Role of optical coherence tomography angiography in the evaluation of peripheral ischemia in retinal vein occlusion

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Abstract:

In the last decade, optical coherence tomography angiography (OCTA) has become part of the clinical management of retinal vein occlusion (RVO), proving in itself a useful technique for both the prediction of visual acuity (VA) outcomes and the risk of complications. In fact, OCTA has been proven a valid imaging technique in detailed assessment of foveal and parafoveal microvascular status in both acute and chronic RVO. Quantitative OCTA data have shown a significant correlation not only with final VA but also with the extension of peripheral ischemia, which represents a major risk factor for macular edema recurrence and neovascularization onset. Finally, wide-field OCTA represents a promising noninvasive technique for the assessment of peripheral ischemia. The aim of this review is to report the main literature findings about microvascular changes and clinical applications of OCTA in the context of RVO-induced peripheral ischemia.

Keywords:

Deep capillary plexus, optical coherence tomography angiography, peripheral ischemia, retinal vein occlusion, wide-field optical coherence tomography angiography

Introduction

Retinal venous occlusion (RVO) is the second most common sight-threatening vascular disorder, with an esteemed prevalence of 0.7% in the population over 55 years old.[1] RVO can be subdivided in central retinal vein occlusion (CRVO), representing around 20% of cases, and branch RVO (BRVO), which affects the remaining 80% of patients.[1,2] In both conditions, age, cigarette smoking, diabetes, and elevated diastolic blood pressure represent the main risk factors.[3] In CRVO, venous blood flow is blocked at or proximal to the lamina cribrosa of the optic nerve due to a decrease in central retinal vein lumen diameter accompanied by high-flow turbulence leading to the formation of a thrombus.[4] In BRVO, venous blood flow is blocked in one of the tributary veins at an arteriovenous crossing due to arteriovenous compression in the context of angiosclerosis in systemic hypertension.[5] Similarly to CRVO, a decreased lumen along with high-flow turbulence is then responsible for the formation of a thrombus.[4] The increased downstream pressure leads to blood flow interruption at the capillary level. As the condition persists, the high pressure in the capillary lumen results in dilation and opening of endothelial gaps with subsequent intraretinal exudation, especially at the level of retinal nerve fiber layer, ganglion cells layer, inner nuclear layer (INL), and outer plexiform layer (OPL). Retinal edema in turn increases the retinal tissue pressure and may further reduce perfusion by compressing the capillaries, especially in the deep capillary plexus (DCP), where capillary walls are poorer in smooth muscle cells.[6] Finally, there is a loss of endothelial cells and pericytes, and the acellular capillaries are invaded by glial cells, producing permanent capillary closure.[7] Despite different clinical presentations and fundus appearance,[8-10] the two conditions thus share the risk for the development of irreversible retinal ischemia and macular edema, with retinal capillaries playing a crucial role in the development of both conditions. It is, therefore, of utmost

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importance to be able to study in detail the status of retinal capillary network both in an acute and a chronic setting. The advent of optical coherence tomography angiography (OCTA) made possible noninvasive and rapid imaging of retinal capillaries.[11] Compared to traditional fluorescein angiography (FA), OCTA also provides a more detailed evaluation of capillary status and morphology due to multiple reasons. First of all, the superimposition of different capillary plexa in FA imaging impedes a layer-by-layer evaluation of ischemic involvement. In fact, the deep capillary network is barely visible on FA as reported by Spaide *et al*.[12] By contrast, OCTA provides depth-resolved information on capillary status with segmentation of each capillary plexus. The foveal avascular zone (FAZ) is also well visualized on OCT-A providing more precise delineation of this area and of its enlargement than on FA. Moreover, especially in the acute phase, the presence of blocking of the fluorescent signal due to retinal hemorrhage and the presence of leakage and pooling in the context of exudation makes it difficult to evaluate capillary status with FA imaging.[13,14] OCTA signal is also attenuated and disturbed by artifacts in case of hemorrhage and edema. Moreover, Heiferman *et al*.[15] suggested caution in evaluating capillary blood flow in the context of an RVO with OCTA alone, since discrepancies between the presence of vasculature detected with en-face OCT and vasculature identified with OCTA. Nonetheless, while capillary network analysis may be less reliable in these settings, OCTA still partially allows assessment of the macular microvascular status. The present review is intended to focus on the role of microvascular information obtained with OCTA technology in the management of peripheral ischemia in RVO.

Assessment of Macular Changes in Retinal Vein Occlusion with Optical Coherence Tomography Angiography

In RVO, macular area is often involved in ischemic damage. While ischemic areas are visible also with FA, OCTA made it possible to document detailed microscopic changes in chronic and acute phases. This allowed the characterization of specific damage for each capillary plexus. Rispoli *et al*.[14] analyzed the status of macular plexa using 3 mm × 3 mm scans acquired with AngioVue (Optovue, Inc., Fremont, CA) OCTA in 10 patients in the acute phase of BRVO. They documented an enlargement of FAZ in both superficial capillary plexus (SCP) and DCP. SCP was prevalently characterized by capillary nonperfusion areas and multiple intraretinal loops located at the margins of ischemic areas. By contrast, the DCP was characterized by the presence of capillary congestion preferentially located at the boundaries of healthy tissue. Capillary congestion was partially restored during the follow-up but complete resolution was never documented.[16] The majority of the authors reported changes in the DCP to be more evident and quantitatively relevant in the DCP [Figure 1].[17-21]

Wakabayashi *et al*.[18] documented how microvascular abnormalities, including capillary telangiectasia, microaneurysm, and disruption of the FAZ, were more common in the DCP than in the SCP. They found that DCP vessel density (VD) shows the most significant correlation with visual acuity (VA) after the resolution of acute macular edema. This highlights the fact that preservation of retinal perfusion in DCP appears to be crucial for visual function. The importance of preserving the capillaries at the outer boundary of INL might be a consequence of the relevant visual role played by ribbon synapses formed between photoreceptor axon terminals and horizontal cells and bipolar cells in this region.[22] In fact, capillaries in the DCP seem to be important for nutritional and oxygen support of the synaptic connections responsible for the transmission of visual signals.[23] Because the area of the INL and OPL is located in the so-called watershed zone where the oxygen level is significantly lower than that in the inner and outer retinal layer and may be particularly vulnerable to ischemia, hypoperfusion in the DCP may cause acute nutritional deficiency in the synaptic connections, resulting in decreased VA.[24] Sellam *et al*.[19] evaluated macular capillary status in 28 eyes affected by RVO (13 CRVO, 11 BRVO, and 4 hemicentral RVO) before and after treatment of macular edema and compared them to healthy controls. They concluded that perifoveal capillary destruction was still evident after treatment. This excludes the possibility that the absence of microvascular network in these areas is completely attributable to signal below the detection threshold of OCTA in the acute phase due to either attenuation by overlying macular edema or reduction of capillary blood flow underneath the sensitivity threshold of the OCTA device.

Kashani *et al*.[20] documented macular microvascular changes in a cohort of 26 patients at various stages of the disease, ranging from 1 month to 5 years after the occlusive event. The main OCTA findings in the acute phase were intraretinal hemorrhage, vascular dilation of the perifoveal capillaries downstream to the occlusion site, and signal attenuation due to both reduced capillary perfusion and signal blocking from the overlying edema. In particular, OCTA offers the possibility to identify the retinal layer interested by the intraretinal hemorrhage. In fact, depending on the capillary plexus interested by attenuation of the signal, it is possible to assume the location of the hemorrhage, which the authors found to be located in intermediate retinal layers in most cases. The preferential location of intraretinal hemorrhage at the level of OPL and Henle fiber layer is confirmed by other postmortem and *in vivo* studies.[25] Main OCTA findings in chronic phase were signal attenuation and decrease in VD prevalently in the intermediate and DCP and formation of vascular dilation and shunting across the horizontal meridian. The authors[20] also signaled capillary rarefaction in the regions surrounding cysts formation. This is coherent with the origin of exudation which is believed to be due to dilation and opening of endothelial gaps in degenerating retinal capillaries. Large hard exudates may also cause OCTA artifacts in chronic RVO. Finally,

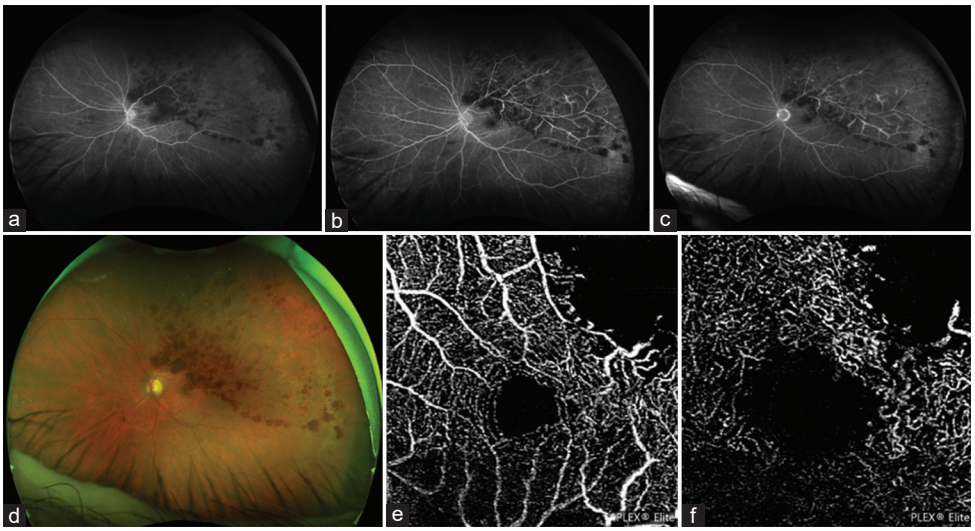

Figure 1: (a) Early phase ultrawide field fluorescein angiography (UWF FA). (b) Mid-phase UWF FA. (c) Late phase UWF FA. (d) Pseudocolor UWF. (e) Macular enface angiogram of the superficial capillary plexus. (f) Macular enface angiogram of the deep capillary plexus of a case of ischemic retinal vein occlusion 2 weeks after the onset of symptoms. Microvascular rarefaction prevalently in deep capillary plexus and watershed area congestion can be noted in optical coherence tomography angiography images

the presence of DCP congestion has been associated to the recurrence of macular edema in ischemic BRVO.[26]

Prediction of Peripheral Ischemia Based on Macular Optical Coherence Tomography Angiography

As explained in the previous paragraph, OCTA helps visualize macular microvasculature in the acute phase of RVO, when the macular signal is altered by the presence of edema in FA imaging. Interestingly, different authors reported a correlation between the status of macular capillary plexa and the extension of peripheral ischemia in RVO. Seknazi *et al*.[27] described a correlation of macular VD in SCP and DCP with peripheral ischemia in CRVO. In particular, a VD <46% was significantly associated with the presence of peripheral capillary nonperfusion in more than one quadrant in FA.

Coscas *et al*.[28] also reported the correlation between disruption of perifoveal capillaries assessed with OCTA and peripheral ischemia in FA. They reported that capillary plex use abnormalities were significantly more common in DCP than in SCP. They theorized that the reason for this preferential involvement was on one hand higher amount of cystoid spaces and resultant disorganization of the deep plexus, and on the other hand, the better perfusion of SCP owing to direct connection to retinal arterioles in contrast to DCP. Specifically, perifoveal capillary arcade changes in the SCP and network disruption in the DCP were significantly correlated with peripheral nonperfusion, defined as 10-disc diameters or more of ischemia on FA. However, the association between perifoveal capillary disruption and peripheral nonperfusion on FA was only noted in 63% of eyes, and the intra-and interobserver agreement for OCT-A parameters varied between 0.61 and 0.82. Mastropasqua *et al*.[29] found not only lower VD in 3 main capillary plexuses but also in the choriocapillaris to be associated with retinal ischemia at FA.

Khodabandeh *et al*.[30] evaluated 40 new-onset (<1 month) treatment naïve CRVO eyes dividing the population in presumably ischemic CRVO (absence of relative afferent pupillary reflex and VA ≤ 20/200) and presumably nonischemic CRVO. Choriocapillaris flow in the macular area was the OCTA parameter with the largest area under the receiver operating characteristics curve (AUROC) (area under the curve [AUC] = 0.889). Parafoveal vascular density of DCP in superior sectors was also a highly performing parameter (AUC = 0.850). The authors found that the following reduced formula could recognize ischemic from nonischemic CRVO with an AUROC of 0.84 and accuracy of 96%, when a threshold of 12.6 is applied (ischemic type <12.6): $(3.9 \times F_{1S} + 0.8 \times F_{3S})$ (F_{1S}: Flow in the central 1 mm-radius-circle of superficial plexus; F_{3S}: Flow in the central 3 mm-radius-circle of superficial plexus).

An important limit to the application of this formula is the fact that it was established without the possibility to confirm the ischemic nature of the occlusion due to the presence of hemorrhages impeding reliable interpretation of FA. Moreover, the quantitative analysis of OCTA parameters was altered by the presence of severe macular edema. Nevertheless, a similar formula could be useful as a screening of patients at risk for ischemic CRVO while FA is of a high enough quality to allow objective assessment of the extension of ischemia. In a cross-sectional study from An *et al*.,[31] 50 eyes affected by acute CRVO and macular edema were evaluated with macular 3 mm × 3 mm OCTA and ultra-wide field FA (UWF FA) for ischemic areas assessment after 3 monthly injections of anti-vascular endothelial growth factor. Ischemic type was

defined by the presence of ≥30 disk areas of retinal capillary nonperfusion on ultra-wide-angle fundus FA as per Central Vein Occlusion Study indications.[32] Significant differences were found between ischemic and nonischemic subgroups as concerns SCP VD in the foveal and parafoveal area, DCP VD in the foveal and parafoveal area and area, perimeter, and avascular index (AI) of the capillary free zone (CFZ). The latter was defined as the ratio between the measured perimeter and a perimeter with the same size circular area (with a perfectly circular CFZ having an AI equal to 1). Receiver operating characteristic curve analysis revealed that the best performance in the differentiation of ischemic from nonischemic subtype was provided by foveal and parafoveal DCP VD (0.926). In particular, a threshold of 38.40% was suggested as an ideal cutoff to this scope. Sensitivity and specificity were 100% and 92.3% for foveal DCP VD and 100% and 84.6% for parafoveal DCP VD, respectively.

Cavalleri *et al*.[33] analyzed treatment naïve CRVO eyes after the resolution of hemorrhages, investigating a correlation of UWF FA ischemic index (ISI)[34] with OCTA macular parameters. ISI is calculated as the pixel area of perfused retina on mid-phase UWF FA acquisitions divided by the total area of the image and multiplied by 100. ISI showed a significant positive correlation with FAZ area and a significant negative correlation with SCP and DCP VD. Ryu *et al*.[35] assessed a similar correlation of macular OCTA parameters with ISI on UWF FA. In particular, fractal dimension (FD) reduction in DCP was the most reliable parameter (AUC = 0.948, $P < 0.001$), and 5.39% was the best cutoff point for predicting ISI >10%. Similarly, Cabral *et al*.[36] analyzed a total of 48 eyes of 48 consecutive CRVO (25 eyes, 52.1%), hemicentral RVO (HCRVO; 3 eyes, 6.2%), and BRVO (20 eyes, 41.7%) eyes. Once again, DCP variables obtained the best performance in the prediction of significant peripheral nonperfusion, defined as FA nonperfusion areas ≥one retinal quadrant. DCP lacunarity (LAC) (AUC = 0.88; 95% confidence interval [CI]: 0.755–0.998; AIC = 37.02) and VD (AUC = 0.73; 95% CI: 0.570–0.892; AIC = 53.1) achieved the best and the worst results, respectively. VD and LAC are indeed two very different parameters. In fact, while VD analyses the percentage of perfused area within an enface angiogram (white pixels over total of pixels multiplied by 100), LAC is a fractal-based parameter expressing the complexity of the vascular structure in terms of segmentation of its void spaces. FD is another fractal-based parameter that can be seen as a counterpart of LAC, thus expressing the complexity of a vascular structure in terms of its ramifications.[37] Finally, vessel length density (VLD) is the percentage of white pixels over the total of pixels after skeletonization of the angiogram; this makes this parameter particularly suitable to analyze the raw extent of the vascular network and to emphasize the role of capillary ramifications versus big microvascular branches. Koulisis *et al*.[21] quantitatively evaluated the central macular microvasculature in human subjects with RVO, using OCT-A, and found a statistically significant difference in FD of all the vascular layers in subjects with BRVO and CRVO compared with controls and unaffected fellow eyes. Furthermore, FD progressively decreased as the clinical severity of RVO increased (BRVO versus CRVO). In a study from Costanzo *et al*.,[38] 17 BRVO and 13 CRVO cases were evaluated with PLEX® Elite. VD analysis showed significant differences in DCP between ischemic versus nonischemic eyes. Finally, Jung *et al*.[39] reported higher quadrant asymmetry in VLD and VD in ischemic group in a series of 22 CRVO cases. No ETDRS quadrant was preferentially interested.

Utility of Wide-field Optical Coherence Tomography Angiography in Ischemic Central Retinal Vein Occlusion

While FA is still the gold standard for the assessment of peripheral ischemia and monitoring of neovascularization onset, wide-field OCTA (WF-OCTA) represents an interesting noninvasive technology which could potentially support FA in these functions in the near future. Some authors evidenced good performance of WF-OCTA in the detection of neovascularization in patients with ischemic RVO. They also added that the characterization of different morphologies of neovascularization detected by WF-OCTA could be of clinical relevance.[40]

Other authors assessed the correlation between ischemia evaluated with WF-OCTA and UWF FA. In particular, they found a correlation between ISI and VD in DCP and SCP and found a significant correlation between qualitative classification of ischemia using WF-OCTA and UWF FA. One-year follow-up of a case of ischemic RVO is illustrated in Figure 2. Colocalization of ischemic areas is clearly visible in FA and WF-OCTA.

For the detection of marked nonperfusion (ISI ≥25%), WF-OCTA had a sensitivity of 100% and a specificity of 64.9%. The authors concluded that, at the state of the art, WF OCTA technology might help in screening of patients eligible for a more invasive exam such as FA in case of detection of large ischemic areas.[41] Finally, other authors reported good results of extended field imaging swept-source OCTA in the assessment of peripheral ischemia in RVO eyes.[42]

Conclusion

In the last decade, OCTA has become part of the clinical management of RVO, proving itself a useful technique in both the prediction of VA outcomes and the risk of complications. In fact, OCTA has been proven a valid imaging technique in detailed assessment of foveal and parafoveal microvascular status in both acute and chronic RVO. Quantitative data deriving from it have shown a significant correlation not only with final VA but also with the extension of peripheral ischemia, which represents a major risk factor for macular edema recurrence and neovascularization onset. Finally, the WF-OCTA represents a promising noninvasive technique for the assessment of peripheral ischemia. Nevertheless, at

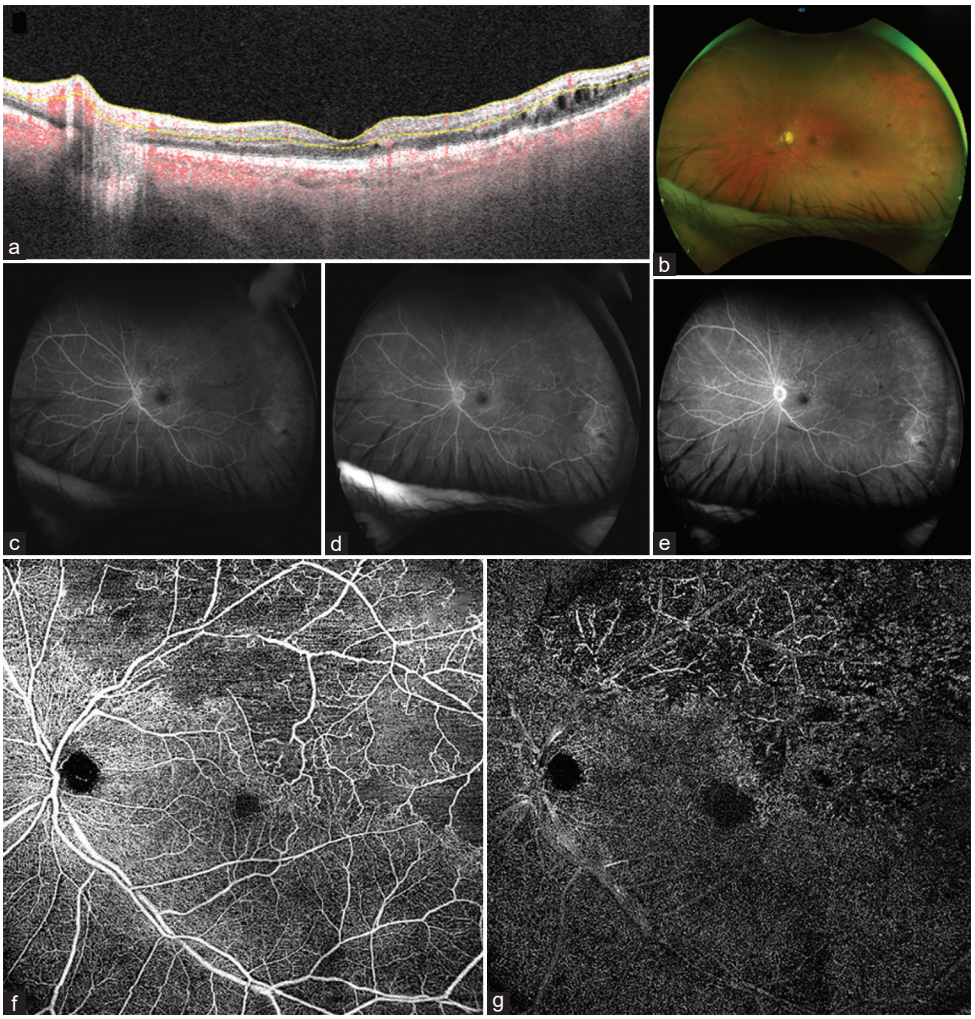

Figure 2: (a) Cross-sectional fovea crossing optical coherence tomography angiography. (b) Ultrawide (UWF) pseudo color fundus image. (c) Early phase UWF Fluorescein angiography (UWF FA). (d) Mid-phase UWF FA. (e) Late phase UWF FA. (f) UWF angiogram of the superficial capillary plexus. (g) UWF angiogram of the deep capillary plexus of a case of ischemic retinal vein occlusion 1 year after the event. Ischemic areas clearly colocalize in fluorescein angiography and optical coherence tomography angiography images

the present state of the art, there is not sufficient evidence to allow the substitution of FA in the evaluation of the extension of peripheral ischemia. Therefore, WF-OCTA application should be limited to screening for peripheral ischemia in patients at risk for ischemic RVO, especially in the acute setting.

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Conflicts of interest
There are no conflicts of interest.

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