in this study suggest that while ERMs increase the overall reflectivity of the retina OCT, presumably due to increased inner retina tissue disorganization, the outer retina ROIs were less reflective, presumably due to loss of border structures. Although cystoid spaces are hyporeflective, the diffuse inner retinal hyperreflective findings in patients with ERMs outweigh the focal hyporeflective findings of cystoid spaces in the measurement of reflectivity in the group of layers from the ILM to the ELM (Figure 2). The outer retina ROIs hyporeflectivity in preoperative patients with ERMs is consistent with findings of previous studies demonstrating outer retinal damage (*e.g.* EZ and ELM disruption)[10,17-18,29-30]. The partial restoration of both the inner and outer retinal reflectivity properties suggests a parallel with anatomic restoration following removal of ERM effects.

Previous studies examining the relationship between BCVA and morphologic SD-OCT findings and retinal thickness have produced conflicting results[10-18,29-30]. Thus, parameters such as reflectivity might offer a more consistent and quantitative metric. Higher preoperative reflectivity of the layers from ILM to ELM (compared to normal eyes) was correlated with better postoperative BCVA (Table 3). One potential explanation for this finding is that preoperative hyporeflectivity of the section from ILM to ELM occurs due to atrophy, accounting for poor postoperative BCVA (Figure 3). Higher reflectivity of the layers from ILM to ELM and lower reflectivity of the outer retina ROIs (compared to normal eyes) was correlated with a larger improvement (Table 4). A possible explanation is that the degree of abnormal SD-OCT parameters correlated with poorer BCVA which, in turn, provides more potential for gains in BCVA.

A limitation of our study method is the possibility of a sampling error inherent in the ROI methodology. Although the area analyzed in the ROI was limited to a 10×15 pixel region in the center of the SD-OCT scan, we took care to select representative regions by choosing a standard point at the foveal center of each scan. In this study we used the ROI data to provide valuable information about the contrasting reflectivity changes between the outer retina and the inner retina, which was not able to be obtained by measuring the reflectivities of the group of layers from the ILM to RPE and ILM to ELM. Another limitation is the relatively short follow-up interval for the patients in the study. Postoperative SD-OCT reflectivity and thickness might improve more towards normal with longer term follow-up imaging. A strength of the study is that reflectivity normalization was implemented to take into account differences in reflectivity factors extrinsic to the retina, such as media opacity, poor focusing, and scanning pitfalls, and factors intrinsic to the retina, such as inner retina hyperreflectivity resulting in shadowing artifact, before assessing variability in study eyes.

Although reflectivity of the retinal tissue is not conventionally used to detect pathological changes, reflectivity-based measures are direct measures obtained from OCT images. Therefore, reflectivity measurements, along with thickness, could facilitate a better understanding of retinal diseases. This study is the first to measure quantitative differences in reflectivity of SD-OCTs between patients with ERMs (both preoperative and postoperative) and normal patients. Reflectivity and thickness data of groups of retinal layers and focal regions of the retina provide quantitative methods to measure changes in the retina

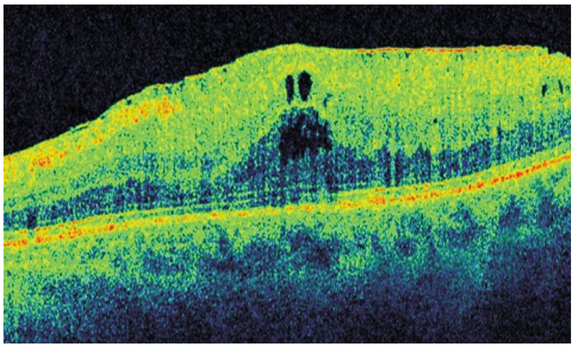

Figure 2 Spectral-domain optical coherence tomography illustrating hypereflective inner retinal findings and hyporeflective cystoid spaces This is an example of a SD-OCT image of a preoperative patient with an epiretinal membrane and diffuse inner retinal hyperreflective findings in a patient which outweighs the focal hyporeflective findings of cystoid spaces in the measurement of mean reflectivity in the group of layers from the inner limiting membrane to the external limiting membrane.

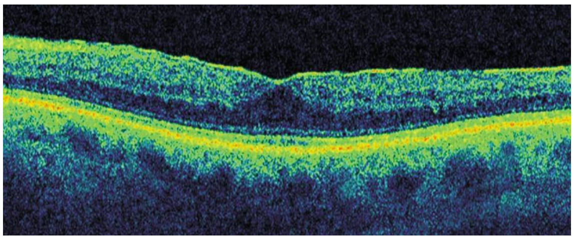

Figure 3 Spectral-domain optical coherence tomography illustrating hyporeflective preoperative findings This is an example of a SD-OCT image of a preoperative patient with an epiretinal membrane and hyporeflective inner limiting membrane to external limiting membrane. Additionally, the retina is thin, suggesting retinal atrophy.

secondary to ERMs, or other macular disorders. These measurements may provide data that augment morphologic assessment of OCTs in patients with ERMs. Our study identified differing changes in reflectivity due to ERMs in the inner and outer retina. Specific reflectivity and thickness values correlate with BCVA, postoperative BCVA, and improvement in BCVA. Future versions of the algorithm that enable additional segmentation of the retinal layers may provide additional data about differing changes in reflectivity and thickness due to ERMs and the relationship between BCVA.

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Conflicts of Interest: Kuriyan AE, None; **DeBuc DC,** Holds a pending patent used in the study and has the potential for financial benefit from its future commercialization; **Simddy WE,** None.

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