

Optical Coherence Tomography Angiography in Central Retinal Vein Occlusion: Correlation Between the Foveal Avascular Zone and Visual Acuity

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Submitted: December 7, 2015

Accepted: May 29, 2016

Citation: Casselholm de Salles M, Kvanta A, Amrén U, Epstein D. Optical coherence tomography angiography in central retinal vein occlusion: correlation between the foveal avascular zone and visual acuity. *Invest Ophthalmol Vis Sci.* 2016;57:OCT242–OCT246. DOI:10.1167/iovs.15-18819

PURPOSE. To investigate the relationship between best-corrected visual acuity (BCVA) and the foveal avascular zone (FAZ) in patients with central retinal vein occlusion (CRVO) evaluated with optical coherence angiography (OCT-A).

METHODS. The study was a prospective consecutive case series including 24 patients with CRVO. All patients received either aflibercept or ranibizumab intravitreal injections prior to analysis. Best-corrected visual acuity and FAZ were evaluated in eyes without macular edema. The FAZ areas were evaluated with OCT-A in both the superficial and deep capillary plexus layers by using 3 × 3-mm images of the macula. Disruption of the ellipsoid zone (EZ) was also analyzed.

RESULTS. The mean superficial FAZ area measured 0.76 mm² (95% confidence interval [CI] 0.50–1.13). The mean deep FAZ area measured 1.12 mm² (95% CI 0.77–1.47). In a multivariable analysis a negative correlation was found between the BCVA and the superficial FAZ area ($r = -0.54$, $P = 0.03$). The correlation between the BCVA and deep FAZ area did not meet statistical significance ($r = -0.43$, $P = 0.09$). In a multivariable analysis, disruption of the ellipsoid zone was significantly correlated to a larger superficial FAZ area ($r = 0.68$, $P < 0.001$) and poor visual acuity ($r = 0.75$, $P < 0.001$).

CONCLUSIONS. Optical coherence tomography-A is a novel technique that allows segmented evaluation of the FAZ in patients with CRVO providing additional prognostic information. The FAZ areas were enlarged both in the superficial and the deep capillary networks. A significant correlation was found between BCVA and the FAZ area in CRVO patients without macular edema (ClinicalTrials.gov, number NCT02274259).

Keywords: CRVO, foveal avascular zone, ellipsoid zone, visual acuity, OCT angiography

Central retinal vein occlusion (CRVO) is a common retinal vasculopathy that may cause severe visual impairment.¹ The predominate cause of decreased visual acuity in most patients is macular edema.² Early treatment of the macular edema improves the visual prognosis.^{2–4} However, retinal nonperfusion may also contribute to poor visual prognosis.⁵ Previous studies have further shown an enlargement of the foveal avascular zone (FAZ) in patients with retinal vein occlusion.^{6,7} Until recently, the only way to evaluate the FAZ was by fluorescein angiography (FA), an invasive and time consuming examination associated with adverse effects including nausea, vomiting, rash, and even anaphylaxis and sudden death.^{8,9} Furthermore, during the early stages of CRVO, FA has several limitations in providing information about retinal capillary obliteration due to hemorrhage and edema. Optical coherence tomography angiography (OCT-A) is a recently developed, new, noninvasive, contrast-free technique for imaging of the retinal microvasculature with high and consistent contrast that overcomes many of the limitations of FA. The technique uses the movement of red blood cells in the retinal vasculature to create an image of retinal blood flow.^{10,11} This allows segmented evaluation of the FAZ and the parafoveal capillary networks.¹² Previously, it has been shown that nonperfused CRVO has poorer prognosis than perfused CRVO

and that ischemic eyes have larger FAZ areas and worse functional outcome.^{1,13} However, the relationship between the FAZ area and its relationship to best-corrected visual acuity (BCVA) in CRVO patients without macular edema has until now not been studied. We hypothesize that an enlarged FAZ area is associated with poorer BCVA and visual prognosis in patients with CRVO. Furthermore, disruption of the ellipsoid zone (EZ; also termed photoreceptor inner segment/outer segment [IS/OS] junction) is commonly considered a consequence of photoreceptor dysfunction and has been associated in retrospective reports with poor visual prognosis in CRVO patients.^{14,15} The aim of this study was to investigate the correlation between the FAZ area and disruption of the EZ and BCVA in patients with CRVO without macular edema using OCT-A.

METHODS

This prospective study was performed at the St. Erik Eye Hospital, Stockholm, Sweden. The study adhered to the tenets of the Declaration of Helsinki and the protocol was approved by the regional ethical review board in Stockholm. Each subject gave written informed consent to participate in the study.



Study Population

The patients in the current study were selected from a cohort of subjects participating in a double-blind randomized trial comparing a treat and extend regimen with aflibercept and ranibizumab for macular edema in CRVO. The key inclusion criteria were: treatment naive CRVO with a disease duration of maximum 12 months, BCVA between 23 and 73 letters (Snellen equivalent approximately 20/40–20/320) and a macular edema greater than 300 μm on Cirrus spectral-domain (SD)-OCT (Carl Zeiss Meditec, Inc., Dublin, CA, USA). The study is listed on ClinicalTrials.gov, under identifier NCT02274259. Patients that had a planned study visit during October 2015 were eligible to participate in the present study. Twenty-four patients met the inclusion criteria and were evaluated for measurement of the FAZ area by OCTA.

Study Design

All patients had a full ophthalmic examination at the study visit. Best-corrected visual acuity was measured at a distance of 4 m (or at 1 m if needed) by using an Early Treatment Diabetic Retinopathy Study (ETDRS) chart. Optical coherence tomography-A and standard horizontal SD-OCT images were obtained using the AngioVue OCTA system (Optovue, Inc., Fremont, CA, USA). AngioVue software automatically segments the area into four layers that include the superficial capillary plexus layer (SL), deep capillary plexus layer (DL), outer retina layer, and the choriocapillaris. We evaluated the FAZ areas in both the superficial and deep capillary plexus layers in each group by using 3×3 -mm images of the macula. The superficial layer was measured from the internal limiting membrane to 15 μm below the inner plexiform layer (IPL) and the deep layer from 15 μm below the IPL to 70 μm below the IPL. Only scans with the entire FAZ area inside the 3×3 -mm cube were included in the analysis. Horizontal SD-OCT B-scans were also evaluated for disruption of the EZ. Eyes were classified as having disruption of the EZ when the line was absent to some extent within a 500- μm diameter from the fovea. All subjects received at least four intravitreal anti-VEGF injections prior to the OCTA evaluation and had then no evidence of macular edema as demonstrated by SD-OCT.

Image Analysis

The size of the FAZ was assessed by one observer that was masked to BCVA. The original OCTA images were individually captured, and converted to jpeg images and imported into the ImageJ software (<http://imagej.nih.gov/ij/>; provided in the public domain by the National Institutes of Health, Bethesda, MD, USA). The area of the FAZ was measured using ImageJ after setting the scale to 3 mm for scan height. When evaluating the deep circulation areas with blood vessels representing projection artifacts from the superficial circulation was considered avascular and not included in the calculation. The boundary of the FAZ was manually outlined and the program calculated the area within this boundary in square millimeters. Examples of measured FAZ and corresponding segmentation images are shown (Figs. 1A–D).

Statistical Analysis

For statistical analyses, the independent Student's *t*-test were used to compare differences in distributions between the groups. Univariable and multivariable regression models were performed to evaluate association between demographic and the different outcome parameters. Pearson's correlation

TABLE. Patient Characteristics

Parameter	CRVO, <i>n</i> = 21
Age, <i>y</i> \pm SD	68.4 \pm 16.3
Sex ratio male:female, %	57:43
Time from inclusion wk \pm SD	42.5 \pm 15.4
BCVA, ETDRS letters \pm SD	73.1 \pm 13.7
CRT, μm \pm SD	252 \pm 35
Number injections, <i>n</i> \pm SD	7.9 \pm 3.0

coefficient was used to estimate relationship between the FAZ area and other parameters.

RESULTS

Twenty-four eyes of 24 patients with CRVO were evaluated for inclusion. Two patients were excluded due to macular edema and epiretinal membrane. Only high quality scans with a FAZ area completely inside the 3×3 -mm cube were included in the analysis. Six patients had a severely enlarged DL FAZ area outside the 3×3 -mm cube making measurement impossible. Twenty-one scans of the SL FAZ and 16 scans of the DL FAZ layer met the inclusion criteria. Characteristics of the patient cohort are listed in the Table.

Foveal Avascular Zone

The mean SL FAZ area measured 0.76 mm² (95% confidence interval [CI] 0.47–1.05). The mean DL FAZ area measured 1.12 mm² (95% CI 0.77–1.47). In a univariable analysis a negative correlation was found between the BCVA and the superficial FAZ area ($r = -0.54$, $P = 0.01$; Fig. 2). The correlation was still significant in a multivariable analysis when corrected for age, disease duration, and number of injections ($r = -0.54$, $P = 0.03$). The correlation between the BCVA and deep FAZ areas did not meet statistical significance ($r = -0.43$, $P = 0.09$; Fig. 3). No significant correlation was found between age and the superficial ($r = 0.24$, $P = 0.22$) or deep FAZ areas ($r = 0.42$, $P = 0.10$). No correlation was found between FAZ area and sex, disease duration, or number of injections.

Disruption of EZ

Disruption of the EZ was significantly correlated to a larger SL FAZ area ($r = 0.68$, $P < 0.001$) and poor visual acuity ($r = 0.75$, $P < 0.001$). In a multivariable analysis when corrected for age, disease duration, and number of injections there was a significant correlation between a disrupted EZ/SL FAZ area ($r = 0.74$, $P = 0.002$) and EZ/poor visual acuity ($r = 0.79$, $P < 0.001$). Patients with disrupted EZ had worse mean BCVA (57.3 \pm 10.8 letters) compared with patients with a normal EZ (79.5 \pm 10.1 letters; $P = 0.002$).

Anatomical Outcome and Number of Injections

None of the patients analyzed showed evidence of macular edema and had a mean central retinal thickness (CRT) of 254 \pm 34 μm . The patients had received an average of 7.9 \pm 3.0 injections (range, 4–14) before evaluation with OCTA.

DISCUSSION

To the best of our knowledge, this is the first study to prospectively evaluate FAZ area and its relationship to BCVA in CRVO patients without macular edema undergoing anti-VEGF

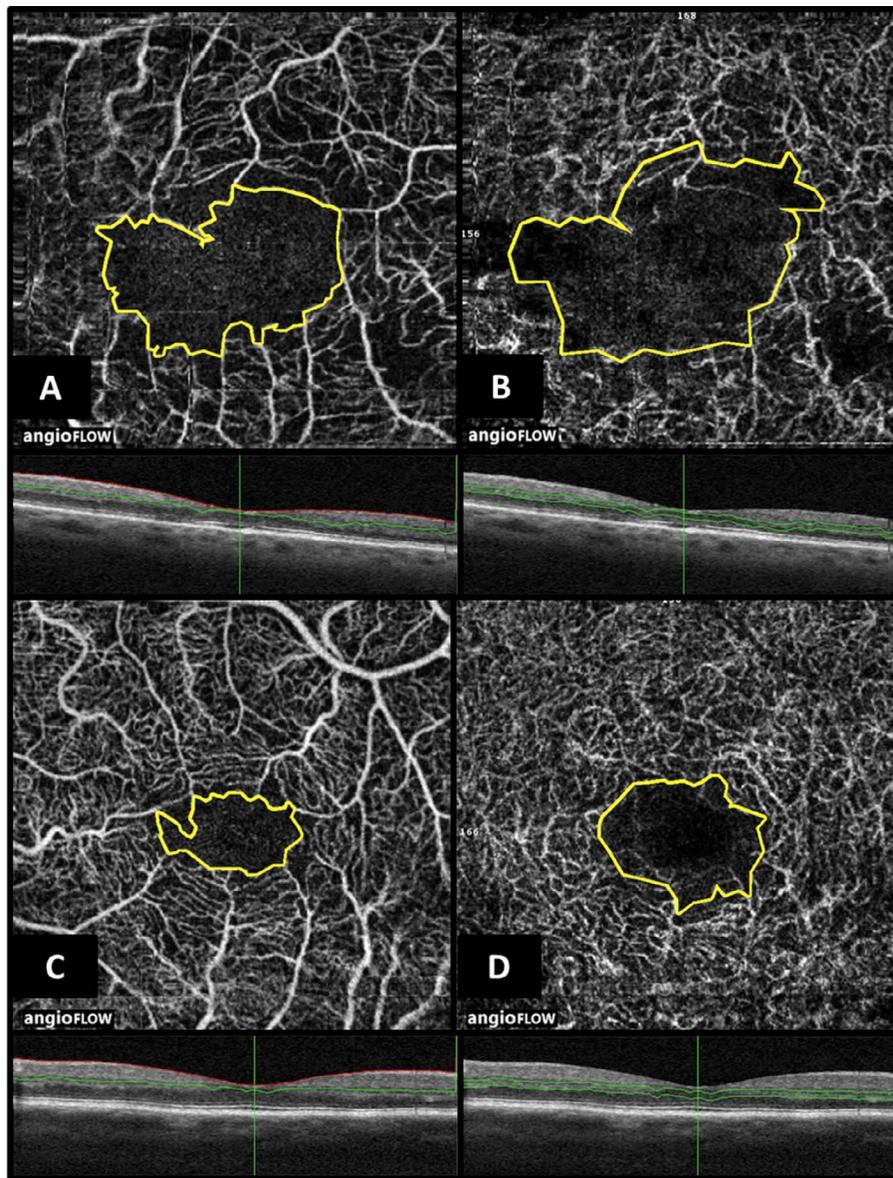


FIGURE 1. (A–D) Representative images of the FAZ area and their corresponding segmentation in two patients with CRVO. In the eye of a 74-year-old woman with a BCVA of 40 ETDRS letters (Snellen equivalent 0.2), the FAZ area was 1.21 mm² in the superficial capillary plexus layer (A) and 1.83 mm² in the deep capillary plexus layer (B). The corresponding segmentation lines are shown below. In the eye of a 70-year-old man with a BCVA of 84 ETDRS letters (Snellen equivalent 0.8), the FAZ area was 0.32 mm² in the superficial capillary plexus layer (C) and 0.65 mm² in the deep capillary plexus layer (D). The corresponding segmentation lines are shown below.

treatment using OCTA. Using this technology, we found a significant correlation between the FAZ area and BCVA. In our study, the patients first received at least four anti-VEGF injections in order to exclude the effect of the macular edema on the visual outcome. Studies in healthy subjects analyzing the FAZ area with FA have shown a considerable variability with area data ranging from 0.205 to 0.405 mm².^{16–18} Comparable values have been found with OCTA with SL FAZ area ranging from 0.25 to 0.30 mm² and the DL FAZ area measuring 0.49 mm².^{19,20} In our study, we found enlarged SL and DL FAZ areas measuring 0.76 mm² and 1.12 mm², respectively. Six patients had a severely enlarged DL FAZ area outside the 3 × 3-mm cube precluding measurement. This data suggests that the DL FAZ area is more affected than the SL FAZ area in CRVO. Previous studies have shown more capillary network abnormalities in the deep capillary microvasculature

in patients with CRVO and BRVO.^{21,22} Several reasons for the more severe deep capillary involvement have been suggested. In a mouse model it has been shown that veins from the superficial plexus drain through transverse venules into the deep capillary plexus.²³ This may in turn cause elevation of the hydrostatic pressure in the deep circulation leading to decreased perfusion in the deep retinal structures. Martinet et al.²⁴ showed that most patients with CRVO first present with edema in the outer retina without changes in the inner retinal layers. Furthermore the SL has a more direct blood supply from the retinal arterioles providing higher perfusion pressure compared with the deeper microcirculation. Edema in the outer retina can cause liquefaction necrosis of the tissue damaging the photoreceptors and reducing foveal function.²⁵ Disruption of the EZ is considered a marker of photoreceptor dysfunction. We found a correlation between the SL FAZ size

OCT Angiography in CRVO

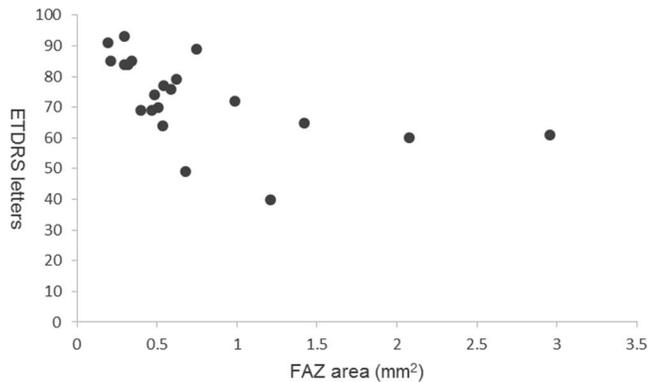


FIGURE 2. Correlation between visual acuity and the superficial FAZ area ($r = -0.54$, $P = 0.01$).

and the disruption of EZ. An even stronger association was found between poor visual acuity and a disrupted EZ. Similar findings have been shown previously in retrospective studies.^{14,15} Optical coherence tomography-A allows segmental evaluation of the retinal capillary networks that are consistent with previous histologic studies.²⁶ Recently, OCT-A images have been shown to visualize the retinal capillary plexus better than FA.²⁷ Selective visualization of the deep retinal capillary plexus, which cannot be accomplished by FA, can provide additional information of the foveal involvement in CRVO. However, the clinical significance of the DL FAZ segmentation has yet to be established.

Coscas et al.²² retrospectively evaluated 29 CRVO patients with OCT-A. As in the present study they found more areas of nonperfusion in the deep capillary plexus compared with the superficial circulation, but they did not find any correlation between the disruption of the perifoveal capillary network and the BCVA. However, they did not specifically measure the FAZ area and the patients had various degrees of macular edema possibly affecting the visual function.

There are several limitations of the study. There was no control group in our material and six of the patients had a DL FAZ area reaching outside the 3×3 -mm cube. Using a larger cube could have helped to evaluate the deep FAZ area better. A segmentation error of the superficial/deep layers could be a concern in a retina with a disrupted morphology. However, by only including patients without macular edema we could reduce this risk. In addition, projection artifacts are commonly seen in the deep layers representing vessels from the superficial circulation. These projected vessels typically have weaker contrast and run the same course as their counterpart

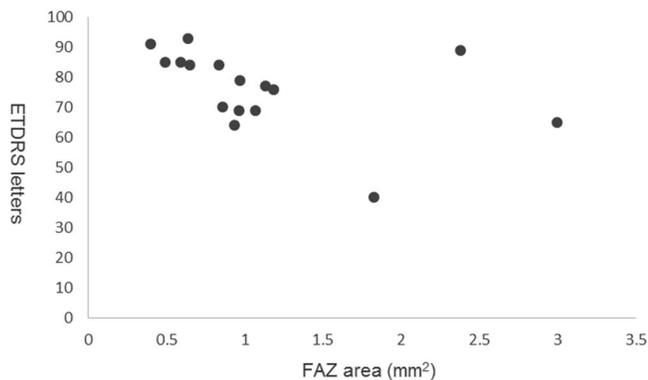


FIGURE 3. Correlation between visual acuity and the deep FAZ area ($r = -0.43$, $P = 0.09$).

in the superficial layer (Fig. 1D). Nevertheless, we cannot exclude that some deep vessels may have erroneously been classified as projection artifacts.

In summary, we have shown that an enlarged FAZ area and disruption of the foveal EZ correlated significantly with poorer visual outcomes. Optical coherence tomography-A can supply additional information in the evaluation of patients with CRVO and can help us predict patient's long-term visual prognosis.

Acknowledgments

Disclosure: **M. Casselholm de Salles**, None; **A. Kvanta**, None; **U. Amrén**, None; **D. Epstein**, None

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