

# Retinal Microvasculature Changes After Repair of Macula-off Retinal Detachment Assessed with Optical Coherence Tomography Angiography

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**Objective:** To characterize the microvascular retinal changes after repair of macula-off rhegmatogenous retinal detachment (RRD) using optical coherence tomography angiography (OCT-A).

**Patients and Methods:** A retrospective review of patients who underwent repair of macula-off RRD. Fellow unaffected eyes were used as controls. Post-operative OCT-A allowed comparison of vessel density (VD) and foveal avascular zone (FAZ) area in the superficial and deep retinal capillary plexus (DCP) as well as VD in the choriocapillaris layer.

**Results:** Seventeen eyes of 17 RRD patients were included in the final analysis. There was a reduction in VD of the deep retinal capillary plexus in affected eyes compared to fellow eyes ( $p = 0.046$ ). RRD eyes with reduced VD in DCP compared with their fellow control eyes had worse visual acuity after repair compared to those without ( $p = 0.032$ ). No significant microvasculature changes were detected in the FAZ area and VD in the superficial capillary plexus and choriocapillaris compared to fellow eyes.

**Conclusion:** In macula-off RRD eyes, significant microvascular changes were detected in the DCP using OCT-A even after successful anatomical repair. Decreased VD in the DCP compared to the fellow healthy eyes was correlated with worse visual acuity.

**Keywords:** microvascular changes, OCT-angiography, macula-off retinal detachment

## Background and Objective

While anatomic success for retinal reattachment after macula involving (mac-off) rhegmatogenous retinal detachment (RRD) is reported as near or greater than 90%,<sup>1-6</sup> there is a wider range of outcomes for final visual acuity. Most large series demonstrate that approximately 40% of patients will attain visual acuity of 20/50 or better.<sup>4,7</sup>

A number of studies have utilized optical coherence tomography (OCT) imaging for enhanced evaluation of the retinal microstructure in the post-operative period, identifying features that correlate with visual outcome.<sup>8-11</sup> These have included outer retinal layer abnormalities, such as loss of external limiting membrane integrity, disruption of ellipsoid zone (EZ), and decreased photoreceptor outer segment length. Although there have been several older studies on the effect of retinal detachment (RD) on vascular flow,<sup>12-17</sup> there is less known about the association between vascular changes and final visual acuity.<sup>18-21</sup>

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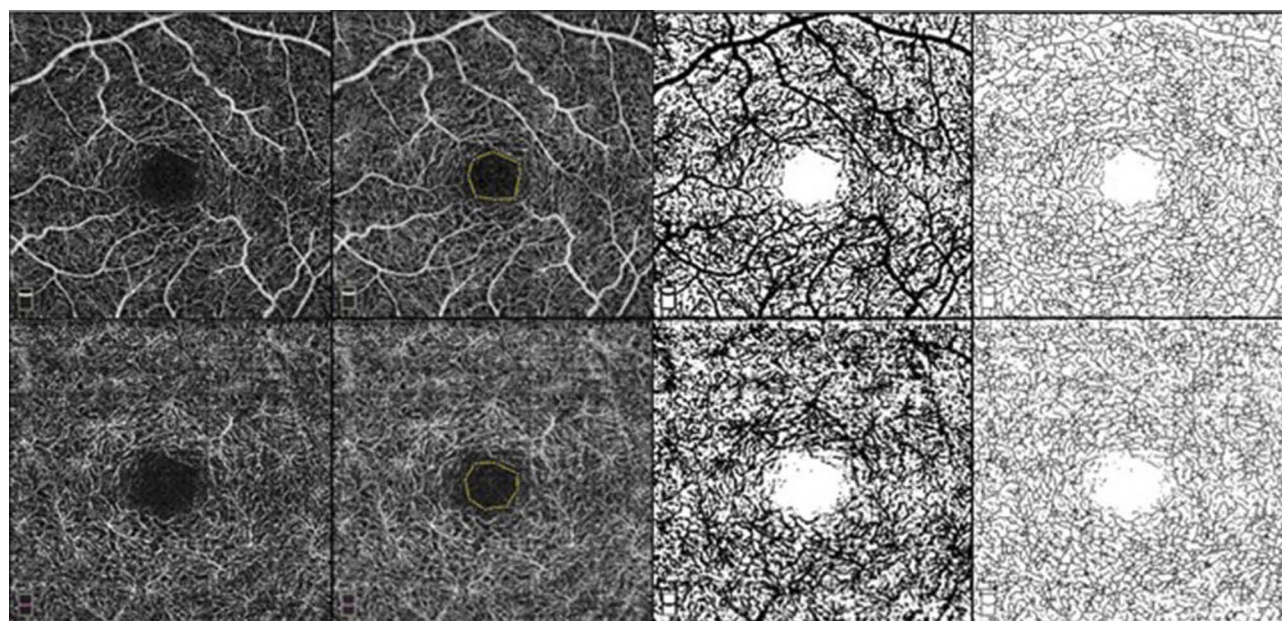
OCT-Angiography (OCT-A) provides in vivo, non-invasive imaging of real-time blood flow through the retinal and choroidal vasculature. It has been extensively investigated in macular degeneration, retinal vein occlusion, diabetic retinopathy, posterior uveitis and optic neuropathies.<sup>22–27</sup> Recently, few reports investigated OCT-A parameters after mac-on<sup>28–30</sup> or mac-off<sup>28,29,31,32</sup> RD repair including vascular density (VD) and FAZ area and correlated those with visual function. Building on those reports, we herein employed OCT-A to evaluate microvascular changes in the superficial (SCP) and deep capillary plexuses (DCP), choriocapillaris and the FAZ area and their correlation with final best corrected visual acuity (BCVA) in eyes after mac-off RRD repair using the fellow eyes as controls.

## Patients/Materials and Methods

We conducted a retrospective review of consecutive patients with a diagnosis of mac-off RRD with foveal detachment who underwent primary repair with pars plana vitrectomy (PPV) by two surgeons (JBM, DW) from November 2015 to August 2017, and who had been imaged with OCT-A. Institutional Review Board approval was obtained from the Massachusetts Eye and Ear Human Studies Committee and the study adhered to the tenets of the Declaration of Helsinki. Informed consent was waived in the present study due to its retrospective nature and data were de-identified to protect patient confidentiality.

Exclusion criteria were eyes with traumatic or tractional RD, previously diagnosed retinal pathology or poor quality OCT-A imaging data, as assessed by an experienced grader (JCW). Only eyes with single surgery anatomic success were included. The unaffected, fellow eyes were used as controls. From medical records, we collected demographic and clinical data, such as patient age, sex, and systemic comorbidities. Each patient had visual acuity assessment and complete ophthalmic examination pre- and post-operatively. OCT-A imaging was acquired on the Optovue Avanti SD-OCT system (Optovue, Inc, Fremont, CA, USA) in both eyes during post-operative visits after resolution of the intravitreal gas bubble. Final best corrected visual acuity was recorded at the most recent follow-up.

For image analysis, we exported the OCT-A images (3mm x 3mm) of the superficial and deep retinal capillaries, and choriocapillaris; and then imported them into ImageJ (National Institute of Health, Bethesda, Maryland, USA). Using this software, we converted them to 8 bit images, binarized them using the “Otsu” algorithm, and then skeletonized them using ImageJ to control for individual vessel thickness (see [Figure 1](#)). Capillary vessel density (VD) was calculated as the percent area occupied by the vessels. The foveal avascular zone (FAZ) of both superficial and deep retinal capillary images was outlined manually with the polygon function, and the FAZ area was subsequently



**Figure 1** Sample OCT-A images of a control, non-RRD left eye of an affected patient. The top row shows superficial retinal capillary plexus. The bottom row shows deep retinal capillary plexus. Left most images represent raw data. Second column images show manually outlined FAZs. Third column images show binarized images. Right most images show skeletonized data on which vessel density was calculated.

calculated for both layers. Image analysis was conducted by one author who was masked to the affected RRD eye (JCW).

All statistics were performed using the computing environment R (R Core Team, 2017, Vienna, Austria). Paired *T*-test analysis was used to compare capillary VD and FAZ in eyes affected by RRD and unaffected control eyes. Wilcoxon rank-sum test analysis was used to compare RRD eyes with and without decreased deep capillary VD. A multivariate analysis with dependent variables the VD OCT-A parameters and independent variables the time interval from the RD repair to OCT-A acquisition and to BCVA measurement was performed.

## Results

### Demographics

Seventeen eyes of 17 patients with macula-off RRD were included in the final analysis. The respective healthy fellow eyes were used as controls. Demographic characteristics are shown in Table 1. Two patients were excluded from analysis for preexisting retinal pathology, and one for chronic RRD which underwent repair by PPV and scleral buckle (SB). The mean age was 57 years (standard deviation 11 years, range 25 to 69 years) and the average time from presentation with RRD to repair was 3 days (range 0–6). The mean post-operative follow-up was 8 months (range 1 to 23 months), and OCT-A was obtained on average 4 months after repair (range 1 to 16 months). Table 2 provides a summary of the individual RRD eyes data sorted by final visual acuity from best to worst. Of the 17 included RRD eyes, 11 were phakic and 6 were pseudophakic at the time of RD repair. Four of these 11 initially phakic patients had undergone cataract extraction with intraocular lens implantation after RD repair by the time of their OCT-A assessment. Table 3 provides individual data for the fellow unaffected eyes.

### Visual Function

Presenting visual acuity ranged from 20/30 to hand motion (HM). After successful repair, the mean final best corrected visual acuity (BCVA) was 20/34. The BCVA in affected eyes ranged from 20/20 to 20/150. Most importantly, there was a high degree of visual recovery with 13 of the 17 eyes achieving a BCVA better than 20/40.

### OCT-A Image Analysis

There was a statistically significant reduction in VD of the deep capillary plexus in eyes affected by RRD compared to the fellow control eyes ( $p = 0.046$ ) (Table 4). This reduction in deep capillary plexus VD was observed in 12 out of the 17

**Table 1** Demographics and Clinical Characteristics

Characteristics	
Age (years)	57±11
Sex	
M	11
F	6
Lens status (RRD eyes)	
Pseudophakic prePPV	6
Pseudophakic preOCT-A	10
Pseudophakic at OCT-A	7
RRD repair procedure	
PPV	17
SB	0
Time from RD to repair (days)	3±2
Time from repair to OCT-A (months)	4±4
Follow-up (months)	8±6

**Abbreviations:** RRD, rhegmatogenous retinal detachment; PPV, pars plana vitrectomy; OCT-A, optical coherence tomography-angiography; SB, scleral buckle.

patients included in this analysis and persisted in eyes with follow-up OCT-A as part of their clinical care. These follow-up OCT-A scans were not included in the current study. Additional studies are underway to obtain OCT-As at more standard intervals in a prospective study design. The 12 patients with VD reduction in the deep capillary plexus of the RRD eye compared with the fellow eye had a mean visual acuity 20/39. On the other hand, those five patients with a higher VD of the deep capillary plexus in the eye affected by RRD had a significantly better mean visual acuity of 20/25 ( $p = 0.03$ ). There was no significant difference in VD of the superficial ( $p = 0.13$ ) or choriocapillaris ( $p = 0.28$ ) layers, nor was there a significant difference in the superficial ( $p = 0.32$ ) or deep ( $p = 0.62$ ) FAZ areas between eyes affected by RRD and fellow control eyes. All four of the patients with final visual acuity worse than 20/40 demonstrated reduction in deep capillary plexus VD; however, the magnitude of VD reduction in those eyes with worse than 20/40 vision compared with the fellow eye was small. Of the 12 RRD eyes which demonstrated decreased deep capillary plexus VD, 10 also demonstrated EZ loss on OCT.

On multivariate regression analysis, there was no statistically significant effect of time interval from RD repair to OCT-A on VD of superficial capillary plexus ( $p > 0.05$ ), deep capillary plexus ( $p > 0.05$ ), choriocapillaris ( $p > 0.05$ ), superficial or deep FAZ ( $p > 0.05$ ). Similarly, there was no statistically significant effect of time from RD repair to BCVA measurement on VD of all the parameters mentioned above

**Table 2** Data for RRD Eyes

Patient	Age	Final VA (LOGMAR)	Time to Repair (d)	Time to OCT-A (m)	Superficial VD*	Deep VD*	Superficial FAZ Area (mm <sup>2</sup> )	Deep FAZ Area (mm <sup>2</sup> )	Choriocapillaris VD*
1	54	0.00	6	12	0.196	0.217	0.131	0.134	0.459
2	56	0.00	4	3	0.220	0.223	0.116	0.230	0.479
3	61	0.10	1	4	0.193	0.203	0.000	0.010	0.478
4	67	0.10	3	4	0.222	0.213	0.265	0.325	0.487
5	48	0.10	3	2	0.205	0.219	0.167	0.168	0.483
6	54	0.10	5	1	0.196	0.227	0.015	0.051	0.479
7	48	0.18	3	8	0.195	0.224	0.140	0.135	0.473
8	57	0.18	1	1	0.204	0.215	0.214	0.242	0.500
9	62	0.18	2	1	0.197	0.215	0.102	0.177	0.483
10	67	0.18	0	16	0.196	0.17	0.018	0.041	0.492
11	63	0.20	1	1	0.174	0.205	0.175	0.289	0.485
12	65	0.20	3	5	0.183	0.207	0.199	0.171	0.469
13	69	0.20	5	3	0.181	0.205	0.272	0.320	0.478
14	61	0.40	3	4	0.207	0.215	0.214	0.212	0.489
15	43	0.48	1	3	0.203	0.221	0.138	0.194	0.468
16	64	0.48	4	1	0.179	0.213	0.222	0.194	0.486
17	25	0.88	6	1	0.175	0.220	0.037	0.078	0.478
Mean	57	0.23	3	4	0.196	0.215	0.143	0.175	0.478

**Note:** \*VD calculated as % area occupied by retinal capillaries of image total area (3mm x 3mm image area).

**Abbreviations:** d, days; m, months; OCT-A, optical coherence tomography-angiography; VD, vessel density; FAZ, foveal avascular zone.

**Table 3** Data for the Fellow Unaffected Eyes

Patient	Age	Time to OCT-A (m)	Superficial VD*	Deep VD*	Superficial FAZ Area (mm <sup>2</sup> )	Deep FAZ Area (mm <sup>2</sup> )	Choriocapillaris VD*
1	54	12	0.194	0.212	0.128	0.140	0.467
2	56	3	0.208	0.220	0.163	0.197	0.473
3	61	4	0.201	0.226	0.028	0.043	0.482
4	67	4	0.214	0.222	0.271	0.340	0.486
5	48	2	0.221	0.232	0.190	0.172	0.486
6	54	1	0.207	0.216	0.038	0.038	0.499
7	48	8	0.174	0.203	0.144	0.150	0.478
8	57	1	0.227	0.253	0.226	0.280	0.492
9	62	1	0.181	0.233	0.086	0.158	0.478
10	67	16	0.187	0.207	0.000	0.000	0.477
11	63	1	0.203	0.216	0.169	0.138	0.483
12	65	5	0.194	0.231	0.231	0.272	0.475
13	69	3	0.211	0.218	0.305	0.367	0.499
14	61	4	0.184	0.214	0.202	0.216	0.471
15	43	3	0.171	0.188	0.110	0.198	0.463
16	64	1	0.196	0.226	0.226	0.208	0.477
17	25	1	0.205	0.225	0.000	0.039	0.498
Mean	57	4	0.199	0.220	0.148	0.174	0.481

**Note:** \*VD calculated as % area occupied by retinal capillaries of image total area (3mm x 3mm image area).

**Abbreviations:** d, days; m, months; OCT-A, optical coherence tomography-angiography; VD, vessel density; FAZ, foveal avascular zone.

except from VD of the deep capillary plexus, where we found a statistically significant effect ( $p=0.001$ ).

## Discussion

In an attempt to elucidate the mechanism by which retinal detachment causes microvascular macular changes, we

herein employed OCT-A in mac-off RRD eyes following repair, using the healthy fellow eyes as a control group. Compared to the fellow healthy eyes, a statistically significant reduction in VD of the DCP was identified in mac-off RRD eyes with evidence of correlation with final BCVA after repair. RRD eyes with reduced VD in the



**Table 4** Mean Vessel Densities and Foveal Avascular Zone Area in RRD Eyes versus Fellow Eyes

OCT-A Metric	Mean RRD Eyes	Mean Fellow Eyes	p-value
Vessel Density (% of total area)			
Superficial	19.6	20.2	0.129
Deep	21.5	22.3	0.046*
Choriocapillaris	48	48.3	0.282
Foveal Avascular Zone (mm <sup>2</sup> )			
Superficial	0.143	0.148	0.319
Deep	0.175	0.168	0.618

**Note:** \*Signifies statistical significance to the level of 5%.

**Abbreviations:** OCT-A, optical coherence tomography-angiography; RRD, rhegmatogenous retinal detachment.

DCP had worse BCVA after repair compared to those with no statistically significant reduction compared to the fellow eyes. No significant microvasculature changes were detected in the superficial or deep FAZ area, VD in the superficial capillary plexus and choriocapillaris compared to fellow eyes. Our results build on the few recent reports that have investigated mac-off RRD eyes following repair using OCT-A.<sup>28,29,31,32</sup> We herein explore the various suggested mechanisms for the microvascular changes observed even following surgical repair of RRD including the effect of the RD itself, the effect of our surgical intervention for RD repair and the effect of macular detachment on the retinal microvasculature.

A neurosensory RD is thought to lead to outer retinal ischemia, although the exact mechanism is not completely understood. There is animal but not human experimental evidence of transient increase in HIF1 $\alpha$  expression<sup>33</sup> as well as data suggesting that hyperoxia in animal models of RD may be beneficial.<sup>34–36</sup> Separation of the photoreceptors (PR) from retinal pigment epithelium (RPE) leads to a cascade of molecular<sup>37</sup> and biochemical changes<sup>38,39</sup> that lead to activation of a multitude of pathways including inflammation,<sup>40–44</sup> gliosis<sup>45,46</sup> and reparative attempts,<sup>47,48</sup> however, there is an ensuing neuronal cell death from apoptosis<sup>49–52</sup> and necrosis<sup>53–55</sup> that contributes to loss of PR cells and decreased visual function.<sup>54,56–59</sup> The vascular changes associated with RD have not been investigated in similar detail. Sato et al in 1971<sup>12</sup> and Tolentino et al in 1976<sup>13</sup> reported the findings of Fluorescein Angiography (FA) on RD with lattice degeneration focusing mostly in the peripheral changes and reporting flow slowdown, vascular occlusions, arteriovenous shunts and permeability

alterations. Picolino in 1983<sup>14</sup> reported the FA findings of 50 patients with RD confirming the prior peripheral retinal vasculature changes and reporting that central retina vasculature also exhibited diffuse dilatation of the capillary network in the detached retina as well as capillary hyperpermeability. In 1989 Satoh reported that the circulation times were slower in the detached retina compared to the attached areas.<sup>15</sup> Recently, Akiyama et al<sup>60</sup> employed focal macular ERG and reported ERG responses to be reduced in the attached macula of macula-on RRD eyes compared to the fellow eyes, suggesting that alterations in the retinal microcirculation could be observed even in the attached macula (or retina) of eyes having RRD.

All the above studies focused on vascular changes in the detached retina prior to repair. The selection of surgical technique might also play a role in the ensuing retinal microvascular changes following RD repair. Ohkubo in 1988 reported on FA findings before and after repair in only 2 cases and concluded that the disturbed retinal circulation in the detached retina improved after surgery at least the area which was not indented by an explant; whereas an encircling element disturbed the choroidal circulation.<sup>16</sup> Sabates et al in 1989 reported on macular changes after repair and reported mostly on the incidence of CME (16%).<sup>17</sup> Eshita et al in 2004 reported that the microcirculation in the macular area in macula-on RD was diminished after SB and correlated to the extent of the RD; however, it showed signs of recovery over a month.<sup>21</sup> Similar information were provided by Kubicka-Trzaska and Górnjak-Bednarz in 2007.<sup>20</sup> Sato et al did a similar study comparing PPV/gas versus SB and found similar conclusions to the prior two studies and no major difference between SB and PPV as it relates to macular microcirculation but did conclude that use of gas tamponade might have a subclinical adverse effect on the neuroretinal disk rim circulation.<sup>19</sup> In 2011 Kubicka-Trzaska examined the macular microcirculation after repair with the use of silicone oil and reported disturbances in the macular microcirculation that may persist longer than what has been reported before for other types of repair.<sup>18</sup> Recently, Tsen et al used OCT-A to compare different surgical techniques for RRD repair and found vitrectomy alone to render a higher post-operative VD in the choriocapillaris, while the combined vitrectomy and SB procedure lead to lower VD in SCP and DCP compared to SB or vitrectomy alone.<sup>32</sup>

Apart from the effect of RD itself on retinal microvasculature and the effect of the ensuing surgical repair, recently there is growing evidence that macular detachment might further contribute to alterations of the retinal microvasculature. Woo et al used OCT-A to examine the FAZ area in 34 eyes after successful RRD repair<sup>28</sup> and found both the post-operative superficial and deep FAZ area to be significantly larger in the 19 mac-off eyes compared to the 15 mac-on eyes and that the deep FAZ zone was larger in the mac-off compared to the fellow eyes. The changes in FAZ zone correlated with visual acuity in their cohort. Recently, Bonfiglio et al<sup>29</sup> retrospectively reviewed 37 mac-off eyes with a 12-month follow-up using OCT-A and reported decreased SCP and DCP VD parafoveally and decreased foveal DCP VD with final BCVA being negatively correlated to parafoveal DCP VD and foveal SCP VD. They also studied 56 mac-on RRD eyes and found decreased DCP VD parafoveally that was negatively correlated with final BCVA. When comparing mac-on and mac-off RRD eyes, the group found mac-off eyes to have lower SCP VD parafoveally and decreased foveal and parafoveal DCP VD suggesting macula detachment may contribute to microvasculature changes in RRD eyes. They found no difference in FAZ zone in mac-off or mac-on eyes compared to fellow eyes yet they only measured FAZ in one slab without separating SCP and DCP.

Few more recent studies employed OCT-A in an attempt to study RRD in either mac-off or mac-on RRD albeit without directly comparing mac-off with mac-on eyes. Wang et al retrospectively studied 14 eyes with mac-off RRD using OCT-A during the first 12 weeks post-operatively and found gradual recovery of macular perfusion over time with a significant increase in flow density in SCP DCP and CC over time progressively approximating but never reaching the values of the fellow eye. They found final BCVA to be negatively correlated with CC flow deficits but not with SCP or DCP VD. Of interest, CC perfusion recovery reached plateau before recovery of the retinal circulation in SCP, DCP and matching BCVA recovery curve, suggesting recovery of impaired choroidal circulation was important for the improvements in visual function and outer retinal morphology in retinal diseases.<sup>31</sup> Tsen et al prospectively evaluated 28 eyes with mac-off RRD using OCT-A and reported VD to be significantly lower in the SCP and DCP in the RD eyes compared to the fellow eyes<sup>32</sup> while Yoshikawa et al investigated 5 eyes with mac-on RRD pre-operatively and reported parafoveal VD and

FAZ to be not significantly different between the eyes with RRD and the fellow eye suggesting that the macular microvasculature remains intact.<sup>30</sup>

In our study of 17 eyes with mac-off RD, we found a reduction of the VD in the DCP employing OCT-A. Furthermore, we report worse visual outcomes in eyes which had reduced VD in the deep capillary plexus compared with those that did not. We found only a small reduction in VD in the superficial capillary plexus that did not reach statistical significance ( $p=0.13$ ). This might be expected because the superficial capillary plexus supplies the region less affected by the RD. There were no significant differences in the choriocapillaris layer but it should be noted that there are limitations in resolving the individual lobules of the choriocapillaris, which are not always clearly demonstrated with spectral-domain OCT-A.<sup>61</sup> This may have limited our ability to detect subtle changes in choriocapillaris perfusion after RRD. Future studies employing Swept-Source OCT-A could potentially improve accuracy and sensitivity for detecting choriocapillaris lesions.<sup>62–64</sup> Unlike the prior study by Woo et al,<sup>28</sup> we found no statistically significant difference in the superficial or deep FAZ area comparing RRD and fellow eyes.

Our study has limitations related to the small number of eyes, its retrospective nature and lack of longitudinal changes in OCT-A after RD repair. To account for the potential effect of variable time interval from RD repair to OCT-A and BCVA acquisition on OCT-A parameters a multivariate analysis was performed. Our study also did not adjust for the potential effect of axial length on the OCT-A parameters, as with the vast majority (92%) of OCT-A studies.<sup>65</sup> Fortunately, we compared our study eyes to the contralateral fellow control eyes for our comparisons so axial lengths disparities should not disrupt our results. Our cohort also had a narrow range of final visual acuity, with 13 out of 17 (76%) achieving better than 20/40 BCVA after RD repair. The unusually high number of patients with good visual outcome in our series may represent an atypical RD repair group that may not be translatable to all populations. Because of the small range of visual acuity outcomes, our ability to statistically correlate VD and FAZ size with visual acuity was limited. More significant differences in macular microvascular structure may only become more apparent in patients with worse visual outcomes, a population not adequately represented in this study. There may also be other functional measures of vision that better correlate with the identified microvascular changes, such as contrast sensitivity and microperimetry. A larger patient cohort, longer duration of

follow-up, inclusion of patients with worse visual outcome, and use of swept-source OCT-A may help to further elucidate the role of microvascular changes in eyes affected by RRD.

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## Disclosure

Dr Thanos D Papakostas is advisory board for Genentech, Thrombogenics, and Alimera, outside the submitted work. Dr John B Miller reports personal fees from Alcon, Heidelberg, Zeiss, and Allergan, outside the submitted work. The authors declare that they have no other conflicts of interest to disclose relevant to the publication.

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