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Morphological implications of vascular structures not visualized on optical coherence tomography angiography in retinal vein occlusion

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Abstract

Background and Objective: Advanced retinal imaging can improve our understanding of retinal vein occlusion (RVO) pathology. We set out to characterize the vascular pathology of RVO on en-face optical coherence tomography (OCT) and OCT angiography (OCTA).

Study Design: This was a cross-sectional study including 17 eyes with RVO. We identified discordance between vasculature on en-face OCT and flow on OCTA, which was correlated with structural findings at the corresponding location on OCT B-scans.

Results: Six eyes had vessels that were seen on OCT without flow on OCTA. The most clinically relevant finding was preserved inner retinal layers in areas where the en-face OCT showed collaterals that appeared non-perfused on OCTA.

Conclusions: Our findings indicate that collaterals can appear on en-face OCT without flow on OCTA in RVO and may be associated with relatively preserved inner retinal structures. Clinicians should consider multimodal imaging to evaluate RVO, including both OCT and OCTA.

Introduction

Retinal vein occlusion (RVO) is the second most common retinal vascular disorder and has the potential for significant loss of vision.[1] Vision loss is most often a result of cystoid macular edema; however, vitreous hemorrhage, ischemic maculopathy, neovascularization and retinal detachments are also potential complications. Currently, optical coherence tomography (OCT) and fluorescein angiography (FA) are used to diagnose and manage RVO and its complications.

Optical coherence tomography angiography (OCTA) offers a promising noninvasive imaging modality that is safer and faster than FA. OCTA visualizes vasculature by detecting signal decorrelation between successive OCT B-scans resulting from blood flow motion. In the present study, we set out to evaluate the discordance between en-face OCT and OCTA to study the structural and functional effects of RVO.

Methods

This was a cross-sectional study of patients with RVO seen at a single institution between June 1, 2015 and December 1, 2016. The study protocol was approved by the Institutional Review Board of Northwestern University and this research followed the tenets of the Declaration of Helsinki. Patients underwent complete bilateral ophthalmologic evaluation including SD-OCT (Heidelberg Spectralis HRA + OCT, Heidelberg Engineering Inc., Dossenheim, Germany) and OCTA (RTVue-XR Avanti system, Optovue Inc., Fremont, CA USA). OCTA used split-spectrum amplitude-decorrelation angiography (SSADA) software. Two consecutive B-scans (M-B frames), each containing 304 A-scans were captured at each sampling location and SSADA was used to extract OCTA information in a 3x3-mm area.

Image Analysis

OCTA image quality was assessed using the signal strength index (threshold ≥50). A single investigator (EJG) used the manual registration feature of ImageJ software (NIH, Bethesda, MD) to compare the en-face OCT and OCTA images. Areas of discordance were defined as retinal vasculature visualized on en-face OCT with no corresponding flow detected on OCTA. In these areas of discordance, the retinal thickness map and OCT B-scans were evaluated in greater detail. An observer (MJH), masked from patient identifiers, marked all areas of discordance. In cases of uncertainty, a second observer (AAF) independently assessed the images to validate accuracy. Full-thickness vessel density was quantified using the integrated analytics software (version 2016.2.0.35) of the Angiovue device. We used the preset segmentation to measure the full thickness retinal vessel density between the internal limiting membrane and retinal pigment epithelium without the need to manually adjust the boundaries.

Statistical analysis

Statistical analysis was performed using Excel (Microsoft Excel for Mac 2017, Microsoft Corporation, Redmond, WA). One-way independent sample t-tests were used for all experiments and a *P*-value <0.05 was considered significant. All results were expressed as mean ± standard error of the mean.

Results

Between June 1, 2015 and December 1, 2016, 25 eyes of 25 patients with RVO underwent OCT and OCTA at Northwestern University. Of these eyes, 8 were of insufficient image quality to perform our analysis and were excluded from the study. None of the remaining cases had significant cystoid macular edema to obscure either segmentation or image analysis. Of the remaining eyes, 7 had branch RVO (BRVO) and 10 had central RVO (CRVO) (Table 1). Average elapsed time since RVO was 766±1024 days with 8/17 occurring within one year and 4/17 occurring within 6 months. Overall, 6/17 eyes had some degree of discordance between en-face OCT and OCTA images (Figures 1 and 2) leaving 11 eyes with complete concordance. Three of the eyes with discordance had BRVO and three had CRVO. In areas of discordance between en-face OCT and OCTA, we further evaluated the thickness maps and OCT B-scans. These areas were found to have better preserved inner retinal layers compared to areas where both modalities showed absent vessels (Figure 2).

Discussion

In the present study, a comparison of en-face OCT and OCTA images in patients diagnosed with RVO revealed discordance in a subset (35.3%) of eyes, where vascular structures were seen on en-face OCT which were non-perfused on OCTA (Figures 1 and 2). These areas were further evaluated using retinal thickness maps and OCT B-scans revealing relative preservation of the inner retinal layers. A potential explanation for these areas of preserved inner retina is through oxygen diffusion from adjacent relatively perfused branch retinal vessels which may prevent ischemic retinal atrophy. This mechanism is suggested in Figure 1 by the presence of collaterals detected on OCTA that are connected to vessels within the area of BRVO that are visible on OCT but not on OCTA. These areas showed relatively preserved inner retina along the collaterals, suggesting potentially functional, though decreased, perfusion. Another possible mechanism is sub-threshold blood flow through the retinal vasculature that is seen on en-face OCT but is below the detection threshold of OCTA.

Muraoka et al. compared en-face OCT and OCTA, as well as FA, in patients with diabetic macular edema.[2] They found inconsistency between the three modalities including larger foveal avascular zones on OCTA compared to en-face OCT and variable visualization of microaneurysms on these modalities. These results are consistent with our findings and suggest the possibility of visualizing vascular structures on en-face OCT without flow signal on OCTA. Like our study, Powner et al. found retinal vessels on en-face OCT without perfusion on OCTA in three patients with BRVO.[3] They speculated that these vessels on en-face OCT were acellular basement membrane tubes and went on to support this hypothesis with histologic evidence from a patient with a chronic CRVO. However, our study suggests that at least a subset of these vessels maintain some perfusion given the observed areas of preserved retina.

The vision-threatening complications of RVO result from retinal vascular occlusion and resulting hypoxia.[4] The ability to accurately quantify the area of non-perfusion may allow clinicians to predict the likelihood of complications and guide recommendations for follow up. Furthermore, the presence of structurally intact blood vessels (without flow) would support the possibility of reperfusion of these structures during anti-VEGF therapy.[2]

Previous studies have described the qualitative and quantitative findings of RVO on OCTA including loss of capillary blood flow, vascular tortuosity and telangiectasia.[5] Additionally, multiple groups have found concordance between OCTA and FA in patients with RVO.[5-7] Interestingly, these authors found lower agreement between OCTA and FA in areas of capillary telangiectasia and collateral formation compared to areas of capillary non-perfusion.[6] One potential explanation for this discrepancy may be wider variation in the speed of blood flow in dilated capillaries and collaterals, where flow could be seen on FA, which is less sensitive to low turbulent flow speed, but may be below OCTA detection threshold. Our findings would support this explanation and suggest that the preserved vessels on en-face OCT are associated with sub-threshold blood flow (undetected on OCTA) that is sufficient to sustain the relatively preserved inner retina in these areas. We also found collateral vessels with flow on OCTA and preserved retina without associated capillaries seen on OCTA (Figure 1). Overall, areas of flow on OCTA may represent more physiologic levels of retinal blood flow compared to FA or en-face OCT given that FA (and potentially en-face OCT) can show capillaries that are perfused with plasma alone without red blood cells.[2]

Limitations

This study has important limitations. The exclusion of eyes due to poor image quality may introduce a selection bias given these patients often have poor fixation. We used a

3x3-mm area to obtain a more accurate measure of vessel density, which does not account for peripheral vascular changes. Nobre Cardoso et al. found that one out of twenty-two patients with BRVO had peripheral ischemia seen on wide-field FA that was not identified on OCTA 8x8-mm scans.[6] However, larger studies are needed to determine the ability of macular OCTA to predict the overall ischemia in RVO.

Summary

In the present study, we show that 35% of eyes had areas of discordance between en-face OCT and OCTA with preserved vessels (consistent with collateral formations) on en-face OCT in areas with no detectable flow on OCTA. Thickness maps and OCT B-scans through these areas revealed relative preservation of the inner retinal layers suggesting sub-threshold perfusion in these collaterals, not detected on OCTA. Our findings support the clinical utility of using multimodal imaging, including en-face OCT and OCTA, in evaluating patients with RVO. Future investigation is warranted to further characterize these findings and their relevance to visual prognosis in patients with RVO.

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Legends

Table 1. Characteristics of the Study Participants. BVCA = best-corrected visual acuity; BRVO = branch retinal vein occlusion; CRVO = central retinal vein occlusion; logMAR = logarithm of minimal angle of resolution; OCT = optical coherence tomography; SSI = strength signal index

Figure 1. Comparison of optical coherence tomography angiography (OCTA), en-face optical coherence tomography (en-face OCT) with thickness map and representative B scans. 54-year-old female diagnosed with a branch retinal vein occlusion one year prior to imaging. 1A: OCTA image segmented at the superficial retinal vessels showing an area without flow (red arrows) and two collateral vessels with flow (yellow arrows). These collateral vessels cross the horizontal raphe and appear to be vein-to-vein channels on infrared reflectance (not shown). 1B: En-face OCT image with the same segmentation showing blood vessels (red arrows) without flow on OCTA. 1C: Retinal thickness map (green is thicker) showing relatively preserved inner retina (yellow circle) adjacent to these collateral vessels (yellow arrows). 1D: OCT-B scan image showing thinning and disorganization of the inner retinal layers in areas with no flow on OCTA (red arrows). 1E: OCT B-scan image showing relative preservation of the inner plexiform, inner nuclear and outer plexiform layers as well as better overall organization of the retina (yellow circle) adjacent to collateral vessels. 1F: OCT B-scan image showing normal flow and thickness outside the RVO area. 1G-I: corresponding OCT B-scan images without flow.

Figure 2. Comparison of optical coherence tomography angiography (OCTA), en-face optical coherence tomography (en-face OCT) and thickness map, with corresponding B-scans. 82-year-old female diagnosed with a branch retinal vein occlusion seven years

prior to imaging. 2A: OCTA image segmented at the superficial retinal vessels showing an area without flow and two large blood vessels with flow (yellow arrows). 2B: En-face OCT image with the same segmentation showing blood vessels in the area without flow on OCTA (red arrows). 2C: Retinal thickness map (green is thicker) showing relatively preserved inner retina (yellow circle) in the area with collateral vessels, crossing the horizontal raphe and seen on en-face OCT without flow on OCTA. 2D: OCT B-scan image showing thinning and loss of organization of all the inner retinal layers. 2E: OCT B-scan image showing relative preservation of the inner plexiform, inner nuclear and outer plexiform layers as well as better overall organization of the retina (yellow circle) in the area with collaterals seen on en-face OCT without detectable flow on OCTA. 2F: OCT B-scan image showing normal thickness and blood flow outside the area of RVO. 2G-I: corresponding OCT B-scan images without flow.

Table 1

Characteristics	RVO N=17	Fellow Eyes N=12	P- Value
Age (y)	66.5 ± 16.2	64.9 ± 19.6	0.26
Male (%)	47	67	-
BCVA (logMAR)	0.28 ± 0.49	0.02 ± 0.13	0.09
OCT Metrics			
Vessel density (%)	46.6 ± 6.2	51.6 ± 4.5	0.03
Foveal Thickness (μm)	263.7 ± 48.0	249.8 ± 36.7	0.48
SSI	58.4 ± 5.9	65.6 ± 7.9	0.02

Figure 1

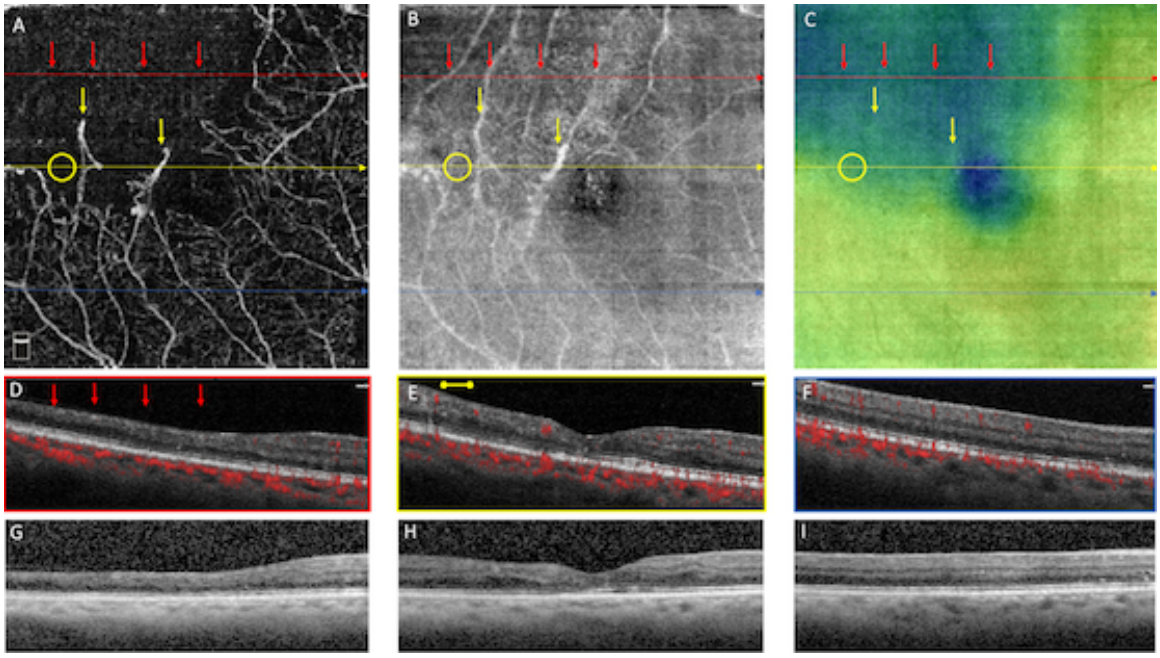

Figure 2