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Vascular changes after vitrectomy for rhegmatogenous retinal detachment: optical coherence tomography angiography study

Vincenza Bonfiglio,[1] Elina Ortisi,[1] Davide Scollo,[1] Michele Reibaldi,[1] Andrea Russo,[1] Alessandra Pizzo,[1] Giuseppe Faro,[1] Iacopo Macchi,[1] Matteo Fallico,[1] Mario D. Toro,[1,2] Robert Rejdak,[2] Katarzyna Nowomiejska,[2] Lisa Toto,[3] Michele Rinaldi,[4] Salvatore Cillino,[5] Teresio Avitabile[1] and Antonio Longo[1]

[1]Department of Ophthalmology, University of Catania, Catania, Italy
[2]Department of General Ophthalmology, Medical University of Lublin, Lublin, Poland
[3]Ophthalmology Clinic, Department of Medicine and Science of Ageing, University G. D'Annunzio Chieti-Pescara, Chieti, Italy
[4]Department of Ophthalmology, Second University of Napoli, Naples, Italy
[5]Department of Experimental Biomedicine and Clinical Neuroscience, Ophthalmology Section, University of Palermo, Palermo, Italy

ABSTRACT.
Purpose: **To analyse the postoperative foveal avascular zone (FAZ) area, superficial vessel density (SVD) and deep vessel density (DVD) and their correlation with functional (best-corrected visual acuity, BCVA) and anatomical outcomes (foveal macular thickness, FMT) after surgery for rhegmatogenous retinal detachment (RRD) repair.**
Method: **Patients with RRD eyes, successfully treated with a single pars plana vitrectomy (PPV) with gas tamponade and a minimum 12 months follow-up, were re-examined. Foveal avascular zone (FAZ) area, SVD, DVD and FMT were evaluated by using optical coherence tomography angiography (OCTA) and compared to fellow eye.**
Results: **Fifty-six patients with macula-on and 37 with macula-off RRD were included in the study. In both groups, no difference in FMT and FAZ area was found compared to fellow eyes. In macula-on RRD eyes, a lower parafoveal DVD ($p = 0.001$) was detected; FAZ area was related to FMT ($p = 0.025$), and the postoperative BCVA was correlated with parafoveal DVD ($p = 0.010$) and FAZ area ($p = 0.003$). In macula-off RRD eyes, lower parafoveal SDV ($p = 0.012$), and foveal and parafoveal DVD ($p = 0.012$ and $p < 0.001$, respectively) were observed. BCVA was related to FAZ area ($p = 0.012$), foveal SVD ($p = 0.005$) and parafoveal DVD ($p = 0.010$).**
Conclusion: **Rhegmatogenous retinal detachment eyes successfully treated with PPV had lower vessel density in the superficial and deep retinal plexus compared to fellow healthy eyes; BCVA was related to FAZ area and vessel density.**

Key words: foveal avascular zone – rhegmatogenous retinal detachment – superficial and deep vessel density – vitrectomy

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Introduction

Pars plana vitrectomy (PPV) with gas tamponade is a well-established and effective procedure for primary rhegmatogenous retinal detachment (RRD) repair (SPR Study group 2003). However, incomplete visual recovery, colour vision defects or persistent metamorphopsia are often reported despite excellent anatomical results, with postoperative intact inner segment/outer segment (IS/OS) junction and external limiting membrane (ELM) layers on optical coherence tomography (OCT) imaging, especially in cases of RRD with macula off (Ross 2002; Abouzeid & Wolfensberger 2006; Delolme et al. 2012; Cheng et al. 2016).

These data suggest the existence of microstructural macular damage not detected by standard fundus biomicroscopy, fluorescein angiography and other advanced techniques such as OCT.

Optical coherence tomography angiography (OCTA) is a novel, noninvasive method to visualize and measure the foveal avascular zone (FAZ) area and providing quantitative vascular information on macular microcirculation, including the superficial and deep capillary plexus, with good repeatability and reproducibility (Jia et al. 2012; Wei et al. 2013; Wang et al.

2014; De Carlo et al. 2015; Savastano et al. 2015; Spaide et al. 2015).

Recently, Woo et al. (2018) found that, after vitrectomy, superficial and deep FAZ areas were larger in eyes with macula-off RRD than in eyes with macula-on RRD and fellow eyes. In agreement with others authors, they supposed that, in the presence of RRD, in addition to hypoxic damage caused by sensory retinal detachment from the retinal pigment epithelium, ischaemic damage could occur because of changes in retinal vessel and an increase in the level of inflammatory mediators (Cardillo Piccolino 1983; Williams et al. 1983; Ohkubo 1988; Quintyn & Brasseur 2004; Alm & Nilsson 2009; Ricker et al. 2010); this could lead to a poor visual outcome despite successful surgery.

Agarwal et al. (2019), in RRD eyes treated with a successful vitrectomy, showed lower microvascular density than in age-matched healthy controls.

In our study, we analysed, by OCTA, the FAZ area size, the superficial vessel density (SVD) and the deep vessel density (DVD) in eyes with macula-on and macula-off primary RRD eyes, successfully treated by PPV. Values were compared with those of fellow healthy eyes since symmetry of macular vascular OCTA parameters of two eyes has been found in healthy subjects (Iafe et al. 2016; Liu et al. 2017).

Moreover, we evaluated the relationship of these parameters with functional (best-corrected visual acuity, BCVA) and anatomical outcomes (foveal macular thickness, FMT).

Materials and methods

We retrospectively reviewed the clinical records of all patients affected by primary macula-on and macula-off RRD successfully treated with a single procedure of PPV and gas tamponade between January 2016 and March 2017 at the Ophthalmological Clinic of Catania, Italy, and at the Ophthalmology Clinic of Lublin, Poland.

Patients were recalled and, after obtaining a written informed consent from each participant, were re-examined with a complete ophthalmic examination that included the measurement of BCVA, slit lamp and fundus examination, measurement of axial length by A-scan immersion biometry, SS-OCT and OCTA, in both RRD and fellow eyes (used as control). We defined macula-off RRD, patients with macular and foveal detachment in preoperative OCT.

The study was approved by the Institutional Human Experimentation Committee Review Boards of Catania and Lublin University Hospitals and conducted according to the ethics standards of the 1964 Declaration of Helsinki, as revised in 2003.

Criteria for the inclusion in the study were as follows:

1 Age 18 years or older;
2 Anatomically attached retina after at least 12 months from surgery;
3 Intact photoreceptor layer, without any IS/OS and ELM layer abnormalities in the foveal area (structural OCT at the study examination);
4 Absence of any cystic intraretinal or subretinal spaces, or epiretinal membrane, or sub-foveal fibrous bands or residual traction bands (detected by structural OCT at the study examination).

Patients with previous retinal surgery, or any other ocular diseases that could affect visual acuity and vascular density such as glaucoma, diabetic retinopathy, uveitis, macular degeneration, macular hole and high myopia (axial length > 26 mm), in both RRD and fellow eyes, were excluded. Those with an anisometropia > 2.0 Diopters were also excluded.

Data collection/Main outcome measures

Preoperative and intra-operative data collected from the medical records were age, sex, smoking habit, hypertension, diabetes, BCVA, lens status, axial length, retinal detachment extension, number of breaks, time from symptoms (visual fields defects to loss of central vision) to surgery and surgical procedure information, such as single PPV or combined phacovitrectomy, and intra-operative 360° retinal photocoagulation laser application.

At the study examination, the time between surgery and the study examination (Time surgery to OCTA), BCVA, FMT, FAZ area, SVD and DVD were evaluated.

Surgical procedure

Standard 23 G PPV was performed under local anaesthesia in all patients by expert surgeons using the same vitreoretinal machine (Stellaris, Bausch and Lomb). After core vitrectomy, a complete vitreous base removal was performed. Endolaser photocoagulation was applied around the break(s), or 360° retinal photocoagulation was performed in the presence of multiple breaks in many quadrants. Tamponade with 20% sulphur hexafluoride (*SF6*) was used. Cataract surgery was performed during PPV procedure (combined phacovitrectomy) in all phakic eyes.

Table 1. Demographics and preoperative data in patients with primary macula-on and macula-off RRD

		Macula-on RRD (n = 56)	Macula-off RRD (n = 37)	p
Age	Years	62 ± 8	64 ± 5	0.179*
Sex	Males	29 (52%)	23 (62%)	0.395†
Hypertension	No	24 (43%)	10 (27%)	0.131†
Smoker	No	24 (43%)	13 (35%)	0.520†
Diabetes	No	6 (11%)	3 (8%)	1.000†
Pseudophakic	No	31 (55%)	22 (59%)	0.831†
Axial length	mm	24.7 ± 0.7	24.6 ± 0.8	0.526*
RRD extension	Quadrants	2.0 ± 0.8 (1–3)	3.1 ± 0.7 (2–4)	0.001*
Preoperative BCVA	LogMAR	0.14 ± 0.18	1.32 ± 0.20	<0.001*
Time symptoms-surgery	Days	2.2 ± 1.1 (1–5)	3.6 ± 1.3 (2–7)	<0.001*
Combined phacovitrectomy	No	25 (45%)	15 (41%)	0.831†
360° laser	No	13 (23%)	14 (38%)	0.163†
Study visit BCVA	LogMAR	0.06 ± 0.06	0.40 ± 0.26	<0.001*
Time surgery to OCTA	Months	17.2 ± 5.6	16.4 ± 5.7	0.433†

BCVA = best-corrected visual acuity; RRD = rhegmatogenous retinal detachment.
* Unpaired t-test.
† Chi-square test.

Best-corrected visual acuity

The BCVA was assessed using Snellen's visual acuity chart and was converted to the logarithm of the minimum angle of resolution units (logMAR) for the purpose of statistical analysis.

OCTA image acquisition and analysis

Optical coherence tomography angiography was performed using an XR Avanti AngioVue OCTA (version 2017.1.0.151AngioVue Phase 7 Software with PAR), in the angio Retina mode and a scanning area of 6 × 6 mm. Retinal vascular layers were visualized and segmented based on the default settings of the automated software algorithm embedded in the XR Avanti AngioVue OCTA.

The superficial plexus consists of capillaries from 3 μm below the internal limiting membrane (ILM) to 15 μm below the inner plexiform layer (IPL). The deep plexus extends from 15 to 70 μm below the IPL. The choriocapillaris consists of capillaries in a 30 μm thick layer posterior to the retinal pigment epithelium–Bruch membrane junction.

The three-dimensional projection artefacts removal (3D-PAR) algorithm was applied to simplify the OCTA imaging interpretation by enhancing depth resolution of vascular layers. This new algorithm retains the flow signal from real blood vessels while suppressing the projected flow signal in deeper layers, avoiding downward tails on cross-sectional angiograms and duplicated vascular patterns on *en face* angiograms (Iafe et al. 2016).

The images were reviewed by two retinal specialists (AR and MT) for correctness of segmentation; if segmentation errors were observed, they were corrected using the segmentation editing and propagation tool embedded in the AngioVue system.

The updated AngioVue software automatically calculates a single FAZ value as automated FAZ boundary detection provided by the AngioVue software, applied on a retinal slab that includes both superficial and deep vascular plexi (from ILM to OPL + 10 μm). This protocol was used on the basis of recent studies validating a single merged quantitative measurement of the FAZ (Coscas et al. 2016).

The vessel density was defined as the percentage area occupied by vessels in a circular region of interest (ROI) centred on the centre of the FAZ with a diameter of 3 mm included inside the 6 × 6 mm scan area. The AngioVue software automatically splits the ROI into three fields: the foveal area, a central circle with a diameter of 1 mm; and the parafoveal area and perifoveal area of 3.0 and 6.0 mm, respectively. Foveal and parafoveal density of SCP and DCP were analysed. Low-quality OCT angiography images with signal strength index < 50 were excluded from the analysis.

Foveal macular thickness

Foveal macular thickness (FMT) was assessed by the same OCT system (version 2017.1.0.151 AngioVue Phase 7 Software with PAR) at the same time as the retinal vasculature using the retina map mode, which covered a 6.0 × 6.0 mm area centred at the fovea.

The end-points of the study

Primary end-point was to analyse the changes in FAZ area, FMT, SVD and DVD in macula-on and macula-off RRD eyes and in fellow healthy eyes. Secondary end-point was to investigate any possible correlation between postoperative BCVA with vascular parameters (FAZ, SVD and DVD) and FAZ with FMT.

Statistical analysis

Mean values of all parameters detected in RRD eyes and fellow eyes were compared by paired *t*-test. Values in macula-on and macula-off RRD eyes were compared by unpaired *t*-test. Correlation between parameters (FAZ area, FMT, BCVA, SVD and DVD) was tested by Pearson regression. Software IBM SPSS Statistics for Windows, version 21 (IBM Corp., Armonk, N.Y., USA) was used. P values lower than 0.05 were considered as statistically significant.

Results

We identified 245 patients successfully treated with a single procedure of PPV and gas tamponade for RRD between January 2016 and March 2017. We were able to contact and re-evaluate 215 patients; 93 patients (52 males, 41 females, mean age was 62 ± 8 years) fulfilled eligibility criteria and were included in the study.

Participants' demographics and preoperative data are reported in Table 1.

There was no significant difference in terms of mean age, axial length, number of pseudophakic eyes between macula-on and macula-off group; in the macula-on group, RRD involved less quadrants (mean 2 versus 3.1), and time between symptoms and surgery was shorter (2.2 versus 3.6 days; both p = 0.001, unpaired *t*-test) than the macula-off group.

Representative images of SVD, DVD and FAZ in eyes with macula-on and macula-off RRD are reported in Figs 1 and 2.

Macula-on RRD group

Fifty-six patients had a macula-on RRD. At the study examination, mean BCVA was increased to 0.06 ± 0.06 logMAR (p = 0.002 versus baseline, paired *t*-test). Mean FMT was 287 ± 31 μm. Compared to healthy fellow eyes, there was no difference in mean FMT and FAZ area; RRD eyes had a lower DVD in parafoveal area (p = 0.001, paired *t*-test; Table 2).

Macula-off RRD group

Thirty-seven patients had a macula-off RRD. At the study examination, the mean BCVA was 0.40 ± 0.26 logMAR, greater than the preoperative value (p < 0.001, paired *t*-test). Mean FMT was 267 ± 28 μm. Compared to healthy fellow eyes, there was no significant difference in mean FMT and mean FAZ; affected eyes had a lower mean SVD in the parafoveal area (p = 0.012) and lower mean DVD in fovea (p = 0.012) and parafoveal areas (p < 0.001; Table 3).

Comparing macula-on and macula-off RRD eyes, we found that macula-off eyes had lower postoperative FMT, parafoveal SVD and foveal and parafoveal DVD (Table 4). No difference was seen between the two groups of fellow eyes in FMT (p = 0.072) and in other parameters.

Correlation analysis

In eyes with macula-on RRD, a correlation was found between FAZ area and FMT (r = −0.299, p = 0.025; Fig. 3 left). The final BCVA was

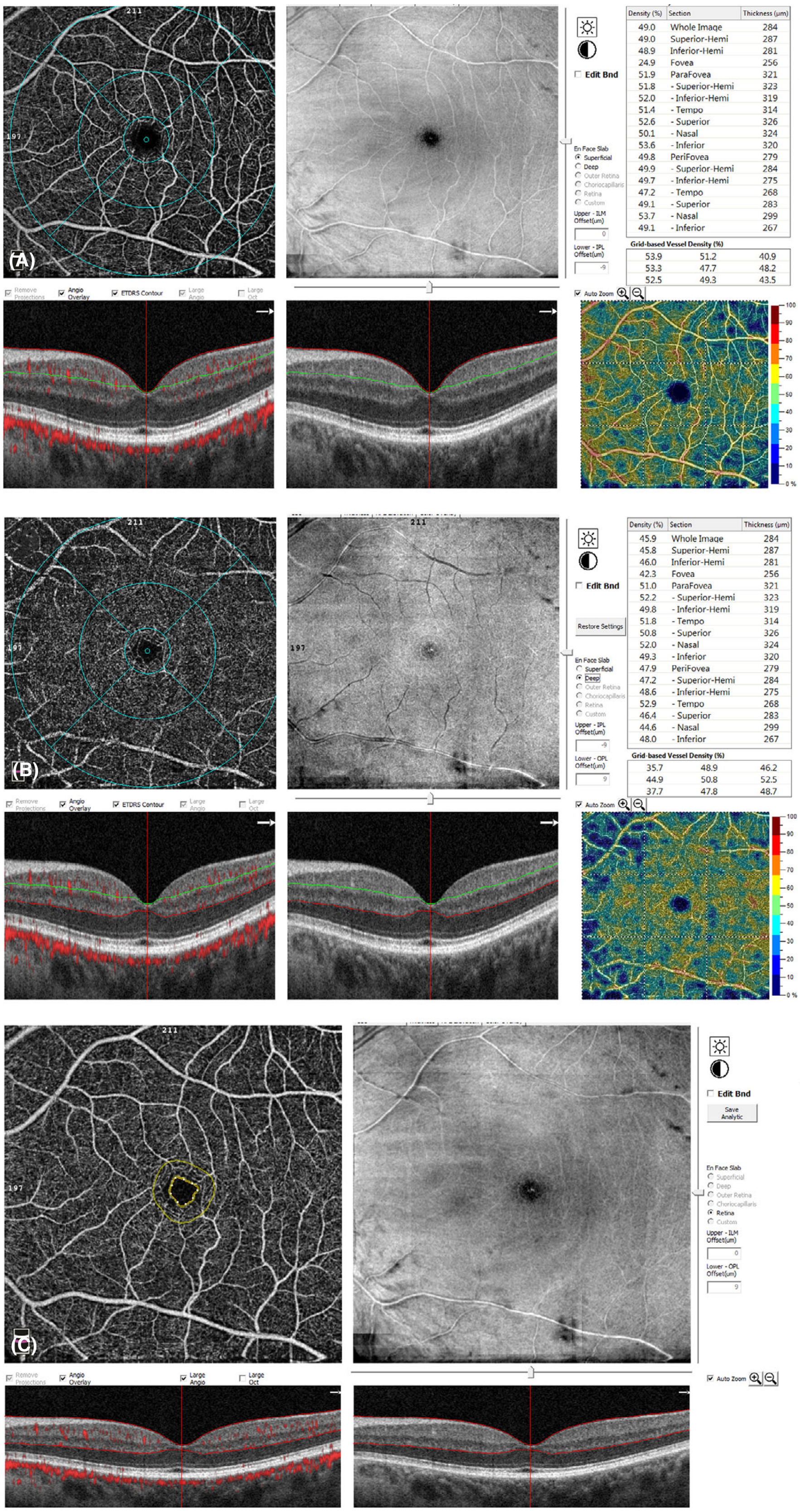

Fig. 1. OCTA in macula-on RRD eyes: (A) Superficial vessel density: above: 6 × 6 enface angiogram with quantitative measurements; below: B scan image (red line = internal limiting membrane; Green line: inner plexiform layer). (B) Deep vessel density: (above) 6 × 6 enface angiogram with quantitative measurements; below: B scan image (green line: inner plexiform layer; red line = outer plexiform layer). (C) Foveal avascular zone (FAZ): area surrounded by the inner yellow line; outer yellow line is 300-µm far from FAZ.

related to parafoveal DVD (r = −0.340, p = 0.010; Fig. 3 middle) and to FAZ area (r = 0.390, p = 0.003; Fig. 3 right). In eyes with macula-off RRD, final BCVA was related to FAZ area (r = 0.408, p = 0.012) (Fig. 4 left), to foveal SVD (r = −0.451, p = 0.005; Fig. 4 middle) and to parafoveal DVD (r = −0.418, p = 0.010; Fig. 4 right). No correlation was found between FAZ area and FMT (r = −0.282, p = 0.080) in this group.

Discussion

In this study, we investigated, by OCT angiography, the vasculature parameters (FAZ area, SVD and DVD) of the macular area in eyes successfully treated by PPV for primary macula-on and macula-off RRD and evaluated their correlation with functional and anatomical outcomes. Other studies have investigated the differences in vascular retinal density after vitrectomy for RRD repair; this is the first reporting the long-term results.

In the macula-on group, compared to fellow eyes, we found no significant difference in postoperative mean FMT, FAZ and SVD, in agreement with Woo et al. (2018) (15 eyes after a 2-month follow-up study)and Yoshikawa et al. (2018) (5 eyes, not specified follow-up); however, we found a lower mean DVD in the parafoveal subfield.

Many hypotheses could be made about the reduction of parafoveal DVD. Landiev et al. (2006), in an experimental model of RRD, found an activation of Muller cells due to inflammation also in not detached retina. Muller cell activation was found to be related with local blood flow alterations in the inner retina and could lead to a secondary decrease in capillary flow density, also in the absence of any clinical structural change (Gaucher et al. 2007).

Another hypothesis is that subretinal fluid could prevent the supply of oxygen from the choriocapillaris to the outer retinal layer, leading to tissue hypoxia and release of cytokines and other inflammatory mediators (Williams et al. 1983; Quintyn & Brasseur 2004; Ricker et al. 2010). Indeed, the levels of inflammatory and vascular mediators, such as the vasoconstrictor peptide endothelin-1, are increased in the subretinal fluid of the detached retina (Alm & Nilsson 2009; Roldán-

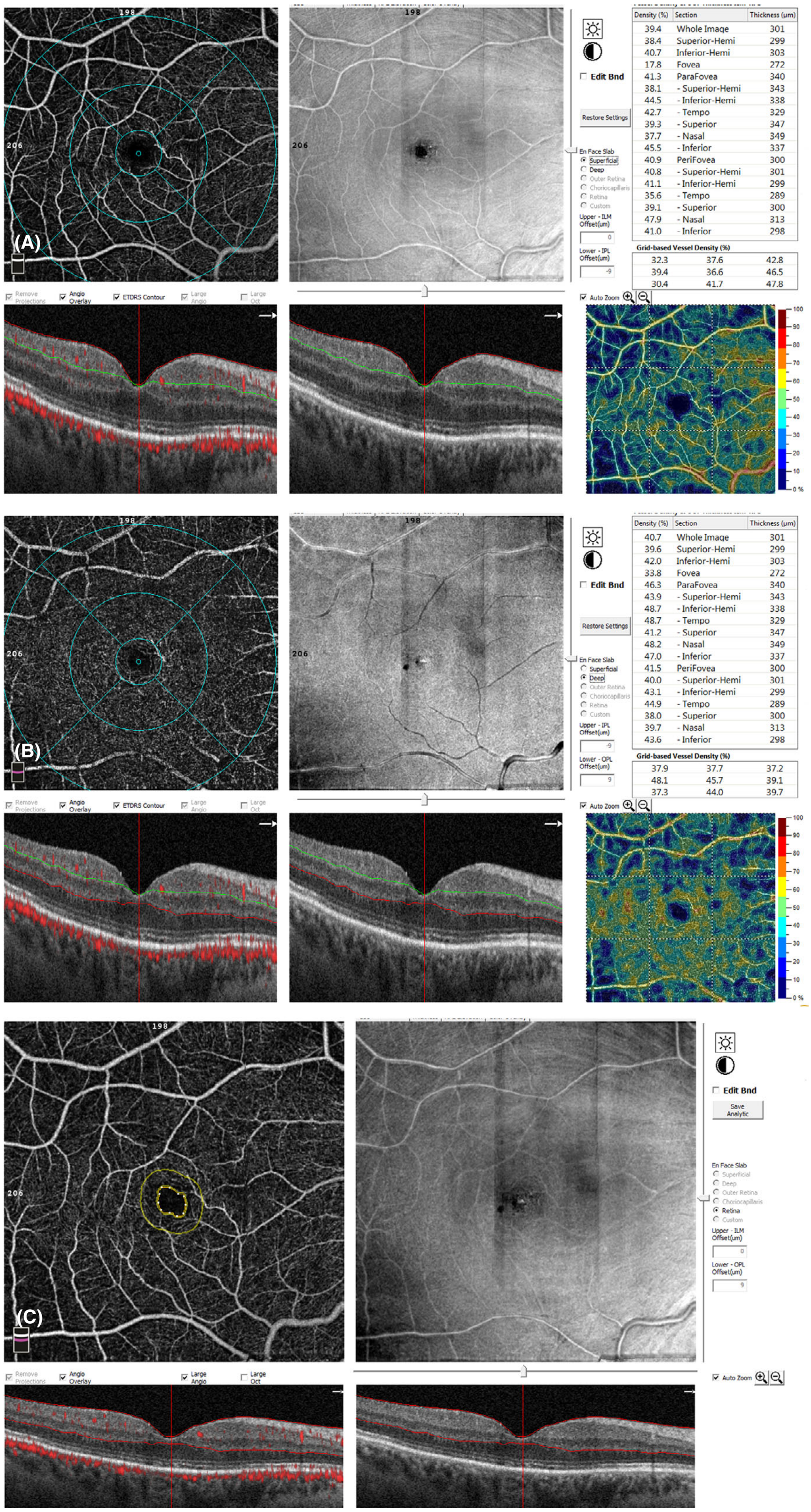

Fig. 2. OCTA in macula-off RRD eyes: (A) Superficial vessel density: above: 6 × 6 en face angiogram with quantitative measurements; below: B scan image (red line = internal limiting membrane; green line: inner plexiform layer) (B) Deep vessel density: (above) 6 × 6 en face angiogram with quantitative measurements; below: B scan image (green line: inner plexiform layer; red line = outer plexiform layer) (C)Foveal avascular zone (FAZ): area surrounded by the inner yellow line; outer yellow line is 300-µm far from FAZ.

Pallarés et al. 2013). These mediators directly and/or indirectly could lead to permanent retinal vascular change, such as diffuse occlusions in superficial and/or deep capillary plexus (Cardillo Piccolino 1983; Ohkubo 1988; Quintyn & Brasseur 2004).

In a previous study, Woo et al. (2018) hypothesized that the deep capillary plexus could be more vulnerable than the superficial capillary plexus to tissue hypoxia and to the secondary cascade of vascular events observed in RD. Moreover, the DCP could have a lower perfusion pressure than SCP, because the DCP is primarily formed by venous collecting channels, differently to the SCP that is directly connected to retinal arterioles (Woo et al. 2018). Furthermore, the DCP is located in the watershed zone where oxygen levels are lower than in inner and outer retinal layers (Woo et al. 2018).

Additionally, in macula-on RRD eyes, we showed a negative correlation between FAZ area and FMT, as reported in healthy eyes (Samara et al. 2015). This finding suggested that in these eyes the normal relationships between retinal structure and vascularity parameters are maintained despite the reduced DVD. Moreover, final BCVA was related to the FAZ area and parafoveal DVD.

In the macula-off group, compared with fellow eyes, we found no difference in postoperative mean FMT and FAZ area, but lower parafoveal SVD, and foveal and parafoveal DVD values; while compared with macula-on RRD eyes, we found lower postoperative FMT, parafoveal SVD and foveal and parafoveal DVD.

Previous studies showed controversial results. According to our results, Woo et al. (2018) reported no difference in term of postoperative mean FMT; whereas Dell'Omo et al. (2015) and Agarwal et al. (2019) detected a reduction of FMT, one and 3 months, respectively, after PPV for RRD. However, Dell'Omo et al. (2015) found a progressive recovery to values of FMT not different from fellow eyes at 12 months, suggesting that the progressive increase of central retinal thickness was associated with the recovery of the integrity of the outer retinal layers.

In contrast to our outcomes, Agarwal et al. (2019) and Woo et al. (2018) reported a greater postoperative mean FAZ area compared with healthy eyes;

however, a longer follow-up period from surgery could explain our results.

In macula-off group, we found that final BCVA was related to FAZ area, and to foveal SVD, and parafoveal DVD; in addition, according to Yui et al. (2018), we found the loss of the correlation between mean FAZ area and mean FMT, reported in healthy eyes (Samara et al. 2015) and in the macula-on group, suggesting that, the normal relationship between vascular parameters and foveal thickness could be lost in the presence of detached macula.

Table 2. Postoperative mean values detected in macula-on RRD eyes and in fellow eyes

	RRD eyes (*n* = 56)	Fellow eyes (*n* = 56)	p (unpaired *t*-test)
FMT (μm)	287 ± 31	280 ± 36	0.220
FAZ (mm^2)	0.228 ± 0.088	0.239 ± 0.084	0.503
Foveal SVD (%)	24.8 ± 8.5	23.0 ± 8.4	0.256
Parafoveal SVD (%)	46.4 ± 6.0	46.4 ± 4.7	0.999
Foveal DVD (%)	37.3 ± 7.5	37.7 ± 7.4	0.751
Parafoveal DVD (%)	49.3 ± 3.4	51.8 ± 4.0	<0.001

DVD = deep retinal vessel density; FAZ = foveal avascular zone; FMT = foveal macular thickness; RRD = rhegmatogenous retinal detachment; SVD = superficial retinal vessel density.

Table 3. Postoperative mean values detected in macula-off RRD eyes and in fellow eyes

	RRD eyes (*n* = 37)	Fellow eyes (*n* = 37)	p (unpaired *t*-test)
FMT (μm)	267 ± 28	270 ± 17	0.667
FAZ (mm^2)	0.237 ± 0.093	0.255 ± 0.132	0.494
Foveal SVD (%)	24.1 ± 6.1	24.2 ± 6.7	0.931
Parafoveal SVD (%)	43.4 ± 5.5	46.8 ± 5.2	0.008
Fovea DVD (%)	33.7 ± 8.7	38.5 ± 7.3	0.011
Parafoveal DVD (%)	47.7 ± 3.3	52.2 ± 4.1	<0.001

DVD = deep retinal vessel density; FAZ = foveal avascular zone; FMT = foveal macular thickness; RRD = rhegmatogenous retinal detachment; SVD = superficial retinal vessel density.

Table 4. Postoperative mean values in macula-on and macula-off RRD eyes

	Macula-on RRD eyes (*n* = 56)	Macula-off RRD eyes (*n* = 37)	p (unpaired *t*-test)
FMT (μm)	287 ± 31	267 ± 28	0.002
FAZ (mm^2)	0.228 ± 0.088	0.237 ± 0.093	0.652
Foveal SVD (%)	24.8 ± 8.5	24.1 ± 6.1	0.650
Parafoveal SVD (%)	46.4 ± 6.0	43.4 ± 5.5	0.017
Foveal DVD (%)	37.3 ± 7.5	33.7 ± 8.7	0.041
Parafoveal DVD (%)	49.3 ± 3.4	47.7 ± 3.3	0.031

DVD = deep retinal vessel density; FAZ = foveal avascular zone; FMT = foveal macular thickness; RRD = rhegmatogenous retinal detachment; SVD = superficial retinal vessel density.

Few studies have already investigated the relationship between postoperative BCVA and OCTA parameters in eyes with macula-off RRD after successful surgery, with controversial results. Woo et al. (2018) (19 eyes in a 2-month follow-up study) showed that final postoperative BCVA was negatively correlated with both superficial and deep FAZ area; while Yui et al. (2018) (27 eyes in a 3-month follow-up study) showed that final BCVA was related only to superficial, but not to deep FAZ area and Sato et al. (2017), (22 eyes in a 6-month follow-up study) did not find any correlation between BCVA and FAZ area. Moreover, Yui et al. (2018) reported no correlation between postoperative BCVA and superficial and deep VD values.

One possible reason for the discrepancies between our results and other studies may be the differences in terms of baseline characteristics of study subjects (i.e. Agarwal et al. 2019 and Yui et al. 2018 included eyes treated with vitrectomy or scleral bucking; different inclusion and exclusion criteria), different OCTA parameters including VD, flow index, fractal dimension from different regions of interest (i.e. whole image, foveal, parafoveal, perifoveal), number of patients included and follow-up period. In a longer follow-up period, anatomical parameters could recover, leading to the disappearance of early alterations, such as the enlargement of the FAZ area, and the significant FMT decrease caused by hypoxic damage to the detached retina (Dell'Omo et al. 2015; Samara et al. 2015). Moreover,

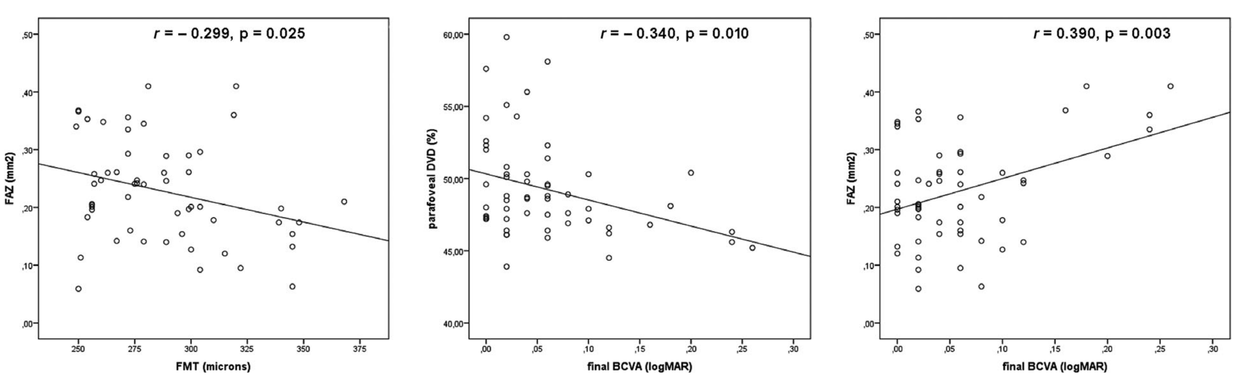

Fig. 3. Scatterplots illustrating macula-on correlation analysis: (left) FAZ area and FMT; (middle) final BCVA and parafoveal DVD; (right) final BCVA and FAZ.

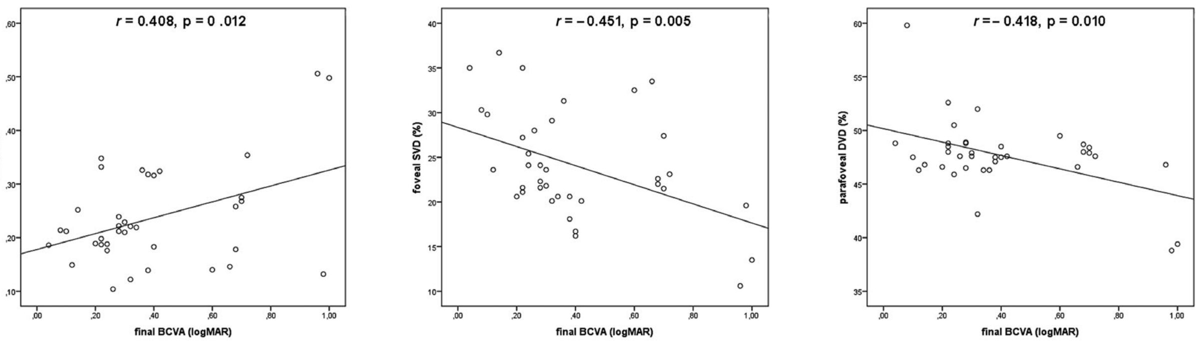

Fig. 4. Scatterplots illustrating macula-off correlation analysis: (left) final BCVA and FAZ area; (middle) final BCVA and foveal SVD; (right) final BCVA and parafoveal DVD.

in some cases, the characteristics of the control group were not reported, leading to possible bias.

The main limitations of this study are its retrospective nature, the inclusion of patients from two different centres, although the same surgical techniques and the same OCTA instrument and software were used. Moreover, the software of OCTA used in this study did not let to measure separately FAZ area into SCP and DCP, giving only one value, measured in one slab including superficial and deep plexus, and not two separate values.

Additional large prospective studies will provide data to better understand the changes in vascular parameters and their relation with functional and anatomical results, also in high myopic eyes and in eyes with alterations in the outer retinal layers, which were excluded from this study.

In conclusion, our study shows that macula-on and macula-off RRD eyes, after successfully retinal detachment repair, had a lower vessel densities compared to fellow healthy eyes; this could affect final visual acuity. In the future, analyses of OCTA quantitative vascular parameter could potentially help evaluate visual acuity recover after retinal detachment successful repaired by PPV.

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Correspondence:
Elina Ortisi, Department of Ophthalmology
University of Catania, via S. Sofia 76
Catania, Italy
Tel 00390953781291
Fax: 00390953781288
Email: elinaortisi@gmail.com

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