Review article

Optical Coherence Tomography Angiography in Eyes with Retinal Vein Occlusion

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Abstract

Optical coherence angiography (OCTA) is a noninvasive technique that has been introduced in recent years to detect ophthalmological pathology. The growing usage of OCTA to detect retinal abnormalities can be attributed to its advantages over the reference-standard fluorescein angiography (FA), although both of these techniques can be used in association. OCTA's advantages include its dye independency, its ability to produce depth-resolved images of retinal and choroidal vessels that yield images of different vascular layers of the retina, and the better delineation of the foveal avascular zone. OCTA's disadvantages include the lack of normalized patient data, artefactual projection issues, and its inability to detect low-flow lesions or pathologic conditions. Different OCTA platforms use unique algorithms to detect microvasculature, which are implemented in both spectral-domain (SD) and swept-source (SS) OCT machines. Microvascular changes in retinal vein occlusions (RVOs) are visible in both the superficial and deep capillary networks of the retina in OCTA. These visualizations include a decrease in foveal and parafoveal vascular densities, non-perfusion areas, capillary engorgement and telangiectasias, vascular tortuosity, microaneurysms, disruption of the foveal perivascular plexus, and formation of collateral vessels. The restricted field of view and inability to show leakage are important limitations associated with the use of OCTA in RVO cases. In this article, we present a brief overview of OCTA and a review of the changes detectable in different slabs by OCTA in RVO cases published in PubMed and Embase.

Keywords: Macular Edema; Macular Ischemia; Optical Coherence Tomography Angiography; Retina; Retinal Vascular Disease; Retinal Vein Occlusion

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INTRODUCTION

Optical coherence tomography angiography (OCTA) has become a valuable imaging tool for the evaluation of retinal pathologies such as diabetic retinopathy, age-related macular degeneration, and retinal artery and retinal vein occlusions (RVOs). Its ability to delineate the fine microvascular detail of the retinal vasculature in the superficial and deep retinal plexus without dyes is advantageous for diagnosing retinal diseases, which will most likely lead to its widespread use in the future.[1-3]

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Angiography has been part of the diagnostic work-up of RVOs. A major aim of these evaluations is to delineate the area of the ischemic retina. Fluorescein angiography (FA), the standard method, can show ischemic areas in both the central and peripheral retina, and these images have been used for both prognostication and treatment decisions in cases of RVOs. However, FA may not always yield clear images of the foveal avascular zone (FAZ), whose intactness has prognostic value.[4]

OCTA images are generated by algorithms that detect either phase and/or amplitude differences of moving parts (notably red blood cells) of successive OCT B-scans to construct an image of the vasculature.[5] As OCTA is fundamentally different from FA, the changes in RVOs detectable with this technique do not always mirror those shown by FA. Some changes are better visualized by OCTA, such as FAZ irregularities that are not obscured by leakage.[6,7] Some changes in the microvasculature that can be evaluated by OCTA, while not visible by FA, include those in the deep capillary plexus.[8,9] However, with the current technology, there are limitations to OCTA as well, which include a restricted field of view and inability to detect leakage. In addition, all software platforms lack normalized data to determine if the vascular patterns seen are truly abnormal or are on the normal spectrum and instead compromise of patient to patient variation. At present, several devices are equipped with OCTA functions: RTVue XR Avanti (Optovue, Inc., Fremont, CA. USA), Triton and Atlantis (Topcon, Tokyo. Japan), Cirrus HD and PLEX Elite 9000 (Carl Zeiss Meditec, Inc., Dublin, CA, USA), Spectralis (Heidelberg Engineering, Heidelberg, Germany), and RS-3000 (Nidek Co, Gamagori, Japan). Literature regarding the use of OCTA in cases of RVOs is vast, and studies have shown that OCTA findings in cases of RVOs correlate well with the clinical, anatomic, and fluorescein angiographic (FA) findings of capillary dropout, retinal atrophy, increased vessel caliber, shunt vessels (collaterals), and the presence of intraretinal edema.[10-13] In this paper, we present a brief overview of OCTA and the findings reported in the English literature.

Method of Literature Search

All papers published from January 2015 to May 2017 describing the use of OCTA in RVO were identified and reviewed through a PubMed and Embase search. The keywords "OCTA," "optical coherence angiography" or "angiography," and "retinal vein" or "retinal vein occlusion" were applied. Relevant papers from the reference lists of articles were also included [Table 1]. Where duplicate information was present, papers with more recent publication dates or larger study groups were referenced.

A BRIEF DISCUSSION ABOUT OCTA

Technology

The OCTA algorithm generates three-dimensional, en face, depth-encoded images of microvascular blood flow in the retinal and choroidal vasculatures. By using motion contrast, OCTA can portray differing reflectance patterns over time due to the phase-shift of RBCs in retinal vessels without the need for intravenous dye injection. The device shows the differences between multiple, sequential B-scans obtained at the same retinal cross-section. Notably, OCTA systems have a characteristic threshold for slowest and fastest detectable flow.[5]

OCTA techniques can be classified into three categories: 1) phase-signal-based OCTA techniques [optical coherence angiography, phase-variance OCTA], 2) amplitude/intensity-signal-based OCTA techniques [speckle-variance OCTA, correlation-mapping OCTA, split-spectrum amplitude-decorrelation angiography (SSADA)], and 3) complex-signal-based OCTA techniques [optical microangiography (OMAG), Eigen-decomposition-based optical microangiography, imaginary part-based correlation-mapping OCTA, split-spectrum phase-gradient OCTA].[14] For example, the AngioVue software of the RTVue XR Avanti SD-OCT employs an SSADA algorithm, whereas the Zeiss AngioPlex uses a proprietary Optical Micro Angiography (OMAGc) algorithm that combines elements of the SSADA and phase-variance methodologies to produce images.[15,16] The application of the SSADA algorithm improves the signal-to-noise ratio of flow detection while minimizing the scan acquisition time to optimize visualization of the retinal vasculature (Optovue, AngioRetina mode, software AngioAnalytics).[17]

Available Platforms

OCTA platforms can be broadly categorized into SD-OCT and SS-OCT instruments. The SD-OCT instruments such as Optovue's AngioVue operate at a ~840-nm wavelength, while SS-OCT devices such as Topcon's Triton use a longer ~ 1050-nm wavelength.[18]

Swept-source systems have a faster acquisition rate and are more expensive than spectral-domain systems. SD-OCT tends to run on a shorter wavelength with better retinal lateral and axial resolution. The longer wavelength light source used in SS-OCT devices may be less affected by ocular opacity and may provide a deeper imaging range through the retinal pigment epithelium (RPE) and choroid, which is a significant advantage for managing diseases below the RPE (age-related macular degeneration or polypoidal choroidal vasculopathy).[19-22] In spectral-domain devices, software enhancement techniques such as improved depth imaging are used to better visualize the choroid and structures below the RPE. Both modalities have adequate imaging range for the retina.

OCTA in use

Currently, the standard field of view for the best image quality measures 3 × 3 mm, and enlarging the field of scanning in OCTA diminishes the details of flow. However, RVO can occur in an area of the retina that extends beyond the limited view scanned in OCTA. Wide-field and montage OCT provide detailed information of large or oblique lesions away from the arcade.[23] Wide-field OCTA images can be acquired by several methods: selecting an automated wide-angle single scan within the OCTA system itself (up to 12 mm) or by using an automatic stitching software such as AngioVueHD Montage within the Avanti RTVue XR (Optovue, Inc., CA, USA) or other semi-automated or manual methods of creating montages. Use of the montage technique allows operators to maintain the microvascular detail that appears at a higher resolution than that in the currently available FA images.[11,23,24]

A novel method using trial frames fitted with a +20 D lens has been described as an extended field imaging (EFI) technique to evaluate RVOs.[25] In this technique, researchers captured OCTA images by using RTVue XR Avanti OCT with AngioVue at a scan size of 8 × 8 mm, with and without EFI, and compared them. EFI images delineated an area 188.5% larger than those without EFI on average. The non-perfusion area was well-defined in the superficial capillary plexus (SCP), and this technique was useful for evaluating retinal ischemia in RVO, but the resolution of the image was not sufficient to study the deep capillary plexus (DCP) or microvascular changes.[25]

Comparison of OCTA and FA

Several studies have qualitatively compared OCTA with FA.[11,26] The features of disrupted flow in vascular occlusions can be well imaged on OCTA and correlate well with the area seen on FA.[10-13]

Advantages of OCTA

In comparison to FA, OCTA is fast, noninvasive, and allows improved and accurate visualization of microvascular changes. Due to the absence of leakage and tissue staining, and the better penetration of the longer wavelengths used in OCTA through intraretinal hemorrhage, OCTA allows better visualization of the microvascular abnormalities in RVO, including neovascular fronds, FAZ, and other microvascular abnormalities.[13,17,27-31]

The limited time frame in which optimal images of the capillary net can be captured under FA and the difficulty in focusing images in the presence of macular edema can complicate the use of FA to obtain quality images of the perifoveal capillaries and visualize RVOs. With OCTA, however, images can be captured rapidly, and when images are of insufficient quality, the process can be repeated immediately until good-quality images are obtained.

Depth-resolved studies of microcirculation are another big advantage of OCTA over FA. The ability of OCTA to delineate the microvascular changes and ischemia in both the SCP and DCP is a major advantage because many of the vascular changes in RVO occur in the DCP, which cannot be visualized by FA.[8,9] Additionally, the reconstructed C scan of OCTA has a better rate of detection of macular edema than FA or SD-OCT alone.[32]

In comparison with FA, OCTA shows a superior ability to precisely delineate the vessels surrounding the FAZ in eyes with RVO compared with the fellow eyes and with healthy eyes.[6,7] However, OCTA imaging of the perifoveal region in the normal retinal vasculature was equivalent to that of FA.[11] Both the retinal and the choroidal microvasculature can be visualized using OCTA while FA is used for observing the retinal vessels. Ultimately, angiography images come cross-registered with structural OCT B-scans. This process allows for precise correlation of the vasculature to the structural scans.[13,33]

Limitations of OCTA

The limitations of OCTA include the small scanning areas, segmentation errors related to variations in macular anatomy, inability to determine the presence of leakage, proclivity for image artifacts caused by patient motion and shadowing from retinal pathologies such as cystoid macular edema, and a limited ability to visualize blood movement out of the detectable flow limit.[8,34] Microaneurysms imaged with FA may not always be apparent on OCTA because they might have flow rates below the detection threshold of OCTA. There are still some challenges for its use as OCTA requires the patient to precisely fixate on a light during image acquisition (approximately 3 seconds), which may be difficult to achieve for patients with low visual acuity.[35]

OCTA's inability to visualize leakage may be both an advantage and a disadvantage, because it means that leakage does not obscure the vascular structures observed by OCTA. The co-registered structural OCT scans can provide indirect information about leakage, such as the presence of macular edema.[13]

OCTA is subject to various artifacts such as shadowing artifacts associated with intraretinal/subretinal hemorrhage, projection artifacts of the superficial retinal vessels over the deeper retinal layers, and motion artifacts. However, these errors are becoming less frequent because of the artifact correction strategies that are being currently implemented.[36-38]

OCTA is dependent on accurate retinal segmentation to delineate retinal vessels at different levels. However, the circumstances in which the retina is sufficiently disrupted to make precise segmentation difficult may lead to inaccurate depth localization of the vessels. 13 This mistake can be easily identified by scrolling through the entire three-dimensional dataset, instead of looking at individual en face printouts. Imprecise segmentation can be adjusted by manually altering the segmentation lines.

In the presence of cystoid edema, besides problems with accurate segmentation, shadowing artifacts of the fluid in the cystoid spaces may hamper detection of capillaries and result in overestimation of the degree of non-perfusion.[33]

Changes in OCTA of Eyes with RVO

The changes visible in OCTA can be described as qualitative and quantitative

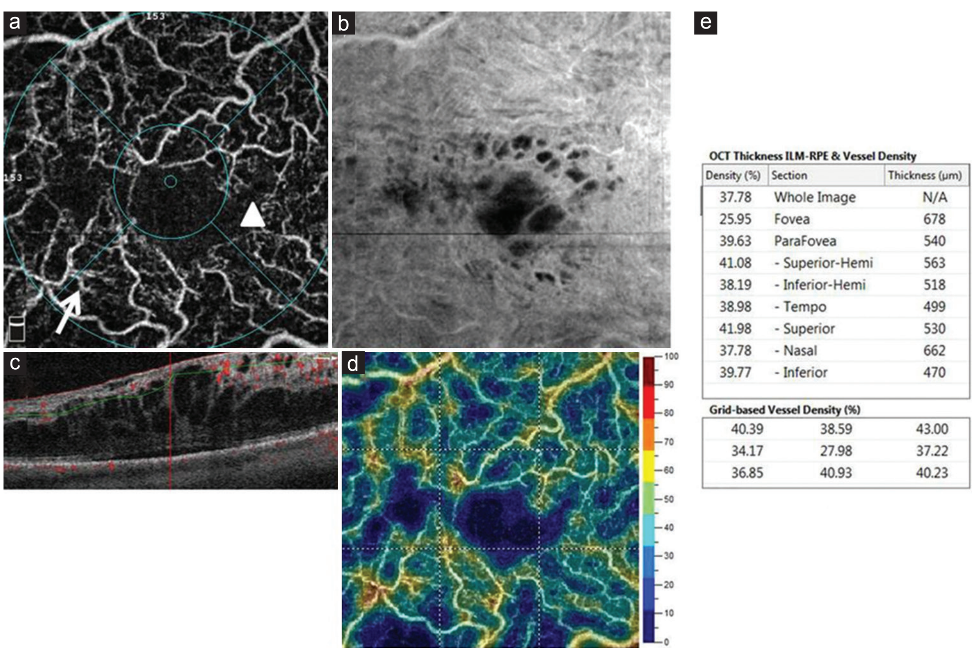
Qualitative changes

a. *Non-perfusion areas (NPAs;* Figures 1 to 4)*:*[32] These are also called grayish areas[39] and areas with decreased vascular perfusion.[6,40] These areas are regions without visible perfused capillaries. In RVOs, they are more extensive in the DCP than in the SCP.[6,10,32,33,39,40] These areas are more readily visible with OCTA than with FA.[12] There may be a decrease in the vascular perfusion in both the SCP and DCP of the fellow eye of RVO patients relative to normal controls, which may be a sign of previous silent RVOs in these eyes.[6] It should be noted that the absence of visible vessels in areas of non-perfusion may not be due to a total absence of flow, but may represent areas in which the blood flow has decreased below the device's detection threshold[41]

b. *Vascular tortuosity* [Figures 1-3]: This is similar to what is visible in larger vessels in OCTA, and may also include kinking, angulation, and/or spiral twisting of vessels. Tortuosity is seen in both central RVOs (CRVOs) and branch RVOs (BRVOs) and in some fellow eyes[7]

c. *Collateral vessel formation* [Figure 4]: This phenomenon manifests as a long vessel traversing the area with blocked perfusion, or as a bunch of tortuous vessels in the vicinity of the area with blocked perfusion. These vessels are visible in both CRVO and BRVO eyes.[6] In some cases, they could be traced to the DCP.[6] The term venous-venous anastomosis by Kashani et al appears to refer to the same finding[10]

d. *Disruption of the perifoveal capillary plexus* [Figures 1-4]:[39,40] The perifoveal capillary net is distorted in ischemic maculopathies including RVOs. Disruption of the FAZ is more common in the DCP than in the SCP.[39] Coscas et al found that the degree of disruption of the perifoveal capillary network is correlated with the presence of peripheral ischemia in FA and the degree of non-perfusion in the DCP



Density (%)	Section	Thickness (μm)
37.78	Whole Image	N/A
25.95	Fovea	678
39.63	ParaFovea	540
41.08	- Superior-Hemi	563
38.19	- Inferior-Hemi	518
38.98	- Tempo	499
41.98	- Superior	530
37.78	- Nasal	662
39.77	- Inferior	470

40.39	38.59	43.00
34.17	27.98	37.22
36.85	40.93	40.23

Figure 1. OCTA (3 × 3 mm) in a case of CRVO. (a) OCTA at the level of the superficial capillary plexus (SCP) showing vascular tortuosity, dilation and telangiectasia (arrow) along with decreased vascular density and non-perfusion areas. Also note the irregular and enlarged foveal avascular zone. (b) En face OCT at the level of the SCP shows the presence of cystoid edema, which corresponds to dark circular areas without vessel signals in OCTA (arrowhead in A). (c) B-scan OCT with perfusion overlay and segmentation lines. (d) Color-coded vascular density map. (e) Numerical report of the vascular density.

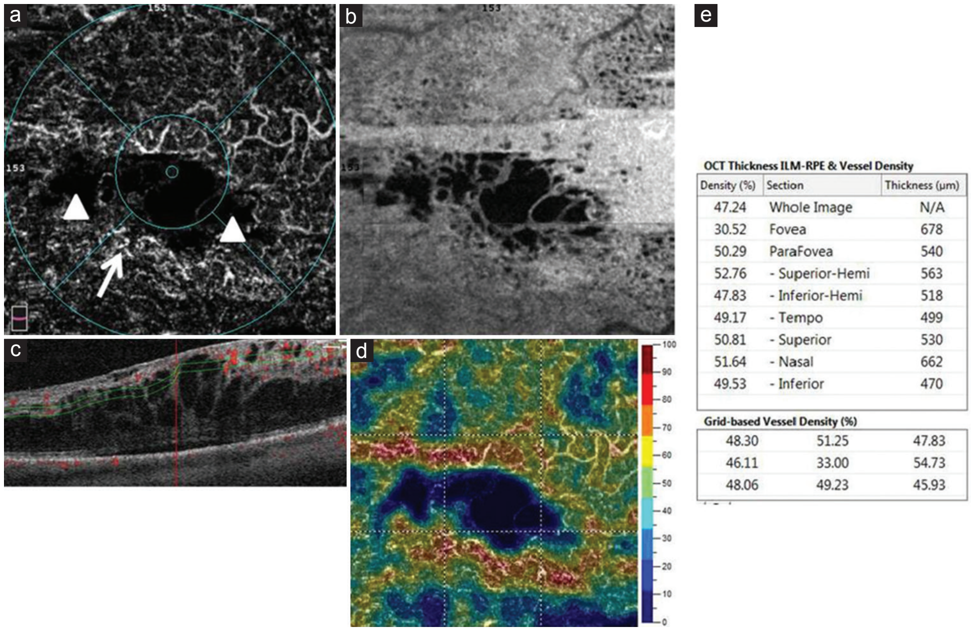


Figure 2. OCTA (3 × 3 mm) in a case of CRVO. (a) OCTA at the level of the deep capillary plexus (DCP) showing vascular tortuosity, dilation, and telangiectasia (arrow) along with decreased vascular density and non-perfusion areas. Also note the irregular and enlarged foveal avascular zone. (b) En face OCT at the level of the DCP. Note the presence of cystoid edema corresponding to dark circular areas without vessel signals in OCTA (arrowheads in a). (c) B-scan OCT with perfusion overlay and segmentation lines. (d) Color-coded vascular density map. (e) Numerical report of the vascular density.

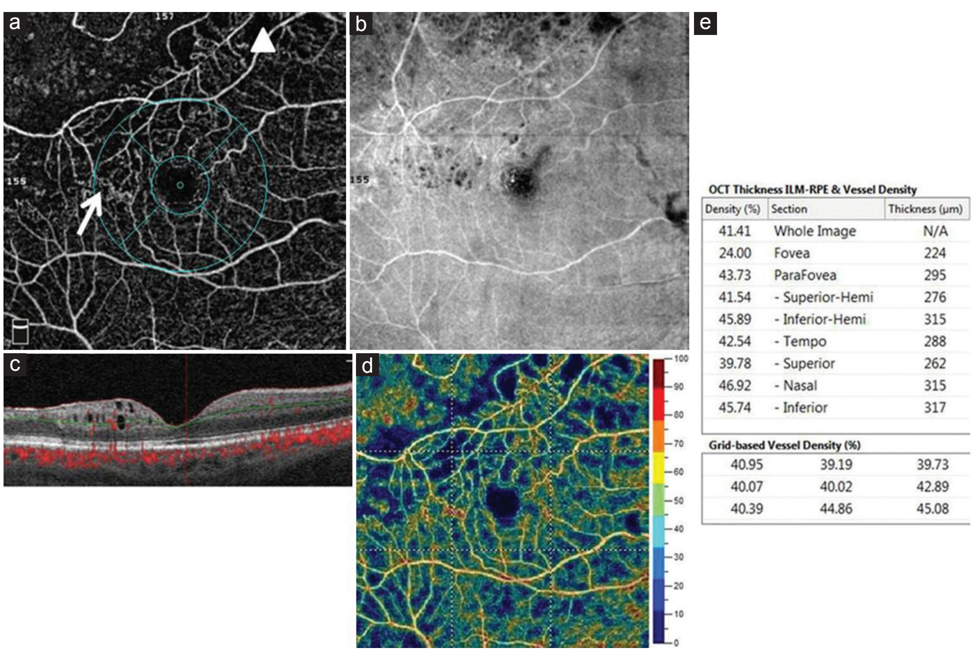
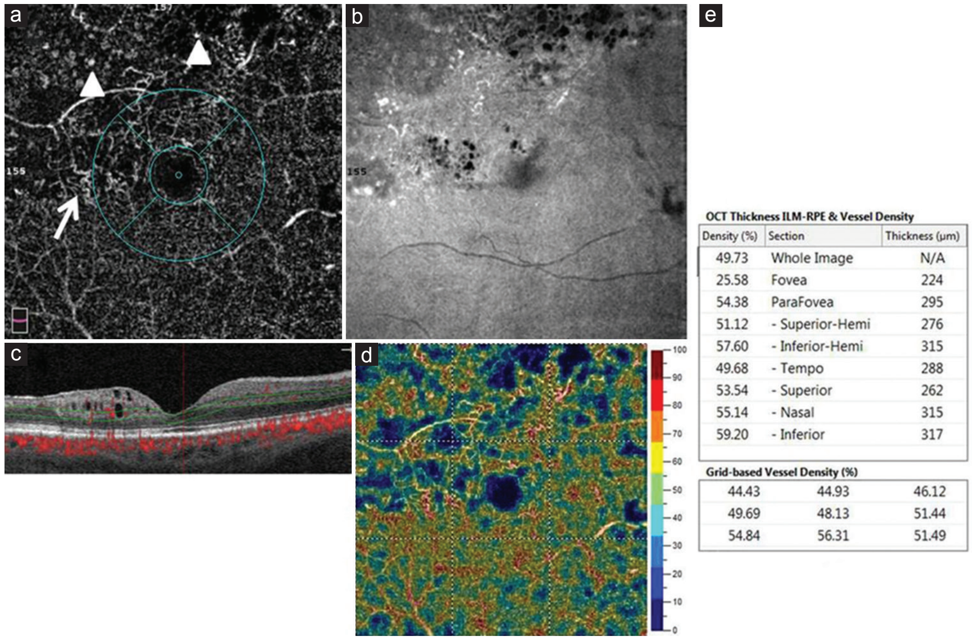


Figure 3. OCTA (6 × 6 mm) of a case of BRVO. (a) OCTA at the level of the superficial capillary plexus (SCP) showing vascular tortuosity, dilation and telangiectasia (arrow) along with decreased vascular density and non-perfusion areas in the superotemporal region (a). (b) En face OCT at the level of the SCP. Note the presence of cystoid edema corresponding to dark circular areas without vessel signals in OCTA (arrowhead in a). (c) B-scan OCT with perfusion overlay and segmentation lines showing the level of OCTA in (a). (d) Color-coded vascular density map. (e) Numerical report of the vascular density.

They did not find any peripheral ischemia in FA in cases with an intact perifoveal capillary network and suggested that OCTA may be a screening tool to decide whether to perform FA[32]

e. *Dilation of the capillary plexus and venous dilation* [Figures 1-3]: These phenomena are more commonly seen in the DCP[7,10,32,37] and better delineated by OCTA than FA.[12,42] This manifestation



Density (%)	Section	Thickness (µm)
49.73	Whole Image	N/A
25.58	Fovea	224
54.38	ParaFovea	295
51.12	- Superior-Hemi	276
57.60	- Inferior-Hemi	315
49.68	- Tempo	288
53.54	- Superior	262
55.14	- Nasal	315
59.20	- Inferior	317

44.43	44.93	46.12
49.69	48.13	51.44
54.84	56.31	51.49

Figure 4. OCTA (6 × 6 mm) of a case of BRVO. (a) OCTA at the level of the deep capillary plexus (DCP). Shunt vessels (arrow) and microaneurysms (arrowheads) are visible in the superotemporal area along with decreased vascular density and non-perfusion areas (a). (b) En face OCT at the level of the DCP. (c) B-scan OCT with perfusion overlay and segmentation lines showing the level of OCTA in (a). (d) Color-coded vascular density map. (e) Numerical report of the vascular density.

is probably caused by two mechanisms: 1) an increase in the intravascular resistance, and 2) the effect of the different cytokines and growth factors produced during the disease process.[43] In the acute phase of BRVO, capillary congestion is mostly present in the DCP at the boundary of the normal retina and will partially resolve with time[7]

f. *Microaneurysms* [Figure 4]*:* These are detected by OCTA in BRVO, and they are more common in the DCP than in the SCP.[40] They usually form at the border of NPAs, and in collateral vessels.[42] The microaneurysms within collateral vessels are a source of persistent leakage and recurrence of edema after resolution of elevated venous pressure[40]

g. *Cystoid spaces* [Figures 1-4]*:* Cystoid spaces in the SCP are more commonly seen in CRVO, and those in the DCP are more common in BRVO than in CRVO. It is easier to find macular cystoid spaces in OCTA than in OCT and FA.[32] Cystoid spaces have no signal and coincide with areas of perfusion abnormalities.[10] This is not a universal phenomenon and there are areas with impaired perfusion without development of edema.[10] There are two explanations for the absence of OCTA signals in the area of cystoid spaces.[44] The first is the displacement of capillaries by cysts, which is favored by the observation of an increase in vascular perfusion indices after treatment in some studies.[39] The second is the development of cysts in non-perfused areas.[10] The previously described "hyper-reflective" cystoid spaces appear as "diffuse and splotchy" OCTA signals.[45] Kashani et al named these pockets as "edema with hard exudates" and proposed that these areas contain intraretinal fluid with high concentrations of lipids (a stage before complete absorption of the intraretinal fluid and formation of hard exudates).[10] The Brownian movement of the lipid particulate matter is the source of the OCTA signals. Because formation of hard exudates is a harbinger of a reduction in vision, this finding may have prognostic value

h. *Intraretinal hemorrhages*: The shadowing effect of intraretinal hemorrhages may obscure images of one or both intraretinal vascular plexuses, and the level of the hemorrhage can be determined from the degree to which the images are obscured: if images of both plexuses are obscured, then the hemorrhage is above both; if neither image is obscured, it is beneath both; and if only the image of the DCP is obscured, then it lies between the two vascular plexuses[10]

i. *Non-perfused ghost vessels:* These can be diagnosed when a vessel is visible on the en face OCT image, but is not detectable in OCTA. These vessels also cannot be seen in FA[46]

j. *Optic disc venous collaterals (OVCs) and neovascularization of disc (NVD)*:[33] OCTA shows optic disc collaterals at the level of the superficial peripapillary plexus whereas neovascular vessels are visible above the retina at the level of the vitreous. OVCs are loopy vessels whereas new vessels are a mesh of fine vessels. OCTA delineates OVCs better than both fundus photographs and FA[47]

Table 1. A summary of important findings in studies reporting OCTA in RVO.

	Number of cases	Time to inclusion	Treatment	Hx of anti -VEGF	F/U time	Study design	Results	Notes
Adhi et al[6]	15 CRVO, 8 BRVO, 8 control			10/15 (67%) CRVO, 5/8 (63%) BRVO			Decrease in vascular perfusion in the deep vascular layer. Vascular tortuosity, in all types of RVO and in some fellow eyes. Collaterals in all types of RVO, some could be traced to the DCP. Larger FAZ than fellow and normal eyes. FAZ in fellow eyes of CRVO patients larger than normal eyes.	
Cassellholm et al[54]	24 CRVO			At least 4 prior anti-VEGF injections		Case series	They found enlarged superficial and deep FAZ, the deep FAZ being larger than the superficial one, and that the size of superficial FAZ (and not the deep FAZ) correlated negatively with VA. And the disruption of EZ also was correlated with VA and superficial FAZ.	
Coscas et al[32]	29 CRVO, 25 BRVO					retrospective	More NPA in DCP than SCP, more cystoid spaces in DCP than SCP, and more capillary dilation in DCP than SCP. Cystoid spaces were more readily visible in OCTA than in FA or SDOCT. Disruption of the perifoveal capillary net, better visualized with OCTA than with FA. Peripheral ischemia was correlated with capillary network disruption and areas of NPA in DCP.	OCTA was performed in the presence of ME
Chung et al[55]	7 BRVO, 3 HRVO, 2 CRVO					Cross sectional	Comparison between FA and OCTA: FAZ in SCP and DCP correlated with each other, but not with FAZ measured with FA. Area of FAZ in SCP and presence of non-perfusion on OCTA correlated with the initial VA.	

Contd...

Table 1. Contd...

	Number of cases	Time to inclusion	Treatment	Hx of anti -VEGF	F/U time	Study design	Results	Notes
Ghassemi Falavarjani et al[61]	13 DME, 5 CRVO		1 anti-VEGF injection		32.5±9.4 (range, 21-50) days.	Prospective non -comparative	No change in FVD and PFVD in the SCP and DCP, and also FAZ after one injection.	
Glacet et al[39]	3 CRVO, 4 BRVO	1-68 median: 5 mo	Dexamethasone implant	3	6-10 mean: 9 weeks	Cohort - before-after	Perifoveal capillary disruption: 6. During F/U mean vascular densities slightly decreased in DCP (44.37% to 43.88%) and SCP (43.21% to 42.76%) No significant difference in capillary densities between CRVO and BRVO. Significant decrease of all measurements relative to controls. Qualitative improvement of perifoveal arcade disruption, vascular dilation and ectasia, after treatment.	Vascular densities at the SCP increased in 4 patients
Kadomoto et al[52]	30 BRVO	3.0±1.0 months	2.2±1.1			Cross sectional -observational	Parafoveal NPA in both SCP and DCP were significantly associated with both VA and macular sensitivity on microperimetry. And this association was more significant than the defect length of EZ with VA and macular sensitivity.	Resolved ME
Kang et al[58]	11 CRVO, 21 BRVO, 33 control			Yes , mean number of 3.48±3.93 injections per eye	31.76±31.01 mo	retrospective	FAZ in eyes with RVO is larger than fellow eyes and control eyes. PFVD was less in eyes with RVO than fellow and control eyes But there was no difference in FVD between RVO eyes and fellow and normal eyes. PFVD in the DCP was correlated with BCVA.	
Kashani et al[10]	26 RVO eyes						Description of OCTA findings in RVO including hemorrhage, venous dilation, venous-venous anastomosis.	

Contd...

Table 1. Contd...

	Number of cases	Time to inclusion	Treatment	Hx of anti -VEGF	F/U time	Study design	Results	Notes
Kimura et al[25]	2 CRVO, 8 BRVO	20±19.6 months (4-72 months)				prospective	Extended field imaging technique (EFI) covers 188% more area than images without EFI). EFI can show the NPA in SCP, but due to low resolution, the NPA area cannot be measured in the DCP.	imaging through trial frame fitted with+20D lens
Koulisis et al[50]	20 BRVO, 14 CRVO, 26 Control	Less than 2 months to more than 12 months	Anti-VEGF, laser, Steroid			Retrospective	1 .In non-segmented images there were lower vascular density and complexity (fractal dimension) of the vascular tree in CRVO and BRVO eyes compared to the control and fellow eyes. The same applied to the superficial and deep vascular layers in segmented images. 2 .Eyes with macular edema had lower vascular density and complexity in the superficial layer compared to eyes without macular edema. 3. Changes in vascular density and complexity in the superficial plexus were more severe in CRVO than in BRVO 4. Fellow eyes of RVO patients have lower vascular density than controls in non-segmented images, and in superficial plexus.	
Manabe et al[59]	27 BRVO		Anti-VEGF, Peripheral scatter laser	24/27	16.0±22.0 mo		Retinal sensitivity over non-perfusion areas of both superficial and deep capillary plexsuses is decreased, more so in the superficial plexus non-perfusion.	Study was performed on eyes after resolution of ME.

Contd...

Table 1. Contd...

	Number of cases	Time to inclusion	Treatment	Hx of anti -VEGF	F/U time	Study design	Results	Notes
Mastropasqua et al[40]	20 CRVO, 40 BRVO, 40 control	less than 3 months in 49 cases	Dex implant	14 (more than 9 months before study entry)		prospective	Foveal and parafoveal vascular density (FVD, PFVD) were measured before and after dex implant. FVD and PFVD of superficial vascular plexus not different in CRVO from controls, but they were different in BRVO relative to controls. PFVD of deep vascular plexus was lower in both CRVO and BRVO relative to the control group. Indices did not improve after resolution of ME with dex implant.	New findings: 1. persistence of changes in VD after resolution of ME 2. decrease in FVD and PFVD in Choriocapillaris layer in CRVO relative to normal, and in PFVD of the affected hemifield in BRVO relative to normal
Nobre-Cardoso et al[35]	40 CRVO, 34 BRVO, 7 HRVO	26.3±36.3 (0.5-180) mo	NA	NA	NA	retrospective	Good agreement between the area of NPA both in 3X3 and 8X8 scans and FA. Good agreement in detection of capillary abnormalities and FAZ measurement for only OCTA 3X3 scan and FA. Agreement was poor for collateral vessel detection. Capillary abnormalities primarily found in the DCP. Excluding retinal cysts, NPA was similar qualitatively between SCP and DCP.	
Rispoli et al[7]	10 BRVO	6-72 mo					Enlargement of FAZ, capillary non-perfusion and decrease in capillary density, and microvascular abnormalities in both DCP and SCP. Vascular congestion mainly in deep layer at the boundary of normal and non-perfused retina.	

Contd...

Table 1. Contd...

	Number of cases	Time to inclusion	Treatment	Hx of anti -VEGF	F/U time	Study design	Results	Notes
Samara et al[53]	17 BRVO	Mean: 8 (0-42) months				Retrospective	1. Lower VD in both SCP and DCP relative to fellow eyes 2. Lower VD in affected sector in both SCP and DCP relative to the unaffected sector 3. Lower VD in the unaffected sector in DCP compared with the corresponding sector in fellow eyes 4. A negative correlation between VD in both SCP and DCP and logMAR VA. 5. Mean FAZ at only DCP was larger in affected eyes compared with fellow eyes and correlated with logMAR VA.	
Seknazi et al[51]	28 BRVO, 9 HRVO, 28 CRVO					Retrospective study	Visual acuity correlated with the vascular perfusion in both SCP and DCP. The authors found significant but weak correlations between vascular density and FAZ area in both SCP and DCP and peripheral non-perfusion. There was a stronger correlation between the qualitative grading of non-perfusion in SCP and DCP and peripheral non-perfusion.	
Sellam et al[60]	13 CRVO, 11 BRVO, 4 HRVO	Median: 3, range0-61 months	Anti-VEGF,	3 (1-7) injections	19 (4-51) weeks		Decrease in intraretinal cysts and vascular dilation in both SCP and DCP, and decrease in FAZ disruption after treatment with anti-VEGF. Whole en face VD in SCP and DCP correlated with initial and final BCVA	
Singh et al[48]	10 optic disc venous collaterals, 10 NVDs						1. OVCs visible as small vessels in the peripapillary retinal capillaries, larger than PRCs and smaller than retinal veins, visible as “loopy vessels”.	

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Table 1. Contd...

	Number of cases	Time to inclusion	Treatment	Hx of anti -VEGF	F/U time	Study design	Results	Notes
							2. Anatomical delineation of OVCs was better in OCTA than both fundus photography and FA 3. New vessels are visible in the vitreous slab of OCTA as a mesh of fine vessels	
Sogawa et al[49]	1 CRVO					Case report	Documentation of neovascularization elsewhere (NVE) with OCTA and noting better visibility of the NVE with OCTA than FA due to the absence of blurring by leakage.	
Spaide et al[44]	9 CRVO, 3 BRVO	65.5 (6-110) months	Anti-VEGFs	28.7 injections per eye		Observational case series	1. The images of SCP and DCP and cystoid spaces were volume rendered 2. Cystoid spaces mostly occurred in areas with disturbed SCP flow, and absent DCP flow 3. The pattern of vasculature in both plexuses did not change after resolution of edema with treatment 4. Recurrence of cystoid spaces occurred in the same areas affected previously	
Suzuki et al[12]	28 BRVO	28.8 months (range, 4-122 months)	NA	NA	NA	Retrospective observational consecutive case series	1. OCTA better delineated the NPA, and microvascular abnormalities including capillary telangiectasia and collateral vessels in BRVO. 2. Differential layer analysis of microaneurysms and collateral vessels is possible with OCTA.	

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Table 1. Contd...

	Number of cases	Time to inclusion	Treatment	Hx of anti -VEGF	F/U time	Study design	Results	Notes
							Most microaneurysms in BRVO form in DCP at the border of NPA and within collateral vessels. These microaneurysms continue to leak even after normalization of venous flow causing recurrent/persistent edema around them. 3. Disadvantages of OCTA: a. limited field of view, b. inability to show non-perfused microaneurysms, c. does not provide flow information like filling speed, leakage, pooling and staining, d. takes much longer time to acquire compared to FA.	
Suzuki et al[43]	4 CRVO, 8 BRVO, 11 control fellow eyes		Ranibizumab for BRVO, aflibercept for CRVO, PRN		6 mo	retrospective	FAZ in DCP was enlarged in RVO eyes relative to normal eyes.FAZ enlarged with treatment, more so in eyes with less injections. A decrease in NPA with treatment, both in SCP and DCP, more so in the DCP. The effect was more pronounced in eyes receiving more injections. Flow area was less in RVO eyes than in normal eyes, and improved especially in the DCP with treatment, more injections, more improvement.	
Tsuboi et al[56]	20 BRVO	40.4 6±33.7(range, 12-124 months)	Anti-VEGF, STTA, laser, PPV	+	12 or more mo	Retrospective case control	More gap vessels (residual vessels present in SCP, over area of NPA in DCP) in eyes with persistent macular edema than in eyes without macular edema.	

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Table 1. Contd...

	Number of cases	Time to inclusion	Treatment	Hx of anti -VEGF	F/U time	Study design	Results	Notes
Wakabayashi et al[42]	85 BRVO	14.3 6±12.8 (5-68)	Anti-VEGF, STTA, laser				Visual acuity was correlated with vascular perfusion area in both SCP and DCP and also the FAZ, but the most significant predictor of visual acuity was the vascular perfusion area in DCP. Microvascular abnormalities of microaneurysms, telangiectasias, and disruption of the FAZ were all present in both SCP and DCP, but were more prevalent in the DCP and their presence in the DCP correlated with final visual acuity, photoreceptor integrity and also the degree pretreatment macular edema.	
Wons et al[57]	11 BRVO, 8 CRVO	Less than 2 years	Anti-VEGF			Retrospective case series	Maximum diameter of FAZ correlated with vision.	

BCVA, best corrected visual acuity; DCP, deep capillary plexus; EZ, ellipsoid zone; FA, fluorescein angiography; FAZ, foveal avascular zone; FVD, foveal vascular density; mo, months; ME, macular edema; NPA, non-perfusion area; NVD, neovascularization of disc; NVE, neovascularization elsewhere; OVC, optic disc venous collaterals; PFVD, parafoveal vascular density; PRCs, peripapillary retinal capillaries; SCP, superficial capillary plexus; STTA, sub-tenon triamcinolone acetonide injection; VA, visual acuity; VD, vascular density

k. *Neovascularization elsewhere (NVE):* This phenomenon can be detected using OCTA, and the visibility of new vessels with OCTA is greater than that with FA because of the absence of leakage in OCTA.[48] This modality may enable physicians to perform quantitative follow-up of new vessels and evaluate the response to treatment.

Quantitative Changes

a. Foveal and perifoveal vascular density: Vascular density both in the foveal and parafoveal areas and all over the scanned area have been reported to be lower in RVO eyes relative to those in control eyes. However, there are different results regarding the layers that are affected in each type of RVO.[7,40,49] Due to the wide variations in foveal vascular density (FVD) in normal individuals, this measure may not always be affected in RVOs.[39]

Vascular perfusion density is another significant factor associated with photoreceptor integrity and visual acuity.[50,51] Changes in vascular density in the presence of macular edema have also been reported, but the results of different studies differ. Mastropasqua et al reported significant positive correlations between macular thickness and the vascular density in superficial, deep, and choriocapillaris plexuses, and this correlation has been ascribed to the high levels of VEGF, which increases both the macular thickness and the vascular diameter, thereby increasing the percentage of reported flow pixels by the instrument.[40] Meanwhile, Koulisis et al described decreased SCP vascular density in the presence of macular edema due to RVO compared to that in eyes without edema, while DCP and non-segmented vascular densities were not affected.[49] This discrepancy may be due to the different inclusion criteria for macular edema or different OCTA platforms used. Seknazi et al, in a retrospective study, found that a vascular density of less than 46% in the DCP in eyes with CRVO is the limit below which peripheral retinal non-perfusion becomes probable and suggested the use of this limit as an indication for performing FA in CRVO patients.[51]

a. *Measurement of NPA:* In a study involving manual measurement of NPA in the parafoveal area, this parameter was found to be the most significant factor associated with VA and macular sensitivity in microperimetry in eyes with RVO, and was even more significant than the ellipsoid zone (EZ) continuity.[52] Qualitative grading of non-perfusion in both plexuses was also reported to be significantly correlated with peripheral non-perfusion[51]
b. *Measurement of FAZ:* Despite the variability of FAZ size in normal individuals,[53,54] the FAZ is enlarged in the DCP of RVO eyes relative to those in normal controls and fellow eyes, and relative to the FAZ of the SCP.[7,42,54] FAZ findings of the SCP may vary. While Rispoli et al and Casselholmde Salles et al found an enlargement of the SCP ischemic area,[7,54] Suzuki et al reported no significant alterations.[42] Casselholmde Salles et al also reported an association between EZ disruption and the superficial FAZ area.[54]

To reduce the artifacts from segmentation errors in eyes with macular edema, Adhi et al used non-segmented OCTA images for calculation of the FAZ. FAZ enlargement was reported in comparison to both fellow eyes and normal controls.[6]

Suzuki et al reported that the FAZ was larger in eyes with CRVO than in eyes with BRVO. The authors proposed that FAZ size may be related to the intraocular VEGF levels, as they found larger FAZs in both plexuses in eyes receiving fewer intraocular injections.[42]

OCTA Parameters Found to be Associated with VA in Eyes with RVO

The FAZ area in the SCP,[54,55] FAZ maximum diameter,[56,57] NPA and the PFVD in the DCP,[52,58] and the DCP vascular perfusion are the factors found to be associated with BCVA.[42] Even though Mastropasqua et al did not find any correlations between vascular perfusion in the SCP, DCP, VA, and microperimetric indices,[40] Manabe et al reported decreased retinal sensitivity over areas with vascular non-perfusion in both the SCP and DCP, with a stronger correlation with non-perfusion in the SCP.[59]

Changes in the OCTA Findings of RVO after Treatment

The qualitative changes of vascular telangiectasia and dilation, and perifoveal vascular disruption have been reported to improve after treatment with both anti-VEGFs and steroid implants.[39,40,60] However, the vascular density (VD) of both the SCP and DCP either remained unchanged or reduced after treatment. This may be due to either the continued expansion of vascular non-perfusion over time, as is observed during conversion from non-ischemic to ischemic CRVO, or the nonreversible ischemic damage of the retinal vessels.[39,40,60]

Suzuki et al reported on FAZ alterations after anti-VEGF treatment in both SCP and DCP, with a greater increase in the SCP despite the concomitant improvement in vision. It is interesting that the degree of FAZ enlargement was bigger in eyes that received fewer anti-VEGF injections.[42]

Reduction of the NPA area in both the SCP and DCP, with a greater decrease in the DCP, has also been reported after anti-VEGF treatment. This effect was more pronounced in eyes receiving more injections. The authors attributed this to reperfusion of temporarily closed vessels by leukostasis.[42] In the same study, the vascular perfusion area (the flow area as stated in the paper) was smaller in RVO eyes than in fellow eyes, and improved in eyes that received frequent anti-VEGF injections, with a greater improvement noted in the DCP. Vascular densities do not show any changes after a single anti-VEGF injection.[61]

Spaide et al studied OCTA images of RVO eyes after volume rendering and found that cystoid spaces are formed at locations of disturbed vascular flow in the SCP, and absent or severely disturbed vascular flow in the DCP. There were no changes in the pattern of the SCP or DCP after resolution of cystoid spaces with treatment, and in cases of recurrence, cystoid spaces reformed in the same areas as previously affected.[62]

Tsuboi et al found that the presence of isolated preserved vessels in the SCP over areas of NPA in the DCP (the prefusion gap between the two layers) showed the best correlation with persistent edema.[56]

Artifacts in the OCTA Images of RVO Eyes

There are multiple sources of artifacts in OCTA images of RVO eyes. The first is the attenuation of signals due to shadowing artifacts of edema or hemorrhage, which results in overestimation of the reduction in vascular perfusion. This may be the cause of the reported rarefaction of the choriocapillaris vascular perfusion in the affected sector of BRVO and under the fovea in CRVO, which improved after treatment with steroid.[40] Difficulty and inaccuracy in segmentation of slabs in OCTA, may lead to difficulty in finding the SCP and DCP in addition to under-sampling the deep vascular plexus.[62] Excessive movement due to poor vision causes significant motion artifacts in OCTA. In a study, 18% of 3 × 3 OCTA images in RVO cases were unreadable, and the strongest predictor for a poor-quality OCTA image was low vision.[35]

DISCUSSION

OCTA is a relatively new noninvasive modality for imaging retinal blood flow. It is based on detection of the motion of blood constituents in OCT images and provides better visualization of the macular capillaries and FAZ relative to FA.

The microvascular changes associated with RVOs in the posterior pole, including NPAs, vascular tortuosity and telangiectasia, disruption of the perifoveal capillary net, and formation of microaneurysms and collaterals, are all readily visible in OCTA images. OCTA is of great help in differentiating between optic disc collateral vessels and neovascular fronds. This technique is better than both FA and OCT in visualizing the microvascular changes and even the cystoid spaces. Currently the most notable limitation of OCTA in RVO cases seems to be the inability to view peripheral vascular perfusion, which is a significant factor in management of these eyes. Montage images, wide-field OCT imaging, and extended field techniques are some solutions that have thus far been proposed, but none of them is still optimal enough for routine clinical use.

The microvascular changes in RVO are more prominent in the DCP than the SCP, which can be described by the architectural organization of vessels in these two plexuses.[6,39,58] DCP is composed of capillaries with a vortex configuration, the center of which is aligned with the course of venules in the SCP.[63] Thus, it seems that the DCP drains into the larger superficial veins. This vessel configuration has previously been reported in animals.[64] Thus, the increase in intravenous pressure in RVO is directly transmitted to the DCP.[64] Besides the direct connection of the superficial capillaries to the retinal arterioles, this provides the capillaries with higher perfusion pressure and oxygenation, which may somewhat protect them from the ischemic changes of increased venous pressure. Quantitative measurements of the FAZ and NPA areas, vascular density, perfusion in SCP and DCP, their correlation with function of the macula, and their changes after treatment are areas of active research in RVO. OCTA will not only help us understand changes in the complex microvasculature of macula after vein occlusion, but will certainly have an undeniable role in the management of RVO patients in the future.

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Conflict of Interest

There are no conflicts of interest.

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