• Clinical Research •

Characteristics of macular microvasculature before and after idiopathic macular hole surgery

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Received: 2021-02-07 Accepted: 2021-04-22

Abstract

● **AIM:** To evaluate the macular microvasculature before and after surgery for idiopathic macular hole (MH) and the association of preoperative vascular parameters with postoperative recovery of visual acuity and configuration.

● **METHODS:** Twenty eyes from 20 patients with idiopathic MH were enrolled. Optical coherence tomography angiography (OCTA) images were obtained before, 2wk, 1, and 3mo after vitrectomy with internal limiting membrane peeling. Preoperative foveal avascular zone (FAZ) area and perimeter and regional vessel density (VD) in both layers were compared according to the 3-month best-corrected visual acuity (BCVA).

● **RESULTS:** The BCVA improved from 0.98±0.59 (logMAR, Snellen 20/200) preoperatively to 0.30±0.25 (Snellen 20/40) at 3mo postoperatively. The preoperative deep VD was smaller and the FAZ perimeter was larger in the 3-month BCVA<20/32 group (all $P<0.05$). A significant reduction was observed in FAZ parameters and all VDs 2wk postoperatively. Except for deep perifoveal VD, all VDs recovered only to their preoperative values. The postoperative FAZ parameters were lower during follow-up. Decreases in preoperative deep VDs were correlated with worse postoperative BCVA (Pearson's r=-0.667 and -0.619, respectively). A larger FAZ perimeter (Spearman's r=-0.524) and a lower deep perifoveal VD preoperatively (Pearson's r=0.486) were associated with lower healing stage.

● **CONCLUSION:** The status of the deep vasculature may be an indicator of visual acuity in patients with a closed MH. Except for the deep perifoveal region, VD recovers only to preoperative levels.

● **KEYWORDS:** macular microvasculature; macular hole; vitreoretinal surgery; optical coherence tomography angiography

DOI:10.18240/ijo.2022.01.15

Citation: Cheng D, Tao JW, Yu XT, Chen YQ, Shen MX, Wu MH, Yu JF, Lian HL, Lu Z, Shen LJ. Characteristics of macular microvasculature before and after idiopathic macular hole surgery. *Int J Ophthalmol* 2022;15(1):98-105

INTRODUCTION

An idiopathic macular hole (MH), caused by tangential traction, can be successfully closed by pars plana vitrectomy with gas-fluid exchange[1]. The anatomic and functional outcomes were further improved by the advent of peeling of the internal limiting membrane (ILM)[2]. However, the postoperative visual acuity (VA) is sometimes poor despite successful anatomic closure[3-4]. Long-term restoration of the microstructure and function of the fovea has been evaluated following surgery for idiopathic MH[2]. Previous studies in eyes with MH have focused mainly on disruption of the outer retina, including the external limiting membrane (ELM), the ellipsoid zone (EZ), and the photoreceptors with respect to the visual prognosis[5-6].

Recently, researchers demonstrated an association of disorganization of the retinal inner layers (DRIL) with VA in various retinal diseases[7-8]. The presence of vitreous cortex, proliferative glial tissue, and retinal hydration has been suggested as factors in the formation of macular holes in histologic studies[9-10] and possibly contribute to DRIL. DRIL indicates specific anatomic damage to the structures in the retinal layers that transmit visual data and also a poor inner retinal circulation[11].

With the development of imaging technology, optical coherence tomography angiography (OCTA) provides high-resolution, depth-resolved images for evaluation of the retinal capillary plexuses in eyes with MH in a noninvasive and dye-free manner[12-15]. In our previous work, we used a commercially available OCTA device with custom-built imaging software and concluded that disorders in the inner retinal vessels corresponded to disruption of the outer retinal layers and VA in the setting of dysfunctional vasculature[16].

The recovery of the retinal microvasculature in patients with a surgically closed MH remains to be elucidated. Meanwhile, limited information is available regarding quantitative evaluation of the preoperative status of the retinal microvasculature in eyes with MH. Accurate OCTA measurements should correct for ocular magnification and require information on axial length. Until now, no study has accurately quantified the changes that occur in the vasculature of the macula in eyes with MH after surgical treatment or the relationship between preoperative vascular parameters and the postoperative VA.

The aims of this retrospective study were to characterize macular microvasculature in the superficial and deep retinal layers following surgery in patients with idiopathic MH using OCTA and to investigate the association of preoperative microvascular parameters in the inner retina with postoperative best-corrected visual acuity (BCVA) and healing.

SUBJECTS AND METHODS

Ethical Approval This study was approved by the Ethics Committee at Wenzhou Medical University and complied with the tenets of the Declaration of Helsinki. Informed consent was obtained from all patients.

Subjects The medical records of patients who had undergone successful MH closure by vitrectomy and ILM peeling in the Fundus Department at the Eye Hospital, Wenzhou Medical University, from June 2018 to May 2020 were reviewed. Each patient underwent a complete ophthalmic examination, including slit-lamp examination, intraocular pressure measurement, fundoscopy, preoperative axial length measurement, OCT (Spectralis; Heidelberg Engineering, Heidelberg, Germany), and OCTA (AngioVue; Optovue, Inc., Fremont, CA, USA). The slit-lamp, fundoscopy, OCT, and OCTA examinations were performed before surgery and 2wk, 1, and 3mo after surgery. The inclusion criterion was a Gass stage 2-3 idiopathic full-thickness MH confirmed on OCT. Eyes with macular disease, such as age-related macular degeneration, epimacular membrane, myopic choroidal neovascularization, a spherical equivalent refractive error >±6.0 diopters, significant cataract (LOCS scale higher than N2, C1, P2)[17] or macular edema after surgery, glaucoma, other marked complications, or a history of intraocular surgery were excluded. Chronic macular holes (defined by visual symptoms of greater than 1y), heavy smokers[18], or patients with systemic disease, such as diabetes, hypertension were also excluded. The patients were divided into groups according to whether or not their 3-month postoperative BCVA was <20/32 or ≥20/32[19].

Image Acquisition and Data Analysis The AngioVue version 2017.1.0.155 software was used. The macular region was imaged using a central 3×3 mm^2 area. Low-quality OCTA images with a scan quality <5/10[20], severe artifacts attributable to poor fixation, or failure of automatic layer segmentation were excluded. The area and perimeter of the foveal avascular zone (FAZ) were determined by the software embedded in the instrument. The vessel density (VD) was calculated as the percentage of pixels with a flow signal greater than the threshold value and automatically measured using custom-built imaging software implemented in MATLAB (Mathworks, Natick, MA, USA)[16,21]. The mean brightness of the FAZ was taken as the threshold for the retinal vessels. Parafoveal and perifoveal VDs were calculated in the regions of the radius between 0.5 and 0.875 mm and between 0.875 and 1.25 mm, respectively, from the foveal center (Figure 1A, 1B). To reduce the effects of decentration of the FAZ and the artifacts at the edge of the scan, a circular area with a diameter of 2.5 mm was used instead of the entire 3×3-mm^2 area.

Preoperative minimum diameter of the MH was measured in the OCT images. The postoperative healing stage, *i.e.*, restoration of the photoreceptor layer, was graded from 1 to 3[5]. Grade 1 was assigned when the EZ and ELM were disrupted, grade 2 when the EZ was disrupted but the ELM was restored, and grade 3 when both the ELM and EZ were restored. DRIL was defined as the horizontal extent within the central 2000 μm for which any boundaries between the ganglion cell-inner plexiform layer complex, inner nuclear layer, and outer plexiform layer could not be identified[8]. Two independent observers interpreted the OCTA and OCT images. The observers reached a consensus in all cases.

To eliminate the effect of magnification, the images obtained by OCTA and OCT were corrected by Bennett's formula using the axial length[22-23]. The relationship between the OCT image measurements and the actual scan diameter was expressed by the formula $t=p\times q\times s$, where t is the actual axial length, p is the magnification factor determined by the camera of the OCT imaging system, q is the magnification factor in relation to the eye, and s is the original measurement obtained from the OCT image. The correction factor q was determined using $q=0.01306\times(AL-1.82)$[23].

Surgical Technique All procedures were performed by a single surgeon. Standard 3-port pars plana vitrectomy was performed using 23-gauge instruments. Cataract surgery was performed on all 20 phakic eyes. A 31-year-old patient underwent cataract surgery for congenital cataract. A concentration of 0.025% indocyanine green (ICG) was injected into the vitreous cavity and washed out no later than 3 seconds by 23-gauge cutter. Then the ILM was peeled by carefully grasping with forceps without retinal damage to about 4-disc diameters centered on the macula. All patients performed fluid-air exchange with air, and the sclerotomies were sutured. Patients were instructed to remain in a prone position for 3-5d postoperatively.

Table 1 Patient demographic and ophthalmic characteristics

Case	Age (y)	Sex	Eye	Stage	Axial length (mm)	Minimum diameter of hole (μm)	Preoperative BCVA	BCVA at 2wk	BCVA 1mo	BCVA 3mo	Healing stage
1	31	F	OS	3	24.46	826	20/100	20/63	20/50	20/40	1
2	60	M	OD	2	24.79	328	20/160	20/63	20/50	20/32	2
3	57	F	OS	3	22.95	409	20/200	20/100	20/50	20/40	2
4	49	F	OD	2	22.63	206	20/50	20/200	20/100	20/25	2
5	63	F	OS	2	24.26	352	20/63	20/200	20/50	20/20	2
6	68	M	OS	2	23.2	266	20/32	20/80	20/25	20/20	3
7	61	F	OD	3	23.34	553	FC/1 m	20/2000	20/200	20/200	2
8	55	M	OS	2	24.88	331	20/500	20/63	20/63	20/63	1
9	65	F	OD	2	25.52	223	20/40	20/40	20/32	20/25	2
10	65	F	OS	2	22.56	285	20/1000	20/400	20/200	20/63	2
11	69	M	OD	2	22.61	307	FC/1 m	HM/1 m	20/100	20/50	2
12	63	F	OD	3	21.77	574	20/125	20/100	20/50	20/40	2
13	54	F	OS	3	22.95	871	20/100	20/63	20/25	20/20	2
14	57	F	OS	3	23.77	695	FC/1 m	20/400	20/63	20/40	1
15	47	M	OS	3	24.85	481	20/125	20/63	20/32	20/32	2
16	46	F	OD	2	25.5	213	20/32	20/125	20/25	20/20	3
17	65	F	OS	3	23.84	480	20/100	20/50	20/63	20/32	2
18	72	M	OS	3	24.53	779	20/400	20/400	20/100	20/100	1
19	63	F	OD	3	24.47	602	20/63	20/63	20/40	20/32	2
20	72	F	OD	3	25.41	476	20/400	20/200	20/63	20/63	2

F: Female; M: Male; OS: Left eye; OD: Right eye; BCVA: Best-corrected visual acuity.

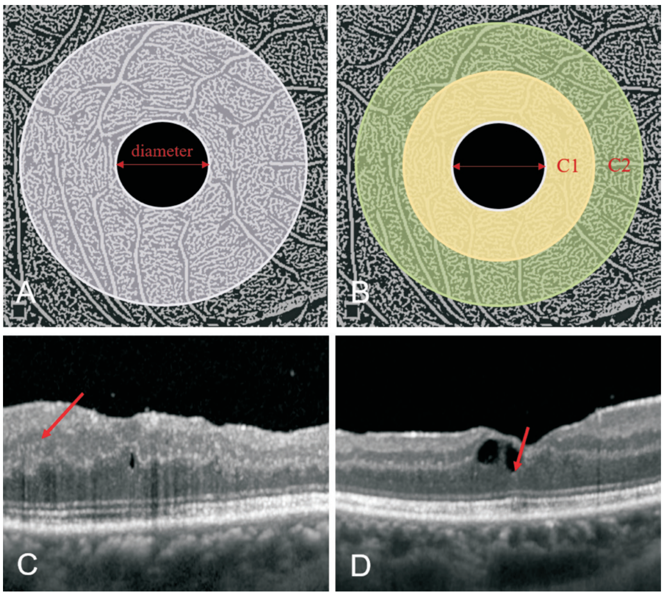

Figure 1 Macular region analyzed for VD and representative OCT images of DRIL during the post-surgery recovery A: Total VD was calculated for the ring-shaped area between a 0.5 and 1.25 mm radius from the fovea center; B: C1 and C2 were 0.5 to 0.875 mm and 0.875 to 1.25 mm radius ring-shaped area from the fovea center, respectively; C, D: Red arrows shows the area where the boundary between the ganglion cell-inner plexiform layer complex, inner nuclear layer and outer plexiform layer cannot be distinguished and is irregular. VD: Vessel density; DRIL: Disorganization of retinal inner layers.

Statistical Analysis Independent *t*-test and Mann-Whitney *U* test were used to compare continuous variables between the groups. Repeated-measures analysis of variance was used to evaluate differences in the chronologic data. Post multiple comparisons were evaluated using the Bonferroni test. The Pearson correlation test was used to determine the associations between preoperative vascular parameters and postoperative BCVA. The associations between preoperative vascular parameters and postoperative healing stage were evaluated using the Spearman correlation test. All data are expressed as the means±standard deviations and analyzed with SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). logMAR values of 2.0 and 3.0 were assigned for counting fingers and hand motion vision, respectively[24]. $P<0.05$ indicated statistical significance.

RESULTS

Patient Demographic and Clinical Characteristics Forty-three eyes of 43 patients with an MH underwent vitrectomy with ILM peeling between June 2018 and May 2020. Twenty-three eyes were excluded (8 for high myopia, 4 for severe cataract that prevented acquisition of high-quality OCTA images, 4 for age-related macular degeneration, 2 for diabetic retinopathy, 2 for myopic choroidal neovascularization, 2 for OCTA images of poor quality, and 1 loss in postoperative follow-up), leaving 20 eyes of 20 patients for inclusion (Table 1).

Table 2 Comparison of preoperative parameters between eyes with BCVA≥20/32 and eyes with BCVA<20/32 at 3mo postoperatively

Variables	BCVA≥20/32 postop. 3mo	BCVA<20/32 postop. 3mo	P^a
n	10	10	-
Age (y)	58.0±8.3	60.2±12.0	0.639
Preoperative stage	2.4±0.5	2.7±0.5	0.196
Axial length (mm)	24.2±1.0	23.6±1.2	0.251
Minimum diameter of hole (µm)	402.2±212.1	523.5±196.0	0.201
Preoperative BCVA (logMAR)	0.531±0.246	1.422±0.491	0.001
FAZ area (mm^2)	0.366±0.127	0.490±0.164	0.076
FAZ perimeter (mm)	2.5±0.5	3.2±0.7	0.032
Superficial parafoveal VD (%)	0.482±0.012	0.467±0.035	0.211
Superficial perifoveal VD (%)	0.480±0.012	0.463±0.036	0.192
Deep parafoveal VD (%)	0.516±0.039	0.468±0.050	0.027
Deep perifoveal VD (%)	0.499±0.038	0.456±0.038	0.023

[a]Independent *t*-test or Mann-Whitney *U* test were performed as appropriate. BCVA: Best-corrected visual acuity; FAZ: Foveal avascular zone; VD: Vessel density.

Table 3 Foveal avascular zone and regional vessel density in the superficial and deep layers

Parameters	Preoperative	Postoperative			P^a
		2wk	1mo	3mo	
FAZ					
Area, mm^2	0.43±0.16	0.19±0.15	0.25±0.17	0.30±0.17	<0.001
Perimeter, mm	2.8±0.7	1.7±0.6	2.0±0.8	2.2 ±0.6	<0.001
Superficial layer					
Parafoveal VD, %	47.4±2.7	43.4±0.04	45.1±0.03	46.8±0.03	<0.001
Perifoveal VD, %	47.2±0.03	42.8±0.03	44.4±0.03	46.2±0.03	<0.001
Deep layer					
Parafoveal VD, %	49.2±0.05	42.2±0.06	48.3±0.04	51.6±0.03	<0.001
Perifoveal VD, %	47.7±0.04	41.3±0.06	47.6±0.04	51.1±0.03	<0.001

[a]Repeated-measures analysis of variance. FAZ: Foveal avascular zone; VD: Vessel density.

The patients mean age was 59.1±10.1y. Fourteen patients were female (70%) and 6 (30%) were male. The mean preoperative axial length was 23.9±1.1 (range 21.77-25.52) mm. Before surgery, the mean minimum diameter of the hole was 462.9±208.3 (range 206-871) µm.

The logMAR BCVA improved from 0.98±0.59 (range 0.22-2.00, Snellen equivalent 20/200) preoperatively to 0.93±0.64 (range 0.30-3.00, Snellen 20/160) at 2wk, 0.47±0.25 (range 0.15-1.00, Snellen 20/63) at 1mo, and 0.30±0.25 (range 0-1.00, Snellen 20/40) at 3mo postoperatively. Ten patients (50%) had evidence of different degrees of DRIL on OCT images during the post-surgery recovery of MHs (Figure 1C, 1D).

Between-Group Differences in Preoperative Data and Vascular Parameters There were significant differences in preoperative VA, perimeter of the FAZ, and parafoveal and perifoveal VD in the deep plexus between the group with a 3-month BCVA<20/32 and the group with the 3-month BCVA≥20/32 (Table 2). In the group with the 3-month BCVA<20/32, the preoperative VA was significantly worse, and the perimeter of the FAZ was larger. In the deep capillary layer, the VDs in both regions was smaller. The minimum diameter of the hole and the area of the FAZ were larger, albeit not significantly so. No significant differences were found in patient age, preoperative stage, axial length, or VD in either region of the superficial layer.

Changes in Vessel Density and Foveal Avascular Zone There were significant changes in all vascular parameters after MH surgery (Table 3). The changes in parafoveal and perifoveal VD in both layers are shown in Figures 2 and 3. Before vitrectomy, the mean parafoveal and perifoveal VD values were 47.4%±2.7% and 47.2%±0.03%, respectively, in the superficial layer and 49.2%±0.05% and 47.7%±0.04%, respectively, in the deep layer. A significant reduction in VD was observed 2wk after surgery. Furthermore, there was evidence of recovery of the macular microvasculature in the superficial plexus at 1 and 3mo postoperatively. In the deep plexus, there was no difference between the preoperative VD and the VD at 1mo postoperatively in either region. The mean

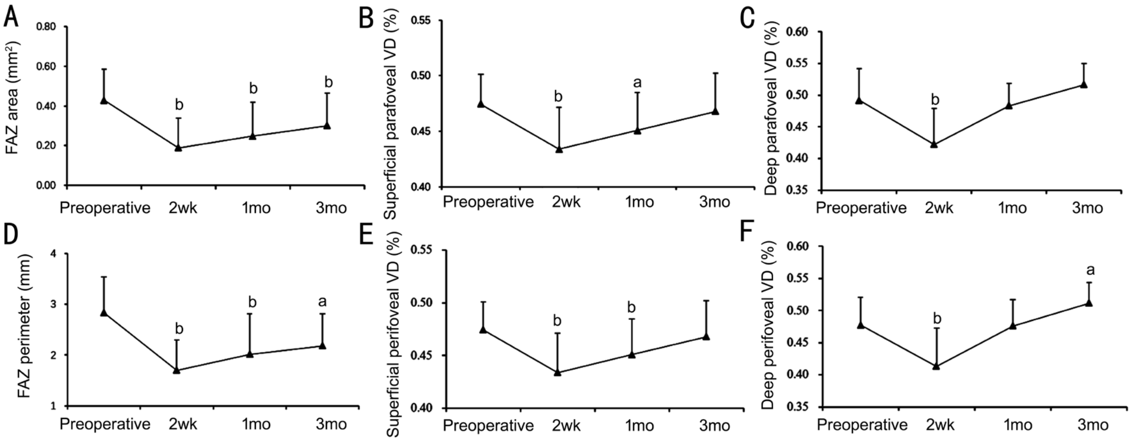

Figure 2 Macular microvasculature before and after surgery using OCTA and algorithm analysis There was a significant reduction in the FAZ area (A) and perimeter (D) during the follow-up period when compared with the preoperative status. The parafoveal and perifoveal VD in the superficial layer (B and E) and deep layer (C and F) show that, with the exception of the deep perifoveal VD, there was a significant reduction in all VD values in both layers at 2wk after surgery with recovery to the preoperative status by 3mo. Each point represents the mean±standard deviation. $^aP<0.01$ and $^bP\leq0.001$ *vs* the preoperative value. FAZ: Foveal vascular zone; OCTA: Optical coherence tomography angiography; VD: Vessel density.

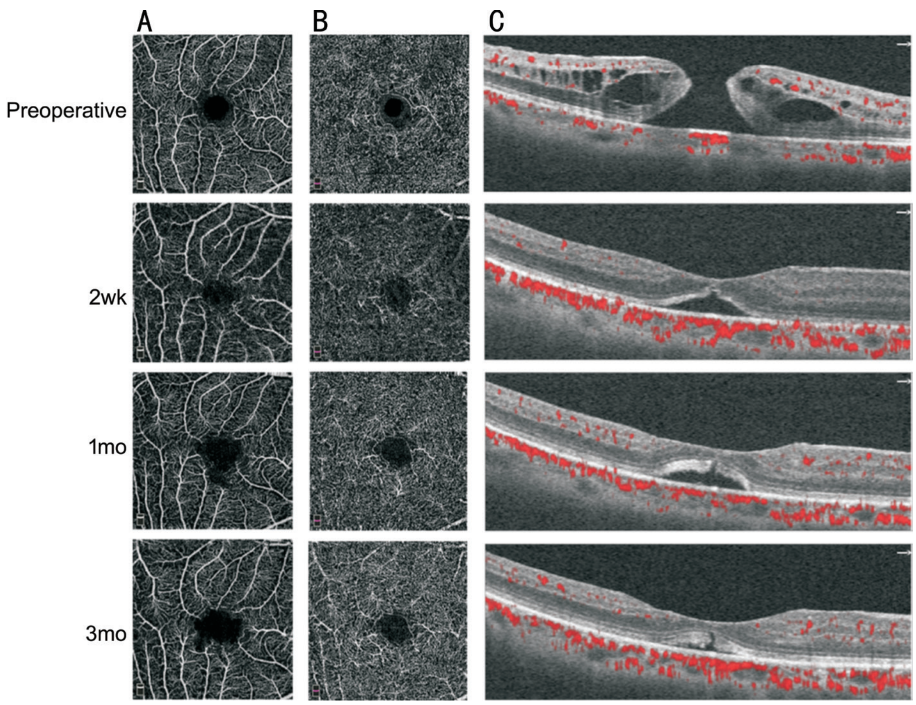

Figure 3 Representative OCTA images for one eye with idiopathic macular hole before and after surgery A: Superficial layer; B: Deep layer; C: Horizontal B-scan. The patient is a 65-year-old woman who had an eye with a Gass stage 2 macular hole. Preoperatively, the minimum diameter of the hole was 223 µm. The preoperative Snellen BCVA was 20/40. The 3-month postoperative Snellen BCVA was 20/25 with stage 2 healing. The FAZ area is shown as an example of the macular vasculature. The FAZ area before, 2wk, 1, and 3mo postoperatively was 0.295, 0.253, 0.260, and 0.269 mm^2, respectively. BCVA: Best-corrected visual acuity; FAZ: Foveal vascular zone; OCTA: Optical coherence tomography angiography; VD: Vessel density.

perifoveal VD at 3mo postoperatively was even greater than that before surgery.

The mean preoperative area and perimeter of the FAZ were 0.43 mm^2 and 2.8 mm, respectively (Figure 2A, 2D). Significant reductions in the mean values for the FAZ parameters were observed during the follow-up period (Table 3 and Figure 2).

Correlation of Preoperative Vascular Parameters with Postoperative Visual Acuity and Healing Stage There was a correlation between decreased preoperative parafoveal and perifoveal VD in the deep layer and worse 3-month VA (Pearson's r=-0.667 and -0.619, respectively; Table 4, Figure 4A, 4C). A larger FAZ perimeter (Spearman's r=-0.524) and

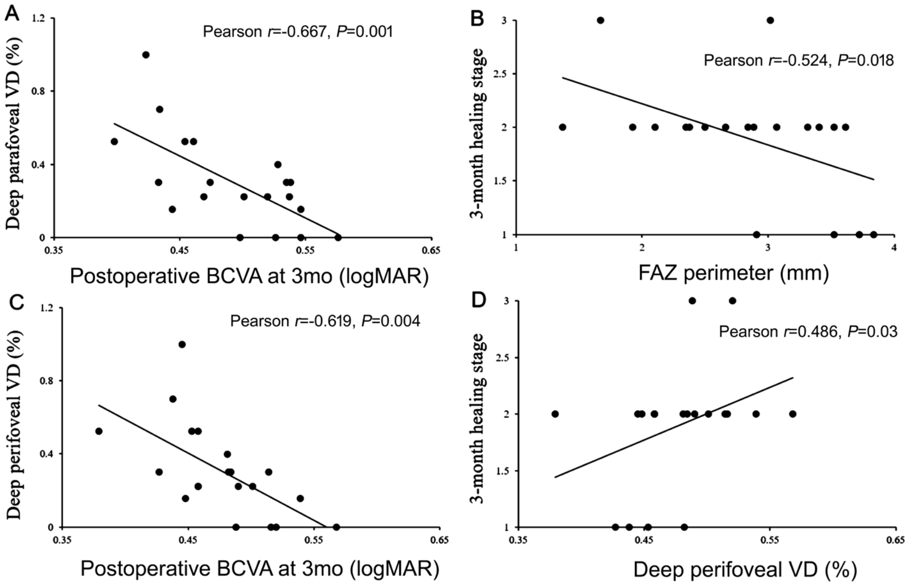

Figure 4 Correlations of vascular parameters with 3-month postoperative BCVA and healing stage A, C: Lower preoperative deep parafoveal and perifoveal VD correlated with worse VA; B, D: Larger FAZ perimeter and decreased deep perifoveal VD were associated with poorer healing. BCVA: Best-corrected visual acuity; FAZ: Foveal vascular zone; VD: Vessel density.

Table 4 Correlation of foveal avascular zone and vessel density measurements with 3-month postoperative BCVA and healing stage

Preoperative parameters	3-month BCVA[a]		Healing stage[b]	
	r (95%CI)	*P*	*r* (95%CI)	*P*
FAZ				
Area	0.308 (-0.07, 0.724)	0.186	-0.418 (-0.80, 0.232)	0.067
Perimeter	0.394 (0.001, 0.762)	0.086	-0.524 (-0.810, -0.078)	0.018
Superficial layer				
Parafoveal VD	-0.189 (-0.730, 0.249)	0.425	0.091 (-0.408, 0.550)	0.701
Perifoveal VD	-0.207 (-0.642, 0.275)	0.381	0.223 (-0.244, 0.620)	0.344
Deep layer				
Parafoveal VD	-0.667 (-0.832, -0.386)	0.001	0.330 (-0.142, 0.678)	0.155
Perifoveal VD	-0.619 (-0.793, -0.420)	0.004	0.486 (0.121, 0.755)	0.030

[a]Pearson correlation test. [b]Spearman correlation test. BCVA: Best-corrected visual acuity; CI: Confidence interval; FAZ: Foveal avascular zone; VD: Vessel density.

decreased perifoveal VD preoperatively in the deep layer (Pearson's *r*=0.486) was associated with lower healing stage of photoreceptor layers (Figure 4B, 4D). There was no correlation between FAZ, superficial vasculature parameters and VA at 3mo after surgery. No correlation was found between preoperative superficial VDs and postoperative healing stage.

DISCUSSION

Several studies have investigated the preoperative configuration of MH using OCT and searched for predictors of the visual outcome after surgery[2,4,6]. To the best of our knowledge, postoperative visual recovery has not been evaluated as a predictive parameter by OCTA in eyes with MH. We demonstrated that the preoperative macular microvasculature was denser in eyes with MH that had better VA after surgery, especially in the deep capillaries. Moreover, correlation analysis revealed that a decrease from the preoperative deep capillary VD was strongly correlated with worse postoperative VA. We speculate that this could be attributed to several possible mechanisms[10,16]. Tornambe[10] proposed the "hydration theory", whereby during formation of an MH, after the posterior hyaloid has created a retinal defect, vitreous fluid first passes through the inner retina and disrupts homeostasis. Liquid vitreous fluid then accumulates, the MH appears to enlarge, and the inner retinal tissue become swollen, especially in the outer plexiform layer. DRIL was recently identified to be a sign of poor inner retinal circulation[7,11], indicating disruption of the pathways that transmit visual information from the photoreceptors to the ganglion cells and seemed to be a correlated predictive biomarker for VA in various diseases. We observed a similar phenomenon in a previous study[16]. Given their special watershed-like position, the deep capillaries may be more prone to ischemia and contribute to disruption of the photoreceptor layer and then visual function. The suggested pathophysiologic changes within the inner retinal vasculature, which are supported by histopathologic and imaging studies, collectively may have accounted for the decreased deep blood flow seen in our study.

We quantitively demonstrated recovery of the macular vasculature with magnification correction before and after surgical intervention in eyes with MH. Scupola *et al*[2] reported significant improvement in retinal function at 3mo after closure of an MH that was confirmed to be maintained at 6 and 12mo by focal electroretinography. Therefore, we compared the microvascular networks in eyes with MH before, 2wk, 1, and 3mo postoperatively. Significant reductions in FAZ parameters were observed 2wk postoperatively, suggesting a movement of foveal tissue toward the central fovea and a centripetal movement when the MH is closed[13]. However, the 2-week postoperative VDs decreased significantly, and the VA improved only slightly, indicating prompt structural recovery but delayed functional repair. Kim *et al*[14] and Demirel *et al*[25] reported that the postoperative VD in eyes with a closed MH, particularly in the deep plexus, was lower than that in either fellow eyes or healthy eyes. In the present study, most VD values recovered only to the preoperative status, indicating a lack of functional vascular integrity after surgery. The disrupted microvasculature may impede the dynamic healing process and provide another explanation for the unsatisfactory visual gain after surgery despite successful anatomic closure of the MH.

Correlational analysis revealed a moderate correlation of a decreased deep perifoveal VD and an increased FAZ perimeter with poor healing. The ischemia in inner retinal vasculature is considered to contribute to the disorganization of the outer retina and to lead to poor restoration of the microstructure of the fovea[16].

This study has several limitations. The first is its retrospective design and relatively small sample size. The second relates to the fact that eyes with MH tend to have poorer stable fixation before surgical closure, leading to exclusion of OCTA images with poor quality upon visual inspection.

In conclusion, OCTA analysis before and after surgery in eyes with MH demonstrated the preoperative macular microvasculature and suggests that the status of the deep plexus could predict the postoperative visual outcome. Quantification of the retinal vasculature postoperatively would provide an explanation for the limited visual recovery after surgical closure of MH.

ACKNOWLEDGEMENTS

Foundations: Supported by the National Natural Science Foundation of China (No.81900910; No.81700884); Natural Science Foundation of Zhejiang Province (No.LQ19H120003; No.LGF21H120005); Key Project Jointly Constructed by Zhejiang Pronvince and Ministry (No.WKJ-ZJ-2037); Basic Scientific Research Project of Wenzhou (No.Y20210194).

Conflicts of Interest: Cheng D, None; **Tao JW,** None; **Yu XT,** None; **Chen YQ,** None; **Shen MX,** None; **Wu MH,** None; **Yu JF,** None; **Lian HL,** None; **Lu Z,** None; **Shen LJ,** None.

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