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Article

Smaller Foveal Avascular Zone in Deep Capillary Plexus Is Associated with Better Visual Acuity in Patients after Macula-off Retinal Detachment Surgery

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Purpose: To associate the change in the foveal avascular zone (FAZ) and vessel density (VD) with final best corrected visual acuity (BCVA) in eyes after macula-off rhegmatogenous retinal detachment surgery, and to investigate the evolution of FAZ and VD during 12 months of follow-up.

Methods: We prospectively evaluated 47 patients with macula-off rhegmatogenous retinal detachment and healthy fellow eyes. At 1.5, 3.0, 6.0, and 12.0 months postoperatively, optical coherence tomography angiography scans were obtained from both eyes on a 3.0 × 3.0 mm macula-centered grid. En face images of the superficial vascular plexus, intermediate capillary plexus and deep capillary plexus were used to quantify FAZ and VD. BCVA was assessed with ETDRS-charts (logarithm of the minimal angle of resolution).
At 12 months postoperatively, the association between the change in optical coherence tomography angiography parameters and visual function in study eyes was evaluated using the Spearman correlation coefficient. We calculated the BCVA difference and the percentage difference of FAZ and VD between the study and control eye. The evolution of FAZ and VD was investigated with linear mixed-effects models with nested random effects (eyes nested within patients).

Results: At 12 months postoperatively, FAZ difference of the deep capillary plexus and BCVA difference were correlated ($P = 0.0004$, $r_s = 0.5$). Furthermore, there was no evidence that FAZ and VD changed during follow-up.

Conclusions: Although FAZ and VD remained stable during 12 months after surgery for macula-off rhegmatogenous retinal detachment, a smaller FAZ in the deep capillary plexus is associated with better BCVA.

Translational relevance: Reduction in FAZ area may be caused by angiogenesis to counteract ischemia, therefore therapeutic stimulation of angiogenesis could be beneficial to visual recovery.

Introduction

Although surgery for macula-off rhegmatogenous retinal detachment (RRD) results in reattachment in the majority of cases, visual recovery varies and is difficult to predict.[1,2] We previously reported that many patients suffer from metamorphopsia and aniseikonia besides visual acuity loss after surgery (H. Ng, et al. *IOVS* 2019;60:ARVO E-Abstract 6570). However, it is unclear which retinal abnormalities are the cause of these visual outcomes.[3,4]

With the advent of optical coherence tomography (OCT), it became possible to visualize microstructural

abnormalities that were not visible with clinical fundus examination.[5,6] Postoperative OCT abnormalities that are related to visual outcome include retinal folds and the disruption of ellipsoid zone.[7,8] However, patients can still suffer from impaired visual function despite the absence of these abnormalities on OCT, which suggests other abnormalities which are not captured by OCT.[7,9]

OCT angiography (OCTA) is a novel extension of conventional OCT that enables the visualization of retinal blood flow and therefore the quantification of the foveal avascular zone (FAZ) and vessel density (VD).[10] Early OCTA algorithms were able to distinguish between two plexuses, the superficial capillary plexus and deep capillary plexus (DCP). Nevertheless, this division does not represent the true retinal anatomy, as histological studies have identified three distinct plexuses: the superficial vascular plexus (SVP), the intermediate capillary plexus (ICP), and the DCP.[11] However, with recent advances in OCTA it is now possible to visualize the three distinct plexuses.[12]

Earlier studies have evaluated the FAZ and VD in the superficial capillary plexus and DCP after macula-off RRD surgery, but no study has evaluated these two parameters in the three distinct plexuses.[13–19]

Photoreceptors receive most of their oxygen from the choroid and about 15% from the DCP.[20] During an RRD, damage to photoreceptor outer segments occurs within 12 hours owing to separation from the choroid, which results in apoptosis of photoreceptors.[21–23] Recovery of photoreceptors takes place after reattachment and may be associated with an improvement of visual outcome.[23–25] Although visual acuity improves most during the first 6 weeks after surgery,[26] previous studies have shown that choriocapillary rehabilitation takes up to 8 weeks and choroidal thinning is still present at 3 months postoperatively.[14,27] Considering that choroidal supplementation to photoreceptors is still compromised after surgery, we hypothesize that upregulation of the DCP occurs to counteract ischemia. This upregulation might result in a decrease of FAZ and an increase of VD. Variations in these parameters could explain the variation in visual function recovery observed in macula-off RRD patients. Moreover, the evolution of the FAZ and VD during the 12 months after surgery is of additional value considering it can take up to 12 months to achieve final visual acuity.[26,28]

Thus, the purpose of this study was to associate the change in FAZ and VD in the three vascular plexuses (in particular the DCP) with final visual acuity, metamorphopsia and aniseikonia in eyes after surgery for macula-off RRD. Furthermore, we investigated the evolution of the FAZ and VD during 12 months after surgery.

Methods

Study Design

This prospective observational study was conducted in The Rotterdam Eye Hospital (Rotterdam, the Netherlands) between April 2017 and September 2019, and was approved by the Medical Ethical Committee of the Erasmus Medical Centre (Rotterdam, the Netherlands, MEC-2016-486 and NL58405.078.16). The research followed the tenets of the Declaration of Helsinki. All patients provided written informed consent before enrolment in the study.

Study Population

Patients with a primary unilateral macula-off RRD and a healthy fellow eye were eligible to participate in the study. All eligible patients were approached by one investigator who also asked the patients to recall the onset of RRD symptoms, which included light flashes, floaters, visual field defects, and central vision loss. The onset of macular detachment was determined as the time when central vision loss occurred. The duration of macular detachment was defined as the time between the onset of macular detachment and retinal surgery.

Exclusion criteria before surgery were patients younger than 18 years, a duration of macular detachment of more than 10 days or if the duration of macular detachment could not be determined, proliferative vitreoretinopathy grade C or more,[29] giant tear, preexisting maculopathy (e.g., macular hole or age-related macular degeneration), and any other preexisting comorbidities which could compromise vision in either study or fellow eye (e.g., diabetic retinopathy, glaucoma or uveitis) with the exception of cataract.

Exclusion criteria after surgery were recurrent RRD, cystoid macular edema, persistent subfoveal fluid, and epiretinal membrane stage 2 or more.[30]

Surgical Procedures

Each surgery was carried out by one of five experienced vitreoretinal surgeons. Surgical technique was either pars plana vitrectomy or scleral buckling. A standard 23G vitrectomy was performed with vitreous traction release around breaks, subretinal fluid drainage, and endolaser photocoagulation. Phacoemulsification was performed according to the surgeon's preference.

Scleral buckling consisted of drainage and indentation by a local radial or circular explant

(with or without encircling band). Retinopexy was either peroperative cryocoagulation or postoperative laser.

All patients received gas tamponade (SF_6 or C_3F_8) and were instructed to posture 6 hours a day for 1 week, in a manner to decrease the risk of residual retinal folds in the macula.

Preoperative Assessments

All patients underwent fundus examination after dilatation with 0.5% tropicamide, OCT examination to confirm macular status, and best corrected visual acuity (BCVA) measurement using Snellen projector optotypes and expressed in decimal.

Baseline data collection included gender, age, study eye, preoperative BCVA, quadrants of detachment, duration of macular detachment and preoperative lens status.

Postoperative Assessments

One investigator performed both retinal imaging and visual function assessments.

Retinal Imaging

At 1.5, 3.0, 6.0, and 12.0 months postoperatively, two consecutive OCTA volume scans were obtained from both the study and fellow eye using a Spectralis OCT2 (Heidelberg Engineering, Heidelberg, Germany) after pupil dilatation with 0.5% tropicamide and 5% phenylephrine. This device operates at a 40 kHz A-scan rate and 840 nm wavelength. The scan was acquired at a 3.0 × 3.0 mm (10° × 10°) fovea-centered grid with 6 µm distance between B-scans, resulting in 256 B-scans per OCT-A image. En face images of the SVP, ICP, and DCP were generated after automatic layer segmentation and projection artifact removal by Heidelberg Eye Explorer system software.

Segmentation and image quality were reviewed by one investigator. Segmentation errors were corrected and images with poor quality owing to motion artefacts or floaters were excluded. The first eligible image of each eye was selected for analysis.

En face images of the SVP, DCP, and ICP were exported and loaded into an automated software designed in MATLAB. The software postprocessed the images and determined the center of the FAZ. After quantification of the parafoveal VD and FAZ, the images containing the FAZ were displayed and assessed by one researcher. In cases when the FAZ center was off, the researcher could select the correct center, resulting in recalculation of the FAZ and parafoveal VD by the software. For the parafoveal VD analysis, an inner and outer circle with a diameter of 1.0 mm and 2.5 mm was centered on the fovea. The parafoveal area was defined as the region between the inner and outer circles.

Final Visual Function Assessments

All assessments were performed without pupil dilatation. The BCVA was measured using ETDRS charts at four meters and expressed as the logarithm of the minimal angle of resolution (logMAR).

The M-CHARTS (Inami Co, Tokyo, Japan) was used to assess the degree of metamorphopsia. Scores for horizontal lines and vertical lines were obtained by presenting the test in horizontal and vertical direction. Metamorphopsia was considered to be absent when both horizontal lines and vertical lines scores were 0°. Scores exceeding 2.4° were considered as 2.4° for the statistical analysis.[31]

The New Aniseikonia Test (Handaya, Tokyo, Japan) was used to measure aniseikonia. Scores for horizontal aniseikonia and vertical aniseikonia were determined by presenting the test in horizontal and vertical direction. Scores of +2% or more were considered as macropsia and scores of −2% or less were considered as micropsia. Aniseikonia was considered to be absent if both horizontal aniseikonia and vertical aniseikonia scores were between –1% and 1%.[32]

The metamorphopsia and aniseikonia assessments were both performed at 30 cm with refraction corrected for this distance.

Reproducibility of FAZ and Parafoveal VD

The reproducibility of FAZ was evaluated with patients who had two consecutive OCTA scans for each eye at 3 and 6 months after surgery. For each visit, the absolute difference of FAZ between two consecutive OCTA scans was calculated and the mean absolute deviation was determined for each plexus. Reproducibility was expressed as the average mean absolute deviation of both visits. The same method was performed to evaluate the reproducibility of parafoveal VD.

Statistical Analysis

Categorial variables were presented as frequencies and percentages. Continuous variables were expressed as mean ± standard deviation in the case of a normal distribution, or as median (interquartile range) otherwise.

Differences in postoperative visual function between the study eye and the control eye, and pre- and postoperative BCVA were investigated with the paired Student *t*-test in case of normal distribution

and the Wilcoxon signed-rank test for non-normal distribution.

The association between the change in OCTA parameters and visual function at 12 months postoperatively was evaluated by bivariate analysis using Spearman's rank correlation coefficient.

To assess the actual change in FAZ, parafoveal VD and visual function parameters caused by macula-off RRD in study eyes, we would need the values before macula-off RRD occurs. Because the values of FAZ, parafoveal VD, and visual function parameters before the macula-off RRD occurs were not available, and considering the FAZ and parafoveal VD are symmetrical in both eyes in healthy subjects, the values of the healthy fellow eye served as a control.[33] FAZ and parafoveal VD are measured on a ratio scale, so we calculated the percentage difference as $\frac{study-control}{control} \times 100\%$. BCVA and metamorphopsia scores are measured on an interval scale for which we calculated the difference as ($study - control$). For aniseikonia, there was no control because each patient had one score for both eyes.

A linear mixed-effects model with nested random effects (eyes nested within patients) were used to investigate the evolution of parafoveal VD for both the study and control eye during 12 months of follow-up, and differences in evolution of parafoveal VD between the study and control eye. The same analysis was performed to investigate the evolution of FAZ for both study and control eye during 12 months of follow-up, and differences in the evolution FAZ between study and control eye.

Preoperative visual acuity values were transformed from decimal to logMAR equivalents for statistical analysis (counting fingers and hand movements were considered as 1.6 logMAR and 1.9 logMAR, respectively).[34]

A paired t-test was used to evaluate differences in reproducibility between study and control eyes.

A P value of less than 0.05 was considered statistically significant. We corrected for multiple testing using the Bonferroni correction to adjust the threshold for statistical significance. This applies to the comparison of postoperative visual functions between study and control eyes (four comparisons, the threshold for statistical significance was adjusted to 0.013), the correlation between the difference in OCTA parameters with the difference in visual function scores (30 correlations, the threshold for statistical significance was adjusted to 0.0017) and multiple mixed effects models (six models, the threshold for statistical significance was adjusted to 0.008).

Statistical analyses were performed using SPSS statistics version 24.0 (SPSS, Inc, Chicago, IL), except for the mixed model analyses, which were performed using R version 3.6.1 (The R Foundation, Vienna, Austria).

Table 1. Patient Inclusion and Exclusion Criteria

Criteria	*n*
Total included	80
Total excluded	33
Re-detachment	8
Cystoid macular edema	6
Poor quality OCTA images	4
Preoperative macular hole	3
Epiretinal membrane stage 2 or more	1
Lost to follow-up	1
Silicone oil tamponade	2
Persistent subfoveal fluid postoperative	2
Uveitis	1
Giant tear	1
Vitreomacular traction	1
Vitreous hemorrhage	1
Vitreoretinal surgery for epiretinal membrane	1
RD in the fellow eye	1
Total patients for analysis	47

Results

We included 80 patients, of which 33 were excluded during the study. Reasons for exclusion are summarized in Table 1. A total of 47 patients remained for analysis.

Patient Characteristics

The majority of the patients were male (77%) with a mean age of 60 years (Table 2).

Four patients underwent scleral buckling and the remaining 43 patients underwent vitrectomy. Of the 43 study eyes that underwent vitrectomy, 10 eyes were pseudophakic and 37 eyes were phakic. Nine patients underwent phacoemulsification combined with vitrectomy, and 15 eyes had phacoemulsification during the 1-year follow-up. At 12 months postoperatively, 34 study eyes (72%) where pseudophakic and 13 study eyes (28%) were phakic.

Visual Function 12 Months Postoperatively

Preoperative BCVA in study eyes was 1.3 (range 0.7–1.6) logMAR and improved to 0.08 (range 0.0–0.2) logMAR 12 months postoperatively ($P < 0.001$). At 12 months postoperatively, the BCVA in fellow eyes was better compared with study eyes ($P < 0.001$) (Table 3).

Table 2. Baseline Demographic Data

Characteristics	
Total patients	47
Gender	
Male	36 (77)
Age (years)	60 ± 9
Study eye	
OD	23 (49)
Preoperative BCVA (logMAR)	1.3 (0.7–1.6)
Quadrants of detachment	
1	10 (21)
2	20 (43)
3	13 (28)
4	4 (8)
Duration of macular detachment (days)	5 (3–7)
Preoperative lens status	
Phakic	37 (79)
Pseudophakic	10 (21)
Surgery technique	
Scleral buckling	4 (8)
Vitrectomy	43 (92)
Combined with phacoemulsification	9 (21)

Values are number (%), mean ± standard deviation, or median (interquartile range).

The presence of metamorphopsia was shown in 42 study eyes, whereas it was not present in fellow eyes. Aniseikonia was present in 25 patients, with micropsia being the most common type as it was perceived by 23 patients.

Correlation between OCTA Parameters and Visual Function

OCTA en face images of study eyes showed both smaller and larger FAZ compared with the control eyes. An example of two patients is presented in Figure 1. Plots of FAZ difference against BCVA difference suggest a positive correlation for the SVP, ICP and DCP at 12 months after surgery (Fig. 2). However, only the FAZ difference in the DCP was correlated with BCVA difference ($P = 0.0004$, r = 0.5); this finding was also true after correcting for central retinal thickness (Supplementary Data). Both metamorphopsia and aniseikonia scores showed no evidence of correlation with changes in FAZ and parafoveal VD.

Evolution of the Microvasculature during 12 Months of Follow-up

For the FAZ, there was no evidence that there was a difference between study and control eyes at 1.5 months postoperatively (Fig. 3) (SVP, $P = 0.009$; ICP, $P = 0.555$; DCP, $P = 0.109$). Furthermore, the FAZ in study eyes did not change over time (SVP, $P = 0.834$; ICP, $P = 0.529$; DCP, $P = 0.226$). At 12 months postoperatively, median FAZ of control eyes was decreased by 0.04 mm^2 and 0.02 mm^2 in the SVP and ICP and increased by 0.02 mm^2 in the DCP compared with 1.5 months postoperatively. However, these changes in control eyes

Table 3. Visual Function 12 Months Postoperative in Study Eye and Healthy Control Eyes

Visual Function	Study Eye	Fellow Eye	*P* Value
BCVA, LogMAR	0.08 (0.0 to 0.2)	−0.08 (−0.1 to 0.0)	<0.001
Metamorphopsia			
M_H score (°)	0.7 (0.3 to 0.9)	0.0 (0.0 to 0.0)	<0.001
M_V score (°)	0.7 (0.4 to 1.0)	0.0 (0.0 to 0.0)	<0.001
Present	42 (89)	0 (0)	<0.001
Aniseikonia*			
A_H score (%)		−1 (−4 to 0)	
A_V score (%)		0 (−3 to 0)	
No aniseikonia		20 (43)	
Micropsia		23 (49)	
Macropsia		2 (4)	
Failed measurement†		2 (4)	

Values are median (interquartile range) or number (%).
A_H, aniseikonia horizontal; A_V, aniseikonia vertical;
M_H, metamorphopsia horizontal; M_V, metamorphopsia vertical
*Binocular test.
†Owing to tilted vision.

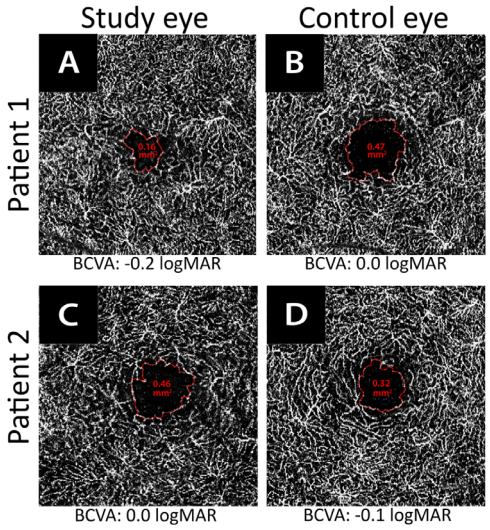


Figure 1. OCTA en face images of the DCP and BCVA of two patients at 12 months postoperatively. The perimeter and size of the FAZ are indicated in *red*. Preoperative BCVA was 1.0 logMAR for both patients. In patient 1, the FAZ of the study eye was smaller compared with the control eye (A, B). In contrast, patient 2 showed a larger FAZ in the study eye compared with the control eye (C, D).

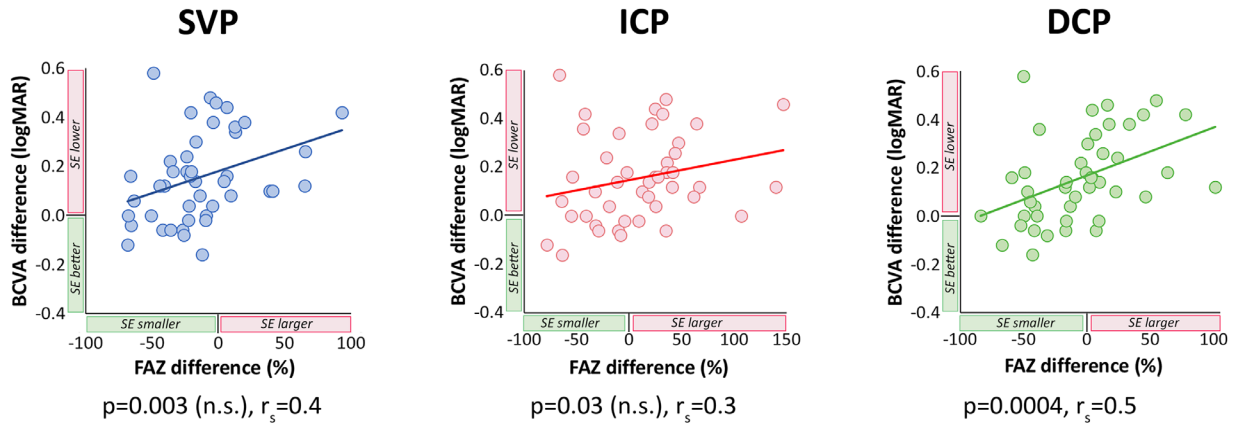


Figure 2. Correlation between FAZ difference and BCVA difference in the SVP, ICP, and DCP at 12 months after surgery. The linear line is the trendline of the values. n.s., not significant; r_s, Spearman's rank correlation coefficient; SE, study eye.

were not different compared with study eyes over time (SVP, $P = 0.901$; ICP, $P = 0.347$; DCP, $P = 0.471$).

Graphs of the VD gave the impression that values in study eyes are lower compared with control eyes at 1.5 months postoperatively (Fig. 4). However, there was no evidence that there was a difference between both eyes (SVP, $P = 0.102$; ICP, $P = 0.114$; DCP, $P = 0.162$). The evolution of parafoveal VD in study eyes did not change over time (SVP, $P = 0.538$; ICP, $P = 0.604$; DCP, $P = 0.950$) and although the parafoveal VD of control eyes changed during 12 months of follow-up, these changes were not different compared with study eyes over time (SVP, $P = 0.611$; ICP, $P = 0.651$; DCP, $P = 0.847$).

Reproducibility of FAZ and Parafoveal VD

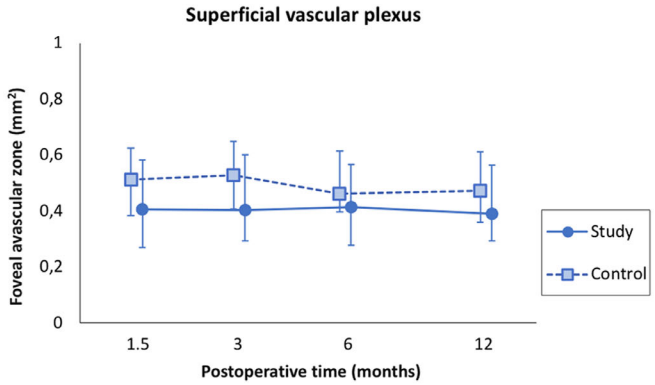
Eighteen patients were included for the evaluation of reproducibility. There was no difference in reproducibly of FAZ between the study eye and control eye ($P > 0.05$). This was also true for the reproducibility of parafoveal VD ($P > 0.05$) (Fig. 5).

Discussion

This prospective study investigated the association between the change in FAZ and VD with final BCVA, metamorphopsia and aniseikonia in eyes after surgery for macula-off RRD. We also investigated the evolution of the FAZ and VD during 12 months of follow-up.

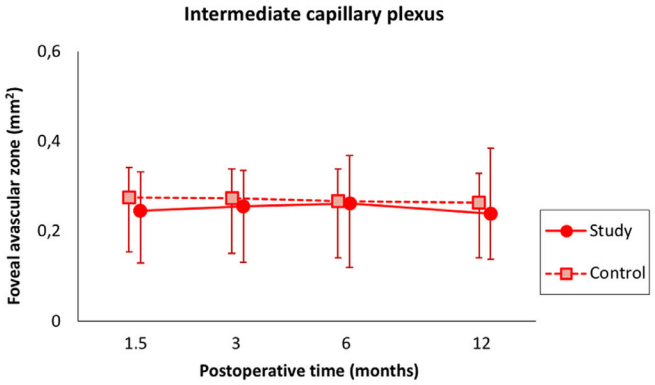
This study is the first to investigate the change in FAZ and VD caused by macula-off RRD. Owing to the interindividual variability of FAZ and VD, it is not possible to use one reference value for all patients. Considering the FAZ and parafoveal VD are symmetrical in both eyes in healthy subjects,[33] we used the healthy fellow eyes as a reference and calculated the difference of FAZ, VD, and visual function in the study eye compared with the fellow eye for each patient. We noted that the FAZ difference of the DCP was strongly correlated with BCVA difference. Previous studies which investigated the association between the FAZ in the superficial capillary plexus and DCP with BCVA produced inconsistent results: Bonfiglio et al.[19] and Yui et al.[16] reported strong correlations between FAZ and BCVA, whereas Sato et al.[18] did not find any correlation between the FAZ and BCVA. These inconsistent results may be due to the fact that the values of the study eyes were analyzed without considering the healthy eye as a control. Thus, for future studies it would be of additional value to interpret the OCTA parameter values of the study eye in reference to the healthy eye, to take the interindividual variability of OCTA parameters into account.

We observed a trend of smaller FAZ in the study eyes compared with the healthy control eyes in all three plexuses, but there was no evidence that there was a difference between both eyes for all plexuses. The current literature reports contradicting results regarding the FAZ after surgery for macula-off RRD. One study[19] reported no difference in FAZ between macula-off RRD eyes and control eyes, and two other studies[15,17] reported larger FAZ in macula-off RRD eyes compared with control eyes. These contradicting results can be explained by differences in control groups. Identical to our study, Bonfiglio et al.[19] measured the healthy fellow eye of the macula-off RRD patients as control. This method is appropriate because the FAZ has been shown to be similar in both



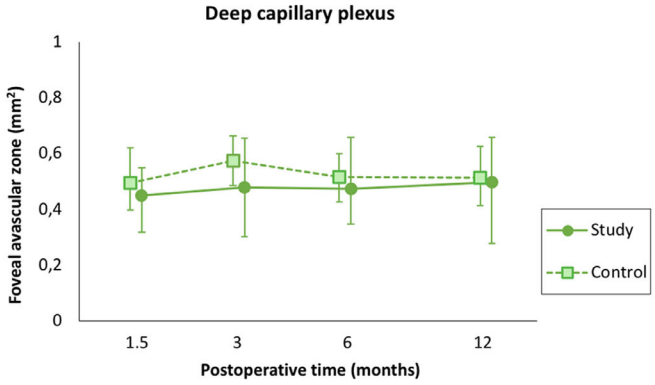
Postoperative time	Foveal avascular zone (mm²) *median (IQR)*	
	Study eye	Control eye
1.5 months	0.40 (0.27-0.58)	0.51 (0.38-0.62)
3 months	0.40 (0.29-0.60)	0.53 (0.41-0.65)
6 months	0.41 (0.28-0.57)	0.46 (0.40-0.62)
12 months	0.39 (0.29-0.56)	0.47 (0.36-0.61)

p=0.009*
p=0.834†
p=0.901‡



Postoperative time	Foveal avascular zone (mm²) *median (IQR)*	
	Study eye	Control eye
1.5 months	0.25 (0.13-0.33)	0.28 (0.15-0.34)
3 months	0.26 (0.13-0.34)	0.27 (0.15-0.34)
6 months	0.26 (0.12-0.37)	0.27 (0.14-0.34)
12 months	0.24 (0.14-0.39)	0.26 (0.14-0.33)

p=0.555*
p=0.529†
p=0.347‡



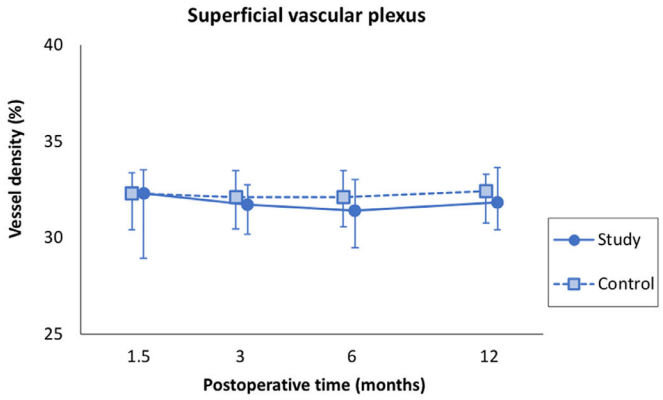
Postoperative time	Foveal avascular zone (mm²) *median (IQR)*	
	Study eye	Control eye
1.5 months	0.45 (0.32-0.55)	0.49 (0.40-0.62)
3 months	0.48 (0.30-0.66)	0.57 (0.49-0.66)
6 months	0.47 (0.35-0.66)	0.52 (0.43-0.60)
12 months	0.50 (0.28-0.66)	0.51 (0.41-0.63)

p=0.109*
p=0.226†
p=0.471‡

Figure 3. FAZ in healthy control eyes and eyes after macula-off RRD in three plexuses during 12 months of follow-up. Results are presented as median, error bars show interquartile range (IQR). *Difference between study and control eye at 1.5 months postoperatively. †Change of evolution in study eye. ‡Difference between study and control eye over time.

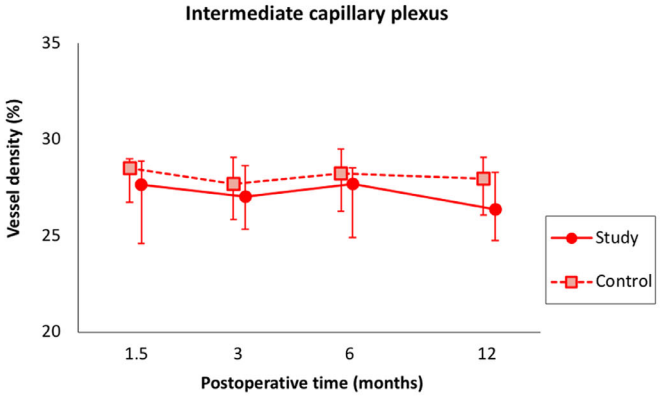
eyes of healthy volunteers, but varies among individuals.[35] Agarwal et al.[15] compared macula-off RRD eyes to eyes of healthy control subjects and found a larger FAZ in macula-off RRD eyes. It is possible that the difference in FAZ between the study and control group is caused by the variability of FAZ in the groups. The study of Woo et al.[17] included patients with macula-on and macula-off RRD, and, although they measured the healthy fellow eyes as controls, macula-off eyes were compared with the control eyes of both macula-on and macula-off patients. Similar to the study of Agarwal et al.,[15] the observed difference could also be due to the interindividual variability of FAZ.

We hypothesized that the DCP may be upregulated after RRD to provide oxygen to the photoreceptors, resulting in a decreased FAZ and an increased VD.



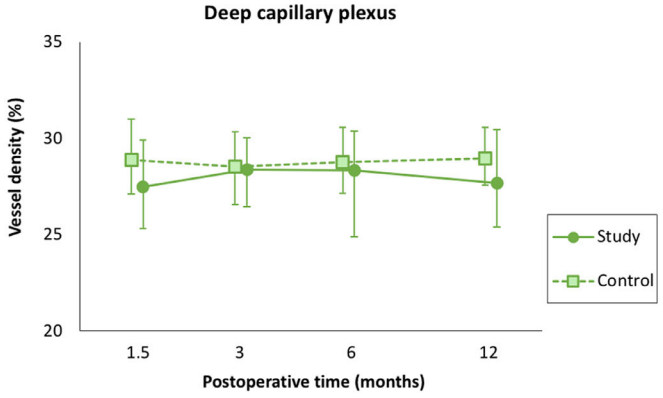
Postoperative time	Vessel density (%) *median (IQR)*	
	Study eye	Control eye
1.5 months	32.3 (29.0-33.6)	32.3 (30.4-33.4)
3 months	31.7 (30.2-32.8)	32.1 (30.5-33.5)
6 months	31.4 (29.5-33.0)	32.1 (30.6-33.5)
12 months	31.9 (30.4-33.7)	32.4 (30.8-33.3)

p=0.102*
p=0.538†
p=0.611‡



Postoperative time	Vessel density (%) *median (IQR)*	
	Study eye	Control eye
1.5 months	27.7 (24.6-28.9)	28.5 (26.8-29.0)
3 months	27.1 (25.3-28.6)	27.7 (25.9-29.1)
6 months	27.7 (24.9-28.5)	28.2 (26.3-29.1)
12 months	26.4 (24.8-28.3)	28.0 (26.1-29.1)

p=0.114*
p=0.604†
p=0.651‡



Postoperative time	Vessel density (%) *median (IQR)*	
	Study eye	Control eye
1.5 months	27.5 (25.3-29.9)	28.9 (27.1-31.0)
3 months	28.4 (26.5-30.0)	28.5 (26.6-30.4)
6 months	28.4 (24.9-30.4)	28.8 (27.2-30.6)
12 months	27.7 (25.4-30.5)	29.0 (27.6-30.6)

p=0.162*
p=0.950†
p=0.847‡

Figure 4. Parafoveal VD in healthy control eyes and eyes after macula-off RRD in three plexuses during 12 of months follow-up. Results are presented as median, error bars show interquartile range (IQR). *Difference between study and control eye at 1.5 months postoperatively. †Change of evolution in study eye. ‡Difference between study and control eye over time

Variations in the two parameters could explain the variation in visual recovery observed in patients with macula-off RRD. The results of our current study partially support our hypothesis. The FAZ difference of particularly the DCP was strongly correlated with the BCVA difference at 12 months after surgery. This finding means that the BCVA is higher when the FAZ in the study eye is smaller compared with the healthy control eye. We also noted that a decrease in FAZ was already present at 6 weeks after surgery, because there was no evidence that the FAZ changed during follow-up. This decrease in the FAZ area may be caused by angiogenesis in the DCP to compensate for the damage caused by RRD. In patients after an ischemic

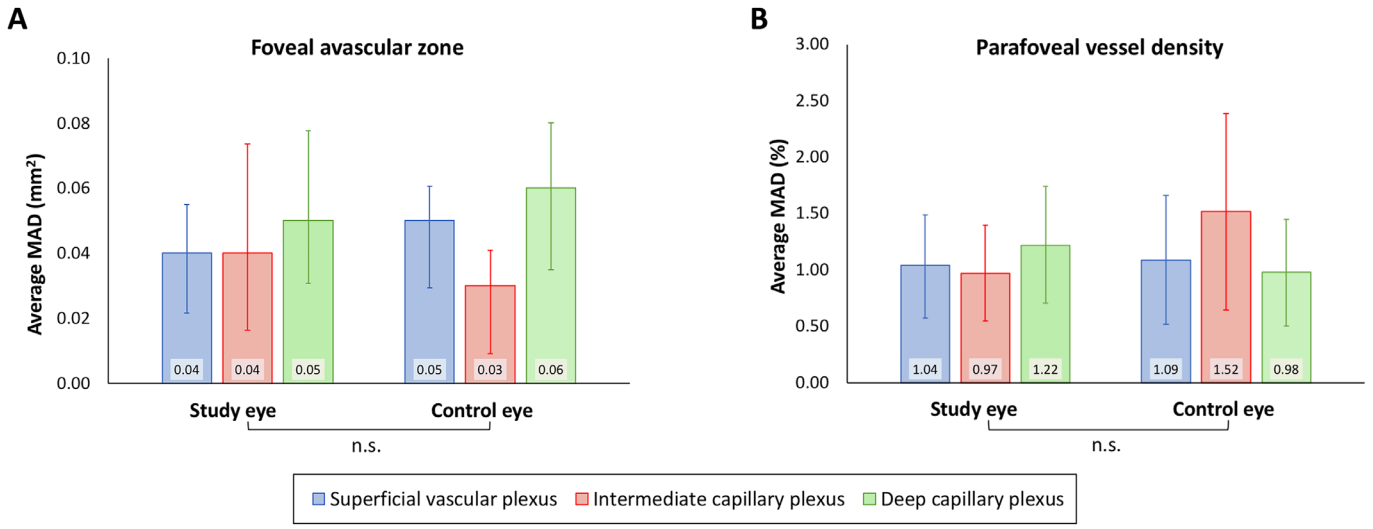


Figure 5. Reproducibility of FAZ (A) and parafoveal VD (B) in healthy control eyes and eyes after macula-off RRD in three plexuses. Results are presented as means, error bars show 95% confidence intervals. MAD, mean absolute deviation; n.s., not significant.

stroke, angiogenesis has been associated with improved functional outcomes, which resulted in interventions to promote angiogenesis in these patients.[36] It is possible that similar pathways occur in macula-off RRD, in which case therapeutic stimulation of angiogenesis in the DCP could be beneficial to photoreceptor regeneration. Hence, stimulation of angiogenesis can be a new possibility of therapeutic intervention to improve visual function outcomes in patients with macula-off RRD.

Another possible explanation for the decrease in the FAZ area is a contraction of the retina, which may occur in RRD eyes.[37] However, retinal contraction would most likely result in macropsia,[38] and the majority of our patients perceived micropsia.

As for the parafoveal VD, there were no differences between the study and control eyes over time and no strong correlation was found between the parafoveal VD difference and BCVA difference. OCTA detects flow but does not provide information about the flow rate,[39] so although the parafoveal VD was unchanged, it is possible that the flow rate was increased in study eyes. Further research is necessary to confirm our hypothesis.

Considering the variation of BCVA in patients after macula-off RRD,[1,2] it would be of additional value to identify early postoperative predictors of final BCVA. We speculated that the FAZ difference of the DCP at 1.5 months postoperatively could serve as an early predictor of final BCVA, because there was no evidence that the FAZ difference of the DCP changed during follow-up, and the value at 12 months postoperatively was associated with final BCVA difference. Unfortunately, our speculation could not be confirmed because additional analyses showed no strong correlation between the FAZ difference of the DCP at 1.5 months and the final BCVA difference.

FAZ and parafoveal VD reached high levels of reproducibility in patients after surgery for macula-off RRD. We expected that the reproducibility would be higher in healthy control eyes, but we found a large variation of average mean absolute deviation for both FAZ and parafoveal VD. This was due to one or two outliers in each series, which had a large impact owing to the small sample size. The outliers were caused by floaters, which resulted in a difference in signal between two consecutive scans. However, there was no evidence that the reproducibility of control eyes was different from study eyes.

This study protocol was initially designed to investigate the correlation between the duration of macular detachment and visual function outcomes.[40] We did not find a correlation between duration of macular detachment and final BCVA in this study, which may seem counterintuitive; animal studies have shown that photoreceptor apoptosis peaks at 2 to 3 days after RD and decreases to a low level 7 days after RD.[21,22] Our inability to determine the exact onset of macular detachment in humans may explain why the results of animal studies do not clearly match those found in clinical studies.

Because the OCTA parameters were the secondary outcome parameters of the study protocol, an a priori sample size calculation was not performed. Therefore, the observed correlations in current study should therefore be interpreted with caution as these results can be

an overestimation of the real effect size.[41] However, an estimate based on the results of current study (sample size = 47, $r_s = 0.5$, one-sided significance level of $\alpha = 0.05$) yields a post hoc power of 98% (G*Power, version 3.1.9.6). These results warrant a properly powered study of the association between the FAZ and BCVA in the near future.

The strengths of our study are that it is the largest OCTA study of patients with macula-off RRD in the current literature; the long follow-up; the analysis of the SVP, ICP, and DCP separately; and preoperative OCT to confirm macular status. Furthermore, all postoperative assessments were performed by one investigator.

As for limitations, not all study eyes were pseudophakic and, although the OCTA scan quality was not compromised, cataract may have influenced the VD measurement as well as visual acuity outcome. In contrast, FAZ measurement is more robust and not strongly affected by cataract.[42] Cataract could also interfere with final BCVA. However, all patients were monitored during 12 months of follow-up, which included BCVA measurement and cataract evaluation. Phacoemulsification was performed when cataract was considered to compromise vision. Hence, the interference of cataract on final BCVA was limited.

In addition, reliable visualization of the choroidal blood flow was not feasible with the OCTA used in this study. Including the choroidal blood flow would offer a more comprehensive evaluation of chorioretinal microvasculature.

In conclusion, although FAZ and VD remained stable during 12 months after surgery for macula-off RRD, a smaller FAZ in the DCP is associated with better final BCVA. Our findings suggest that angiogenesis has occurred and is associated with improved BCVA, which may offer new possibilities in therapeutic interventions for patients with RRD.

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