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Short Communication

Preoperative and postoperative features of macular holes on en face imaging and optical coherence tomography angiography

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ABSTRACT

Purpose: To characterize and quantify the pre- and postoperative foveal structural and functional patterns in full-thickness macular holes.
Methods: Subjects presenting with a full-thickness macular hole that had pre- and postoperative imaging were included. En face optical coherence tomography (OCT) and OCT angiography (OCTA) was performed. Foveal avascular zone (FAZ) area, macular hole size, number and size of perifoveal cysts were measured.
Results: Five eyes from 5 patients were included in the study. The hole was closed in all eyes after the initial surgery. OCTA showed enlargement of the FAZ and delineation of the holes within the FAZ. Mean preoperative FAZ area was 0.41 ± 0.104 mm^2. Visual acuity was improved and mean FAZ area was reduced to 0.27 ± 0.098 mm^2 postoperatively ($P < 0.05$) with resolution of the macular hole and adjacent cystic areas. En face images of the middle retina showed a range of preoperative cystic patterns surrounding the hole. Smaller holes showed fewer but larger cystic areas and larger holes had more numerous but smaller cystic areas.
Conclusions and Importance: Quantitative evaluation of vascular and cystic changes following macular hole repair demonstrates the potential for recovery due to neuronal and vascular plasticity. Perifoveal microstructural patterns and their quantitative characteristics may serve as useful anatomic biomarkers for assessment of macular holes.

1. Introduction

The foveal microstructure of macular holes has been extensively investigated using spectral-domain optical coherence tomography (SD-OCT). Most studies in this regard have utilized cross-sectional imaging analysis of the retinal layers, implicating the external limiting membrane,[1,2] ellipsoid zone,[3,4] interdigitation zone of the photoreceptors,[5] and the photoreceptor outer segment integrity[6] on preoperative visual function and postoperative visual outcome after surgical hole closure.

Recent advancements in image acquisition and processing provide the ability to use en face projections of volumetric data obtained by SD-OCT, allowing for simultaneous assessment of structural and functional (blood flow) information. Such en face images have recently been used to characterize full-thickness macular holes as well as the perifoveal hyporeflective intraretinal spaces observed surrounding them. Matet et al.[7] showed a marked concordance between en face OCT images of perifoveal cysts in full-thickness macular holes and histology of flat-mounted retinas, demonstrating the paramount contribution of Müller cells to macular microstructure. How subsequent pars plana vitrectomy and macular surgery affects these cystic areas and the underlying foveal retinal vasculature has not been reported to date.

OCT angiography (OCTA) is a novel imaging platform that utilizes motion contrast to visualize macular microvascular perfusion in a rapid, non-invasive, and depth-resolved fashion. Co-registration of structural en face projections of corresponding retinal layers is also performed with micrometer scale depth resolution. This offers the potential to perform quantitative assessment. New OCTA findings have been reported in a variety of fundus abnormalities.[8–11] The purpose of this report was to characterize and quantify the pre- and postoperative foveal structural and functional patterns in eyes with a full-thickness macular hole.

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2. Methods

Institutional review board approval was obtained through the Wills Eye Hospital (Philadelphia, PA) for a retrospective nonconsecutive interventional case series. Research adhered to the tenets of the Declaration of Helsinki and was conducted in accordance with regulations set forth by the Health Insurance Portability and Accountability Act (HIPAA).

2.1. Study subjects

Patients presenting with an idiopathic full-thickness macular hole that had pre- and postoperative imaging were included in the study. These eyes had been imaged between March 2015 and September 2015 at the Retina Service of Wills Eye Hospital. Cases with poor image quality, or any other concurrent macular disorder (such as epiretinal membrane, choroidal neovascularization, macular atrophy, macular edema), were excluded. All patients had been evaluated with comprehensive ophthalmologic examination including full medical history, best-corrected visual acuity (BCVA) testing, slit-lamp biomicroscopy, and funduscopy. A standard three-port 23-gauge pars plana vitrectomy, indocyanine green staining, internal limiting membrane peeling, and gas-fluid exchange with SF_6 was performed in all cases.

2.2. Imaging

A commercial SD-OCT system (RTVue-XR Avanti, Optovue, Fremont, CA) was used for imaging. All images were acquired over a 3 × 3 mm region centered on the macula with 304 raster B-scans obtained through each dimension.

Using this volumetric information, the retinal layers were automatically segmented between the internal limiting membrane (ILM) and the retinal pigment epithelium. Built-in software offset settings (version 2015.100.0.35) were used for this purpose. The boundaries for superficial network were from 3 μm below the ILM to 15 μm below the inner plexiform layer (IPL). The deep capillary network boundaries extended from 15 to 70 μm below the IPL. The split-spectrum amplitude-decorrelation angiography (SSADA) algorithm was used to generate flow information by computing inter-B-scan decorrelation from two consecutive raster B-scans performed at each location. En face structural and OCTA images were co-registered between the segmentation lines.

2.3. Image processing

Calculation of foveal avascular zone (FAZ) area was performed on the superficial retinal OCTA slab using the non-flow function of the imaging software (Fig. 1A and B). Quantification of cystic areas was performed semi-automatically from structural en face images acquired from the deep retinal slab. The public domain ImageJ software, version 1.49 (National Institutes of Health, Bethesda, MD) was used for this purpose. Following conversion to 8-bit grayscale images, hyporeflective spaces were identified via the auto threshold v1.15 function using the “minimum thresholding” method. The identified areas were then highlighted on the original image and “particle analysis” was used to calculate the number of hyporeflective spaces and their area (Fig. 1C and D). In order to reduce noise, an area of greater than 0.001 mm^2 was set as the threshold for inclusion in particle analysis calculations. SPSS, Version 20 (SPSS, Inc., Chicago, IL) was used for statistical analysis. Significance level was set at $P < 0.05$ for performing comparisons.

3. Results

Five eyes from 5 patients presenting with a full-thickness macular hole were included in the study. The hole was closed in all eyes after the initial surgery as demonstrated by structural volumetric scans (Fig. 2). En face structural imaging demonstrated hyporeflective areas corresponding to the hole and surrounding cystic areas that were best visualized on the deep retinal slab obtained just below the inner plexiform layer. Co-registered OCTA images showed enlargement of the FAZ and flow void in the areas with cystic changes. These cystic areas could clearly be delineated due to lack of the background noise that was otherwise present in the non-flow areas of the OCTA images (Fig. 3). Postoperative imaging was performed at a mean of 70 (range 56–91) days following surgery. Comparing pre- and postoperative images showed resolution of the cystic structures along with a decrease in superficial and deep FAZ size demonstrating preserved macular blood flow (Fig. 4).

The baseline, clinical, and imaging characteristics of the patients are presented in Fig. 5. OCTA images of the superficial vascular network showed enlargement of the FAZ and delineation of the holes within the FAZ. Mean preoperative FAZ area was 0.41 ± 0.104 mm^2. Visual acuity was improved and FAZ area was reduced to 0.27 ± 0.098 mm^2 postoperatively in all cases ($P < 0.05$) with resolution of the macular hole and adjacent cystic areas. En face images of the middle retina showed the preoperative cystic areas surrounding the hole in all cases. These appeared as different patterns ranging from larger, regular, and well-defined radial cystic areas with a petaloid or “grapefruit” configuration (Patient 1) to smaller, more dispersed cystic areas with a “sponge-like” appearance (Patient 5). The cross-sectional areas of the macular hole, cumulative area of the cystic spaces, and number of cystic areas appearing on the deep retinal slab were calculated using the automated algorithm previously described. Fig. 5 demonstrates increasing hole area from patient 1 through 5. As such, smaller holes showed fewer but larger cystic areas and larger holes had more numerous but smaller cystic areas.

4. Discussion

Evolving technologies such as en face OCT and adaptive optics have helped expand our understanding of the foveal ultrastructural changes that occur during macular hole formation and following surgery, as well as the impact of these changes on functional vision. With its improved acquisition speed and sensitivity, SD-OCT allows for three-dimensional (3D) imaging of the macular area. This form of volumetric imaging is clinically useful both for the physician and also for patient education. Previous studies on 3D imaging have demonstrated the ability to visualize intraretinal microstructures in consecutive orthogonal cross-sectional and sectioned volume images.[12] This enables for much more precise and minute observations of structural changes associated with macular holes than conventional OCT imaging. Furthermore, the volumetric data obtained allows for comprehensive measurement of retinal layer thickness. Novel image processing algorithms such as SSADA also enable simultaneous characterization of blood flow using OCTA.

Using OCTA, we demonstrated enlargement of the FAZ in eyes with full-thickness macular hole prior to surgical intervention. OCTA has recently been shown to measure FAZ area in healthy subjects in a reproducible and reliable manner,[13,14] especially when obtained at the level of the superficial vascular network.[14] We found that the mean FAZ area in our patients was larger compared to prior studies with healthy individuals, which showed mean

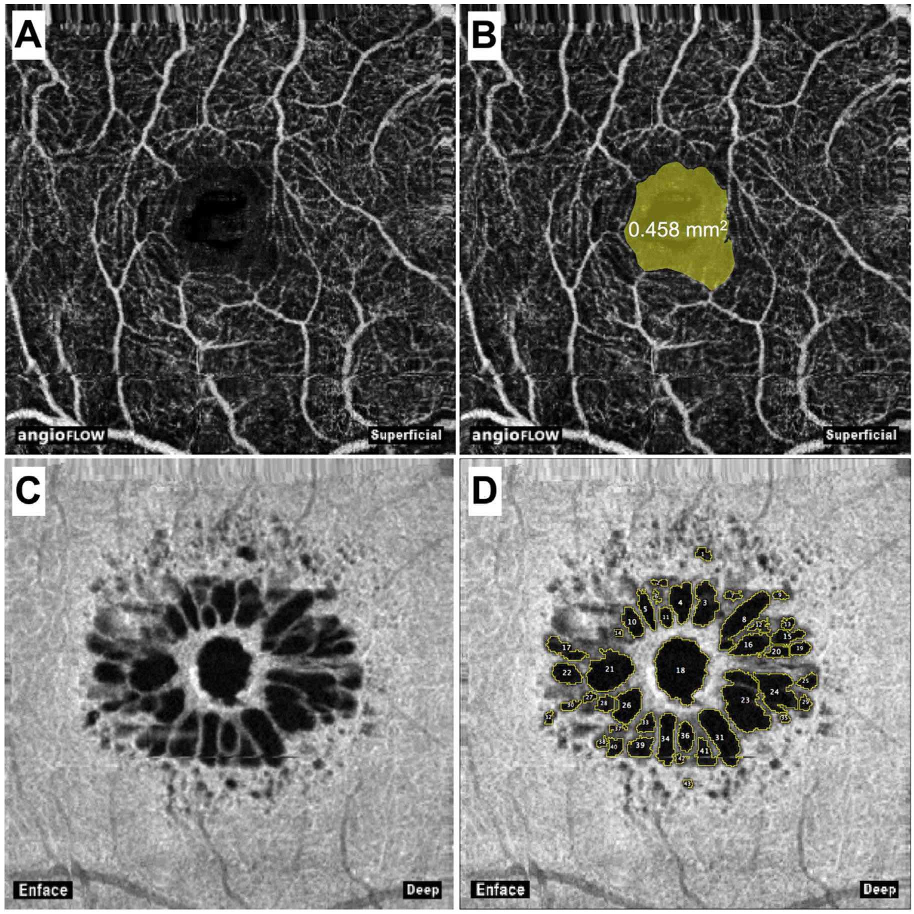


Fig. 1. Superficial capillary network of a patient with macular hole showing enlargement of the foveal avascular zone (A,B). En face structural optical coherence tomography image of the middle retina demonstrates multiple hyporeflective spaces reflecting the macular hole and surrounding cystic areas (C). These spaces have been outlined and quantified (D).

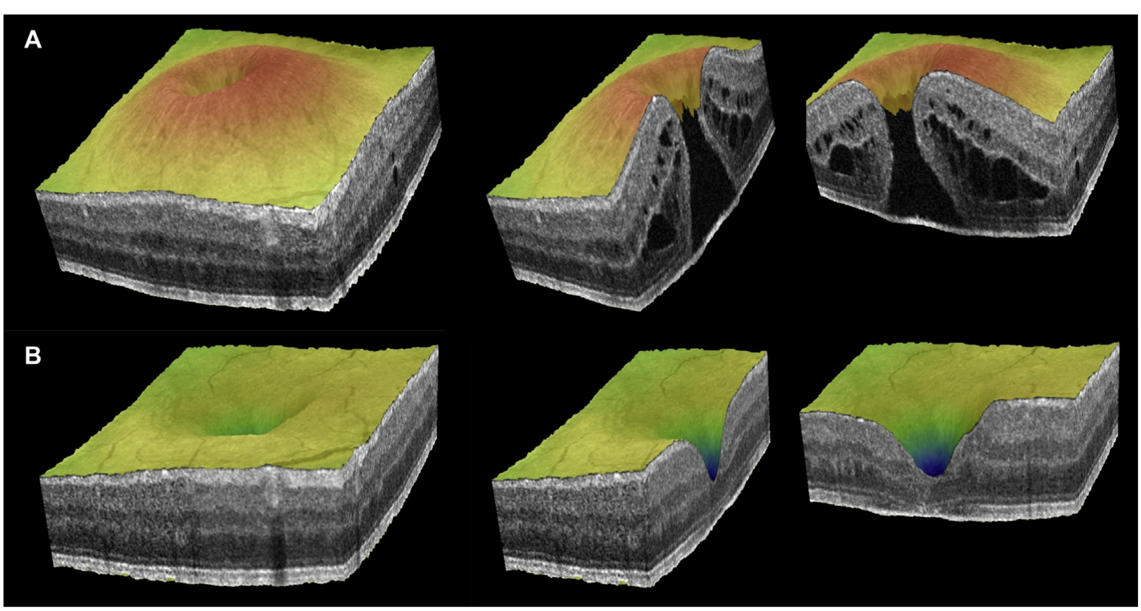


Fig. 2. Volumetric structural optical coherence tomography scan of a macular hole on baseline preoperative (A) and two-month postoperative (B) visits. The relative thickness has been projected onto a color map on the surface of each cube scan. X- and Y-axis cross sectional scans through the fovea have been obtained demonstrating structural characteristics and changes to the hole.

values of 0.251 ± 0.096 mm^2 (average age, 28.9 years),[13] 0.266 ± 0.097 mm^2 (42 years),[15] and 0.27 ± 0.101 mm^2 (38 years).[14] Since the macular hole falls within the FAZ, it presumably causes an apparent expansion or enlargement. Another possible

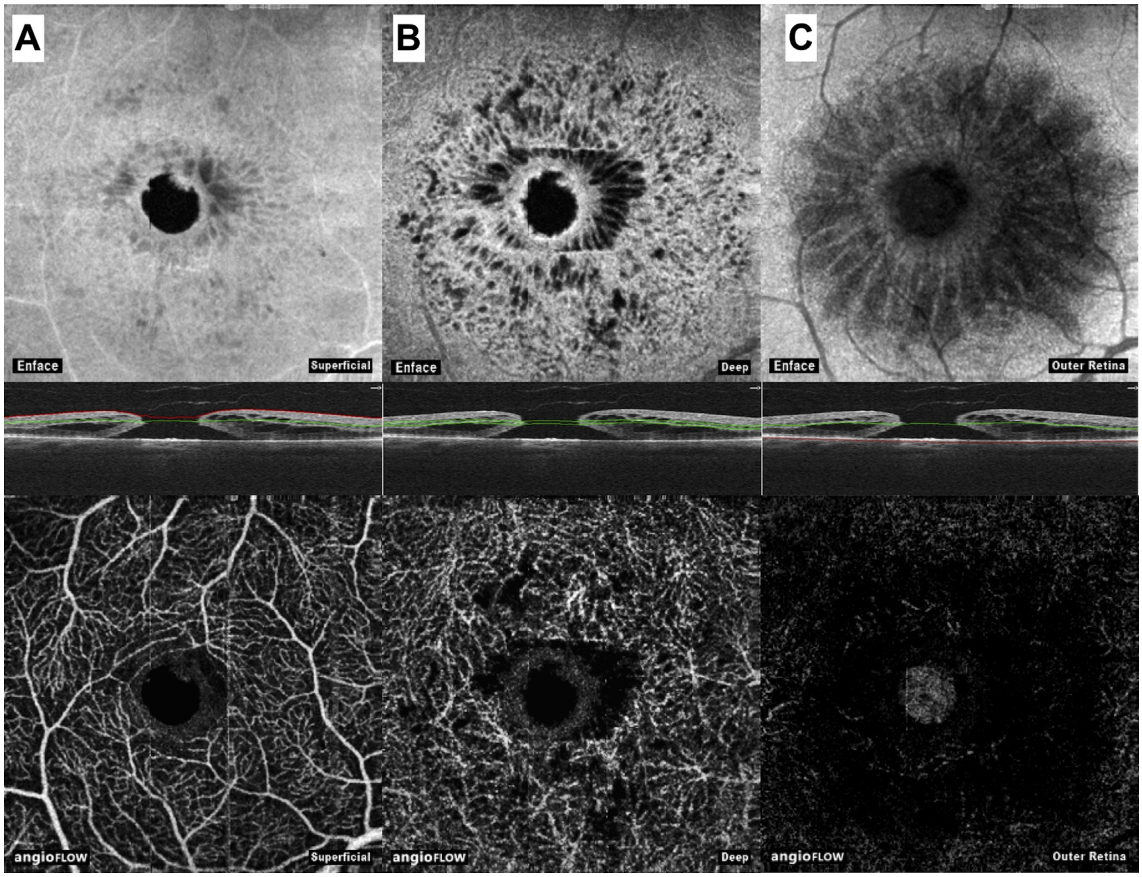


Fig. 3. En face and optical coherence tomography (OCT) angiography images of a macular hole obtained at the level of superficial (A), deep (B), and outer retina (C). Corresponding central B-scans and segmentation lines have been shown for each image. Hyporeflective areas on en face imaging correspond to macular hole and surrounding cystic areas. OCT angiography shows flow void in these areas along with enlargement of the foveal avascular zone.

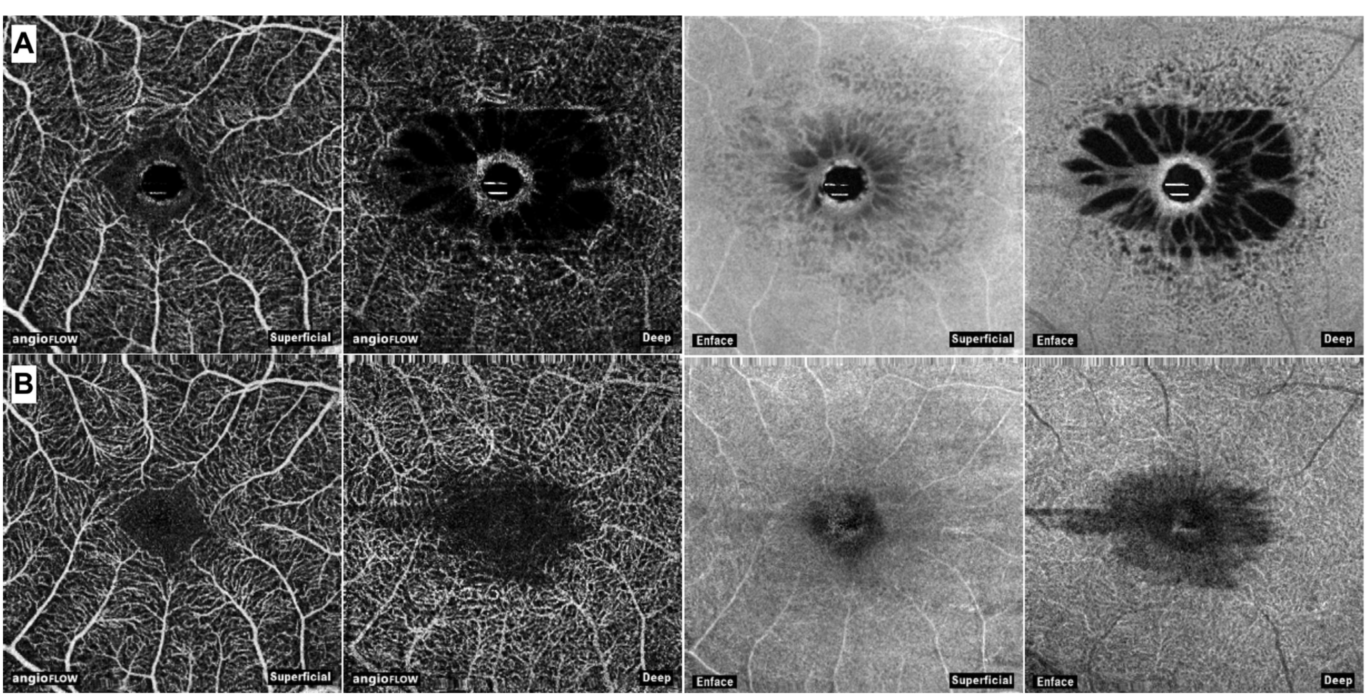
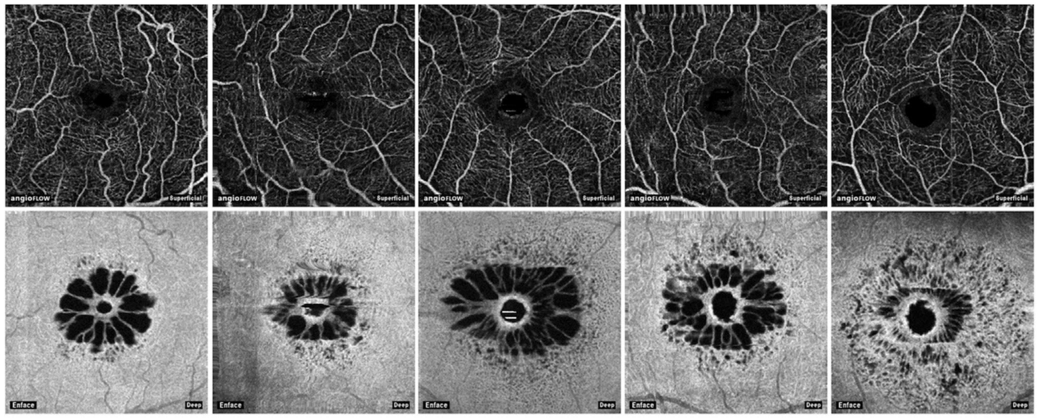


Fig. 4. Pre- (A) and postoperative (B) optical coherence tomography (OCT) angiography and en face OCT images demonstrating preserved flow patterns in the superficial and deep networks. Foveal avascular zone contraction is seen with reduction of macular cystic areas.



Subject	1	2	3	4	5
Age	73	77	63	69	76
Gender	F	M	F	F	F
Eye	OS	OD	OD	OD	OD
Hole Area (mm^2)	0.028	0.035	0.091	0.113	0.142
Cyst No.	18	23	58	42	76
Cyst Area	0.793	0.342	1.33	0.75	0.28
Preoperative BCVA	20/100	20/60	20/50	20/100	20/100
Preoperative FAZ Area (mm^2)	0.332	0.297	0.557	0.458	0.385
Postoperative BCVA	20/50	20/40	20/30	20/50	20/60
Postoperative FAZ Area (mm^2)	0.219	0.155	0.400	0.233	0.333

Fig. 5. Clinical and en face imaging characteristics of five patients presenting with a full-thickness macular hole. Hole area is increasing from case 1 through 5. Abbreviations: BCVA, best-corrected visual acuity; F, female; FAZ, foveal avascular zone; M, male.

explanation is the older age of our patient population, since FAZ area appears to increase on average 1.48% per year.[16] Nonetheless, mean FAZ values reduced to the aforementioned normative values following successful surgical closure with improved visual outcome. The influence of FAZ size, and its reduction following surgery on visual acuity outcomes may be an area worth exploring.

Our study also demonstrated how en face imaging can provide a novel detailed view of pathological features of the retina. By reconstructing multiple cross-sectional B-scans into a single image at any desired depth of the retina, this imaging modality improves visualization of the extent of cystic and often subtle changes surrounding the macular hole. In the past, most prognostic features related to macular holes have been attributed to cross-sectional characteristic such as minimum linear diameter, basal hole diameter, and properties of the outer retinal layers. However, additional biomarkers based on the en face image may provide additional prognostic features. For example, we observed a range of patterns in the configuration of cystic areas. Interestingly, we found that the en face area of the holes contributed to these patterns. Smaller holes showed fewer but larger cystic areas and larger holes had more numerous but smaller cystic areas. The clinical significance of these patterns and their impact on macular hole staging as well as visual and surgical outcome would be an interesting subject for future studies.

The etiology of these observed patterns is not completely understood. In a study of 8 patients, Matet et al.[7] proposed a graphical interpretation of the orientation and shape of the cavities surrounding full-thickness macular holes. They hypothesized a dual pattern for cystic cavities with radial and vertical aspects following the “Z-shaped” configuration of Müller cells. We observed a transition from the radial pattern to smaller more dispersed cystic areas with increased hole size. This may indicate accumulation of fluid along horizontal and subsequently vertical portions of Müller cells throughout the process of macular hole development and progression, which is compatible with the “hydration theory”.[17] In 2003, Tornambe theorized that the progression of macular holes may be the result of destabilization of the underlying retina with progressive hydration. Subsequently, a case series of serial OCTs and morphing videos demonstrated anterior posterior vitreofoveal traction with a break in the internal limiting membrane as the initiating event that then seems to promote retinal hydration.[18] Clamp et al.[19] found further evidence of tractional forces along pathways of minimal resistance in sequential en face SD-OCT analysis of an evolving macular hole in one patient. They demonstrated the late appearance of the septated radial cystoid abnormalities around the hole extending from the periphery of the macular hole within the Henle fiber layer. Ultimately, larger case series with sequential en face imaging over longer durations may help further our understanding of the underlying evolution and importance of the patterns we observed.

Regarding the superficial and deep vascular networks as seen on OCTA in our study, pre- and postoperative comparisons confirmed both structural recovery and functional (flow) preservation following surgery. While the overall blood flow pattern was preserved in both networks, resolution of the cystic changes likely resulted in contraction of the FAZ with blood vessels and retinal tissue replacing the fluid-filled cystic areas. Previous OCT studies have similarly demonstrated the dynamic healing process that occurs after surgical repair of macular holes.[20] Such potential for recovery due to neuronal and vascular plasticity is in concordance with functional studies showing increased macular sensitivity using microperimetry.[21,22]

Our report has several limitations. Chief among these are the retrospective design, small number of eyes, and short postoperative observation period of two months. Hence, no conclusion could be made as to the prognostic impact of our quantitative assessments on surgical and visual outcomes. Furthermore, despite the trend observed in regard to hole size and cystic configuration, this might not be generalizable to all macular holes. Further studies with a larger sample size and a longer observation period would be necessary to assess the practical utility of such quantitative assessments and confirm our findings. Another limitation is related to the technical shortcomings of the current imaging technology. Since stable fixation is required for a few seconds in order to obtain good quality images, this may lead to a selection bias towards patients with better visual function. In the future, increased scanning and image processing speed along with incorporation of eye tracking technology could potentially compensate for such shortcomings.

In conclusion, our study characterized and quantified vascular and cystic changes surrounding macular holes as well as their resolution following surgical repair using simultaneous en face OCT and OCTA. The combination of en face images, conventional longitudinal and cross-sectional images, and sectioned volume images has enabled identification of intraretinal microstructures and their 3D extension associated with macular holes. These perifoveal microstructural patterns and quantitative characteristics may serve as useful anatomic biomarkers for assessment of macular holes and perhaps prediction of visual recovery following surgical closure. Further investigations are needed to determine the clinical utility of such indices.

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

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Conflict of interest

ACH, Optovue (Fremont, CA); JH, Optovue (Fremont, CA). The following authors have no financial disclosures: AS, ER, OPG.

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