Central retinal vein occlusion (CRVO) is a common retinal vasculopathy that may cause severe visual impairment. The predominant cause of decreased visual acuity in most patients is macular edema. Early treatment of the macular edema improves the visual prognosis. However, retinal nonperfusion may also contribute to poor visual prognosis. Previous studies have further shown an enlargement of the foveal avascular zone (FAZ) in patients with retinal vein occlusion. 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. 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.

This allows segmented evaluation of the FAF and the parafoveal capillary networks. 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 outcomes. 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. 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 naïve CRVO with a disease duration of maximum 12 months, BCVA between 25 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 OCT-A.

**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 OCT-A 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 was defined 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 OCT-A 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 OCT-A 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 was 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 was 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 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 < 0.0001). Patients with disrupted EZ had worse mean BCVA (57.3 ± 10.8 letters) compared with patients with a normal EZ (79.5 ± 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 ± 54 μm. The patients had received an average of 7.9 ± 3.0 injections (range, 4–14) before evaluation with OCT-A.

**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 therapy.
treatment using OCT-A. 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 mm$^2$. Comparable values have been found with OCT-A with SL FAZ area ranging from 0.25 to 0.30 mm$^2$ and the DL FAZ area measuring 0.49 mm$^2$. In our study, we found enlarged SL and DL FAZ areas measuring 0.76 mm$^2$ and 1.12 mm$^2$, 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. 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. 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. 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. Disruption of the EZ is considered a marker of photoreceptor dysfunction. We found a correlation between the SL FAZ size

![Figure 1](image-url)

**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 mm$^2$ in the superficial capillary plexus layer (A) and 1.83 mm$^2$ 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 mm$^2$ in the superficial capillary plexus layer (C) and 0.65 mm$^2$ in the deep capillary plexus layer (D). The corresponding segmentation lines are shown below.
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 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 poor 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.

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### References

15. Lima VC, Yeung L, Castro LC, Landa G, Rosen RB. Correlation between spectral domain optical coherence tomography...