Macular Microcirculation after Rhegmatogenous Retinal Detachment Repair Evaluated by OCT-Angiography

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In the process of rhegmatogenous retinal detachment (RRD), retinal homeostasis may be adversely affected with resultant modifications in retinal and choroidal tissue. Hypoxia and nutrient deprivation along with inflammation at the detached retina may lead to morphological and microvascularity alterations. These changes imply that the functional status of the macula may not be entirely restored despite anatomical repair [1-8]. OCT-Angiography (OCT-A) provides depth-resolved vascular information in a non-invasive procedure producing in situ representation of retinal and choroidal circulation, thus enabling physicians to examine foveal microstructure in detail. Interestingly, microcirculation changes in each capillary network including superficial capillary plexus (SCP), deep capillary plexus (DCP), intermediate capillary plexus (ICP) and choriocapillary plexus (CCP) seem to occur in a distinct way dependent on their location and tolerance to tissue hypoxia. Retinal microvasculature of the two capillary plexuses (SCP and DCP) and choriocapillary network are evaluated in detail, while ICP is not always included in most studies due to projection artifact [9-11]. Notably, the currently available evidence concerning potential macular alterations as seen on OCT-A after RRD repair has stirred controversy as the results of the studies have not been unequivocally confirmed [12-31].

RRD may lead to irrevocable visual impairment if left untreated [1,3,5-8,32,33]. The management options for treatment include surgical procedures such as pars plana vitrectomy (PPV) with internal tamponade by either gas or silicone oil (SO) and scleral buckle. Obviously, gas is a widely utilized tamponading agent and its use accounts for a large fraction of cases [32-39]. Indeed, most studies comprehensively examine OCT-A characteristics of RRD eyes after PPV with gas tamponade [13-23,29-31], while there is limited evidence of those treated by PPV with SO or by scleral buckle [14-28]. The primary anatomical success rates for RRD repair by PPV have been found to range from 64% to 96%. Of note, postoperative visual acuity (VA) appears to vary among cases. Especially in cases with preoperatively detached macula, functional results are seldom not as expected in a subset of individuals [40-46]. Emerging evidence suggests that RRD may change OCT-A values in the macula capillary plexus, concerning foveal avascular zone (FAZ) area, vessel density (VD), flow density (FD). The latter may in turn comprise potential predicting factors of postoperative functional outcomes in clinical practice. In our recent review article, we evaluated OCT-A characteristics after successful PPV with gas tamponade and in some cases scleral buckle, including macula-on and macula-off RRD cases and investigated possible explanations for suboptimal visual recovery. We examined a number of series that have reported differences in OCT-A parameters, regarding alterations in FAZ area, VD and FD in retinal and choroidal layers of eyes undergoing surgery for RRD as compared to normal eyes. The diversity of their results possibly reflects the reasons for variability of final VA. Therefore, we sought to investigate the potential for recovery of postoperative VA by analyzing OCT-A based studies and identifying parameters in macular capillary plexus as biomarkers [12].

Reports addressing a comprehensive assessment of flow density indicate that capillary density might be a quantitative measure of detecting flow change. Especially capillary density index and fractal geometry provides an objective evidence of reduction in macular vasculature among patients undergoing surgery for RRD compared with

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healthy controls [21]. Macular perfusion has been shown to decrease at 2 weeks postoperatively in macula-off eyes, though with progressive recovery over time from 2 to 12 weeks in all retinal and choriocapillary layer [16]. Despite the apparent amelioration of VD and perfusion values in macula-off RRD eyes after surgery, it seems that they still remain lower than those of the fellow unaffected eyes until 6 months of follow-up [16,17]. Our results of a recent study were consistent with data reported in literature, indicating that vascular density and perfusion in SCP were lower in macula-off eyes than the fellow at 12 weeks postoperatively. The latter was more evident in eyes with preoperative macular detachment duration of more than 10 days than those treated earlier [31]. Of note, macular capillary plexus microcirculation might be more vulnerable to tissue destruction caused by RRD in long-standing than in recent onset cases [5,7,31,45-47]. Concerning macula-on eyes, the preoperative values of vascular density have been found to be reduced in comparison to the fellow unaffected eye, though they gradually recover over a 6-month period [20]. The improvement of VD concerning retinal capillary plexuses (both SCP and DCP) in operated eyes, either with or without macular involvement, has been further confirmed until 12 months postoperatively. The values of VD seem to approximate or reach the levels of normal eyes in different studies [19]. To provide explanations for the variation in vascular density, the hypothesis of a remitting hypoxic mechanism may be suggested. In cases of RRD, hypoxia occurs in the detached retina leading to increased metabolic demands from the retinal vasculature. In addition, the vasconstrictive peptide, endothelin-1 causes vasospasm on retinal microvasculature of detached and attached regions with a consequence the reduction in blood flow and vascular density. This mechanism could explain macular ischemia, even reversible; the later may characterize an initial decrease of VD values even in cases without macular involvement followed by amelioration over time [1,2,8].

Interestingly, combined procedure with PPV and scleral buckle seems to adversely affect flow density in a greater degree than each procedure alone [17]. Albeit, it has been demonstrated that VD might be lower in eyes treated with PPV than in those treated with scleral buckling, potentially suggesting that PPV could affect the microvascularity structure [22]. We speculate that the reduction of VD might be caused due to permanent vascular retinal changes by direct or indirect mediators causing diffuse vascular occlusions and insufficient supply of oxygen at the detached retina which is more prominent in long-standing cases. Macular vasculature seems to be susceptible to ischemic tissue destruction feasibly caused by macular detachment itself or the surgical intervention [2,3,48].

Concerning cases treated by PPV with intravitreal SO for RRD, the values of vascular density in the SCP seem to be decreased compared to fellow unaffected eyes. In fact, there might be amelioration of VD in the SCP at subsequent follow-ups post-surgery, however being insignificant with the values still remaining lower than those of the contralateral eyes. Interestingly, eyes of cohorts treated by SO do not experience vascular recovery at the post-treatment period to the degree that the gas-filled eyes do [25,49]. It is a hypothesis that prohibited penetration of oxygen into the vitreous seems to occur in SO-filled eyes with subsequent microcirculation changes, potentially attributable to SO usage as a tamponade. Indeed, reperfusion of damaged vessels in the retina appears to be partial and possibly impeded by the presence of intravitreal SO [50-52]. To the contrary, there is no evidence for significant differences in the SCP VD between eyes treated by PPV with SO tamponade and normal eyes following SO removal, possibly suggesting an improvement of vascular insufficiency in those eyes [27]. Whether the initial capillary plexus alterations in SO-filled eyes may be attributed to ischemic tissue damage on account of macular detachment per se, surgical procedure or the effect of SO should be further clarified [24-28].

OCT-A evaluation of macular microvascularity may be useful for predicting vascular structural changes in eyes undergoing pneumatic retinopexy [53]. It seems that in macula-off cases there is a significant decrease of SCP and DCP VD at the early post-treatment period of 1 month. However, VD values seem to increase to the levels of the fellow eyes by the third month after pneumatic retinopexy. It is a hypothesis that the activation of Muller cells due to inflammatory mediators in subretinal fluid is not restricted to detached retina but it may be observed in attached retinal regions as well. The latter may cause local blood flow changes in the inner retina and could lead to secondary reduction in capillary flow density, though without any anatomical distortion [48,54-56].

A number of studies have reported that internal limiting membrane (ILM) peeling may cause microstructural mechanical damage to the retina including the formation of retinal dimples, dissociated nerve fiber layer and focal retinal thinning [57-59]. Regarding the effect of ILM peeling on macular microcirculation after PPV for RRD, a reduction of vessel density seems to be present in the SCP, while this finding is not present in the DCP. The latter may be possibly attributed to the direct impact of surgical manipulation to the SCP, potentially not affecting the DCP [60].

Changes in the foveal capillary plexus indicate the presence of ischemic damage to retinal vessels causing distortion of FAZ area. Of note, authors do not serve unequivocal perspectives in literature [12-15,17,19,20,22-24,28]. Enlargement of SCP or DCP FAZ area has been attributed to tissue hypoxia leading to foveal derangement.
and capillary dropout [14]. Especially in macula-off RRD eyes, subretinal fluid inhibits diffusion of oxygen from CCP to the detached macula leading to pronounced alterations of macular capillary plexus. The DCP seems to be mainly affected as it is located in the watershed zone; oxygen saturation is lower than in the inner and outer retina. SCP seems to be less vulnerable to hypoxia as it is directly connected to retinal arterioles and may have higher perfusion pressure than the DCP [1-3,61,62]. The formation of the ICP seems to depend more on hypoxia-induced factor than the other capillary networks [11]. In fact, postoperative FAZ area has been observed to be larger in macula-off RRD eyes than the macula-on and fellow eyes after retinal reattachment, possibly resultant of ischemic changes of macular capillary plexus [14]. In addition, FAZ SCP has been found to be marginally larger, but not significantly, in eyes with long preoperative macular detachment duration (11-30 days) compared to recent onset cases (0-10 days) [31]. Regarding the long-term follow-up (12 months), no differences were observed at operated eyes (either with or without macular involvement) as compared to fellow [19]. A possible explanation of these results might be recovery of anatomical parameters over time leading to disappearance of early alterations at FAZ area which were caused by hypoxic damage to the detached retina [63,64]. Contrary to these findings, a decrease of FAZ size has been demonstrated after PPV for variable clinical etiology (including RRD cases). The reduction of FAZ has been mentioned even in cases where PPV did not directly influence macular status, such as in cases of macula-on RRD [65]. A speculation explaining this outcome supports the role of PPV in retinal oxygenation and microcirculation. In fact, the replacement of vitreous by a less viscous medium facilitates the retinal oxygen transport to ischemic areas leading to increase of vascular endothelial growth factor and alterations of retinal capillary function via regulation of postoperative oxygenation. Notably, the changes in the physiology of the vitrectomized eye may provide explanations for the foveal capillary alterations even in cases where macular status appears normal pre-operatively [65,66]. Another causal factor of FAZ reduction may be the removal of ILM; the intrinsic forces of ILM stretch the retina centrifugally, while its removal may release such forces leading to centripetal movement. Additional structural changes to the Muller cells may influence the inner retinal movement. Finally, the distribution of forces on the retina changes even after surgical reattachment. The loosely attached retina to the retinal pigment epithelium may lead to stretching of retinal tissue ‘towards the macula’ with resultant decreased FAZ [67].

Despite FAZ area alterations are thoroughly analyzed after PPV with gas tamponade, the evidence to characterize retinal capillary changes in SO-filled eyes is inadequate. The values of SCP FAZ seem to demonstrate no significant changes between macula-off RRD eyes treated with PPV and SO tamponade and the contralateral at post-treatment period, while the values of DCP FAZ seem to be affected most leading to FAZ enlargement [27]. These findings further support the hypothesis that DCP is more vulnerable to hypoxia providing an explanation for more extensive morphologic changes at that layer [1-3,61,62]. Interestingly, eyes with longer pre-operative duration of RRD demonstrated enlargement of FAZ after PPV with SO tamponade [28]. Since enlargement of FAZ has not been confirmed in eyes that underwent PPV with gas tamponade with regards to the preoperative macular detachment duration, we may support a possible compounding effect of SO on FAZ.

Visual recovery after RRD, especially in cases that involve the macula, in not fully understood. The trend in current literature is to identify OCT-A characteristics in macular capillary plexus potentially related with visual outcomes after successful surgery [12]. It is noteworthy to recognize OCT-A parameters that may lead to guarded visual prognosis [5-8]. An interesting point that should be mentioned is that in most cases there is improvement of VA after surgery, despite alterations in macular capillary plexus [12]. Conceivably, in these cases visual recovery might be attributed to intact ellipsoid zone especially in cases that are treated promptly.

By evaluating choroidal microcirculation, we could explain various postoperative visual outcomes since anatomical and functional restoration of the outer retinal layers is related to rehabilitation of the CCP. Conceivably, if the CCP FD is not properly normalized, visual outcomes would not be as expected even after anatomical repair. It is speculated that CCP VD might be a potential indicator of the final VA, especially in cases that RRD involves the macula [16,17,20]. Concerning the association of VD of the retinal layers with postoperative VA the results remain controversial supporting a possible association with either SCP or DCP VD even after 12 months of follow-up [15,16,19,20,22,23]. Our data of a previous cohort demonstrate that 12 weeks post-operative VA strongly depends on VD SCP in cases that underwent surgery with duration of macular detachment of more than 10 days. Our results imply that reduced macular vascularity, possibly due to ischemic tissue damage in chronic RRD cases with macular involvement, could contribute to impaired postoperative visual function [31]. Indeed, it is widely suggested that one of the main preoperative factors that may unfavorably affect visual prognosis is the duration of macular detachment. Retinal detachment duration on average beyond 2 weeks results in development of degeneration throughout the retinal tissue, the vessels and the photoreceptors. This may be an explanation of microvasculature and microstructure alterations in long-standing cases leading to visual impairment [6-8,12,34,44].
Changes in the macular capillary plexus, denoting the presence of ischemic damage, may result to poor visual outcomes. The association between FAZ area and the final VA in RRD eyes postoperatively has produced controversial results. Few studies support that enlargement in both SCP and DCP FAZ area has been found to inversely correlate with VA from 2 to 12 months after PPV, while this association has been confirmed regarding either SCP or DCP by some authors [12]. To the contrary, some series have demonstrated no association of FAZ with post-operative visual outcomes, as we reported in a previous cohort [13,14,16,20,22,23,31]. Interestingly, DCP FAZ area at the early post-treatment period (1 day) seemed to negatively correlate with VA at 3 months after PPV with SO tamponade, proposing an indicator of visual prognosis in SO-filled eyes [25]. Obviously, there is little evidence concerning these results and should undoubtedly be confirmed by further reports.

Our understanding of the pathophysiological mechanisms involved in microcirculation and microstructural alterations of the macula during RRD provides possible explanations of the anticipated changes in FAZ area and vascular density of retinal and choroidal layers. Many hypotheses could be made regarding the mechanisms causing retinal vascular insufficiency in patients with RRD treated by PPV. The retinal non-perfusion areas in these cases may be attributed to vessel changes that are directly or indirectly caused by vascular and inflammatory mediators (such as prostaglandins, cytokines). In addition, the mechanically induced neuronal damage may lead to retinal ischemia. Another potential pathophysiologic mechanism for localized flow reduction leading to hypoperfusion may be a reversible vasoconstriction. In fact, an autoregulation phenomenon secondary to hypoxia may protect the retinal tissue from the inconsistent blood flow. A severe blood flow reduction may lead to ischemia causing structural vascular changes and capillary dropout in fovea leading to guarded visual prognosis [1-3,6-8,34,44,61,62].

It is a speculation that up-regulation of the macular capillary plexus, especially of the DCP occurs to counteract ischemia until CCP rehabilitation is present. The microvasculature changes may be caused by angiogenesis in retinal capillary plexuses to compensate for the destruction caused by RRD. Since angiogenesis has been associated with improved functional outcomes, we could expect recovery of VA. Indeed, therapeutic stimulation of angiogenesis in these cases could be beneficial to photoreceptor regeneration and in turn improved functional outcomes [30,68].

We should mention a number of discrepancies among the results of the studies in current literature. Clearly, possible reasons include the separate design of each study, the baseline characteristics of the subjects, the duration of the follow-up period, the region of the macula that is analyzed, the number of eyes included in each study or the OCT-A technology that was used. Potential selection bias could be confounding factor of their results. Owing to the inter-individual variability of OCT-A parameters, it would be of additional value for all studies to interpret the OCT-A parameters of the RRD eye in reference to the fellow eye to avoid physiological differences among healthy subjects that may produce inconsistent results [12-31].

Obviously, additional large prospective studies should be conducted to clarify the roles of OCT-A values and to provide data referring to the changes in vascular parameters and their potential association with functional outcomes. Controlled evidence should establish the OCT-A parameters as predicting factors of visual outcomes after successful surgery for RRD and characterize their long-term effectiveness in clinical practice.

References


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