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Correlation of En Face OCT Angiography Averaging versus Single Image Quantitative Measurements with Retinal Vein Occlusion Visual Outcomes

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Abstract

Purpose: To demonstrate the effect of averaging multiple en-face optical coherence tomography angiography (OCTA) images on the correlation between retinal microvasculature quantitative metrics and best corrected visual acuity (BCVA) in eyes with retinal vein occlusion (RVO).

Methods: A cross-sectional cohort with unilateral RVO were imaged in both eyes. Five 3×3mm spectral-domain OCTA images were averaged, and quantitative parameters from averaged versus single images were correlated to LogMAR BCVA. Regression analyses were performed to correlate quantitative metrics to BCVA.

Results: Ten patients (5 male, average age 64.3 years) were included. Among RVO eyes, vessel length density was significantly less in averaged versus a single image for both the superficial retinal layer (15.5± 2.5/mm vs. 17.8±2.4/mm, p=0.05) and deep retinal layer (16.2 ±1.4/mm vs. 18.5±1.6/mm, p=0.003). Multivariate linear regression showed an increased R^2 value with averaging (0.93 to 0.95, for single and averaged groups, respectively). Foveal avascular zone circularity was associated with BCVA on single images (coefficient=−0.96, p=0.002), but not with averaged images (p=0.063).

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Conclusion: Scan-averaging of en-face OCTA images improves the clarity of vessels and may allow for more accurate quantification of vessel metrics. Quantitative metrics are significantly associated with BCVA and averaging does not further improve this association compared to single scan analysis.

Summary:

Scan averaging of en face spectral-domain optical coherence tomography angiography improves the visualization of angiographic images and accuracy of quantification compared to single images in retinal vein occlusion. Vessel density is significantly associated with best corrected visual acuity, and this correlation is not further improved with averaging.

Keywords

Averaging; Foveal avascular zone; Quantitative OCTA; Retinal vein occlusion; Spectral-domain optical coherence tomography angiography; Vessel density

Introduction

Retinal vein occlusions (RVO) due branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO) remain one of the leading retinal vascular causes of significant visual loss, second only to diabetic retinopathy. The primary major complication affecting visual acuity is the development of cystoid macular edema (CME).[1] Recent epidemiologic studies have shown that the prevalence of RVO is 5.2 per 1000 persons and will continue to rise as advanced age is the highest risk factor,[2] and the overall aging population continues to grow, globally.

Recent advances in optical coherence tomography angiography (OCTA) have allowed clinicians to noninvasively image blood flow using signal decorrelation between successive optical coherence tomography (OCT) B-scans within the macula in cases of RVO without the use of exogenous fluorescein dye. OCTA has demonstrated that quantitative metrics including foveal avascular zone (FAZ) enlargement[3–6] and parafoveal capillary non-perfusion measured by vessel density (VD) are correlated with best corrected visual acuity (BCVA).[3, 7–13] Even with these advancements, fluorescein angiography (FA) still remains a common method to image retinal non-perfusion and neovascularization in RVO, although with significant limitations. These include the need for invasive intravenous dye injection, which can rarely induce an allergic reaction with anaphylaxis,[14] the loss of retinal vascular detail due to dye leakage and pooling, as well as the inability to evaluate the depth and extent of disease within the various retinal plexuses.[15]

Even with the ability to image quantitative flow in normal and diseased eyes, OCTA imaging is still limited by several factors, including the relatively small field of view, motion artifacts in patients with poor fixation leading to discontinuities, segmentation errors leading to misinterpretation of flow or lack thereof, and the absence of vascular leakage information.[10, 16] Software enhancements have improved some of these issues with the use of montaging to increase the field of view and eye tracking for motion artifacts.[10] Furthermore, two recent studies that utilized image averaging of multiple en face OCTA images of the retinal

capillary plexuses[17] and choriocapillaris[18] were also successful in enhancing image quality, reducing discontinuous vessel segments, and reducing noise, allowing for more reliable calculation of vascular quantitative metrics in normal eyes.

Given the recent success of en face OCTA image averaging in normal eyes, in this present study, we utilized an algorithm developed by Uji and colleagues[17] to average multiple en face OCTA images and evaluated the quantitative parameters of the retinal vasculature in eyes with RVO and their normal contralateral eyes. We then correlated the single versus averaged OCTA images' quantitative metrics to BCVA.

Methods

Institutional review board approval was obtained from Salus IRB (Austin, TX) for this cross-sectional cohort study. It complied with the Health Insurance Portability and Accountability Act of 1996 and followed the tenets of the Declaration of Helsinki.

Participants

Ten patients with history of unilateral RVO (including BRVO, hemi-retinal vein occlusion (HRVO) and CRVO) and the contralateral, normal control eye were imaged in this study. Diseased eyes did not have active CME at the time of imaging as this would interfere with quantitative measurements of the superficial retinal capillary layer (SRL) and deep retinal capillary layer (DRL). Eight achieved this "dry" state with prior treatment following anti-vascular endothelial growth factor (VEGF) treatment.

Optical Coherence Tomography Imaging

All OCTA images were obtained using the Food and Drug Administration-approved spectral-domain OCTA Zeiss Cirrus 5000 with AngioPlex using the Angiography 3×3 mm scan pattern (Carl Zeiss Meditec, Dublin, CA). Each OCTA scan consists of 245 A-scans at 245 B-scan positions, repeated 4 times at each location. En face OCTA images were generated using the optical microangiography (OMAG) algorithm. All eyes were centered on the fovea and obtained repeatedly until 5 OCTA cubes with good image quality were obtained. Images had signal strength >7 (maximum signal strength for the AngioPlex software is a value of 10), uniform illumination without areas of darkness, foveal centration and minimal artifact or saccades (identified as horizontal misalignment of vessel segments on en face images). All images were obtained using the standard commercial default automated segmentation boundaries and exported at a size of 1024×1024 pixels for further analysis.

Multiple En Face Image Averaging

The averaging of SRL and DRL en face images was performed using ImageJ (developed by Wayne Rasband, National Institutes of Health, Bethesda, MD; available at http://rsb.info.nih.gov/ij/index.html) as previously described.[17] Briefly, for each eye, the SRL and DRL en face images generated from 5 different OCTA cube scan sets were stacked to create a 5-frame video and were registered before multiple image averaging. The selected reference scan for averaging was the one with the best image quality including the highest signal

strength, least amount of motion defects, and sharpest vessel details. A central square area of 819 × 819 pixels was cropped for registration and averaging. Registration was first performed on the 5-frame video based on the superficial capillary plexus en-face images, as previously reported.[17] This same transformation was then applied to the DRL layer. After registration, the 5 frames of the SRL and DRL were compounded into a single image by projecting the average intensity.

Quantitative Measurements

Quantitative parameters including the size and circularity of the FAZ, parafoveal vessel length density (VLD) and perfusion density (PD) of the averaged versus single images were analyzed by exporting the OCTA en face images, and processing the images offline with the Zeiss AngioPlex algorithm (version 10.0; clearance by the US Food and Drug Administration pending, Carl Zeiss Meditec, Dublin, CA). FAZ circularity is defined as the measure of the shape of the FAZ relative to a circle, with a higher value indicating a more circular shape.[19]

VLD is defined as the total length of perfused vasculature per unit area (mm/mm^2). PD is defined as the total area covered by perfused vasculature per unit area (%). Regions of measurement were based on the Early Treatment of Diabetic Retinopathy Study (ETDRS) subfields. VLD and PD measurements of the SRL and DRL were acquired for each ETDRS subfield and inner ring, which includes all of the parafoveal subfields. Both the single reference and averaged image was analyzed using the commercial Zeiss AngioPlex algorithm and the resultant quantitative metrics were compared.

Both VLD and PD have been used to quantify retinal vascular density in OCTA en face images. Previous studies have shown that VLD and PD measurements have similar repeatability and reproducibility, though VLD has marginally better diagnostic efficacy.[20, 21] For the purposes of this study, FAZ parameters, PD, and VLD were used for statistical analysis.

Statistical Analysis

Data was analyzed with the Stata 13.0 statistical package (StataCorp LP, College Station, TX, USA). All quantitative values were expressed as the mean with ± standard deviation (SD). For continuous variables comparing the FAZ size and circularity and VLD of the SRL and DRL of the RVO eye versus the contralateral normal eye, an independent 2-tailed *t* test was performed. For binary demographic variables, the Fisher exact test was performed. Univariate and stepwise multivariate linear regression with clustering on the individual level were performed to correlate quantitative metrics to BCVA. Statistical significance was defined as $p < 0.05$.

Results

Demographics

Ten patients with unilateral RVO were included in the analysis: 6 with BRVO, 2 with hemi-RVO and 2 with CRVO. Five participants were men and 5 were women. All patients were

phakic except 1 patient who was pseudophakic in both eyes. Average age of the cohort was 64.3 ± 11.3 years (range 47–88). Eight patients were previously treated with anti-VEGF (bevacizumab only in 2 patients; bevacizumab and ranibizumab in 1 patient; ranibizumab only in 2 patients; aflibercept only in 2 patients; and ranibizumab and aflibercept in 1 patient). At the time of image acquisition for the cross sectional study, the average length of follow-up was 56.7±29.7 weeks (range 3–98). Mean number of injections was 8.6±4.0 injections (range 1–13) with the average number of weeks per injection based on a treat-and-extend regimen at 7.9±5.3 (range 4–19.6) for CME in 7 patients; and as needed every 4 weeks for neovascularization in 1 patient. One patient with HRVO was treated only with segmental peripheral panretinal laser photocoagulation for neovascularization. One patient with BRVO did not require treatment for CME or neovascularization. The minimum interval between the OCTA scan date and last anti-VEGF treatment date was 4 weeks.

Visual Acuity and Baseline OCT Parameters

Mean LogMAR BCVA of the contralateral normal eyes was 0.056±0.064 (Snellen equivalent 20/20); and the involved eye was 0.29 ± 0.29 (Snellen equivalent 20/40), which was significantly different (p=0.03). Mean central foveal thickness of the control eyes was 255.6± 24.6 μm and 254.1 ± 24.3 μm in the RVO eyes with no statistical difference (p=0.90).

Single versus Averaged OCTA Images

Figure 1 shows the qualitative differences in a single (Figure 1B and 1D) versus averaged (Figure 1A and 1C) images after registration. Averaged images of the SRL (Figure 1A) and DRL (Figure 1C) showed fewer discontinuous vessels, fewer artifacts including artefactual flow signals in nonvascular areas such as the FAZ, better visualization of collaterals especially in the DRL, as well as smoother and more uniform capillaries. Table 1 summarizes the quantitative measurements including the VLD and PD measurements of both the SRL and DRL and compares the single versus averaged images. Figure 2 is an example of an eye with a infratemporal branch RVO in the right eye with the parafoveal Early Treatment Diabetic Retinopathy Study subfields comparing the VLD values of the averaged SRL (Figure 2A), DRL (Figure 2B) and FAZ circularity (2C) images and SRL (Figure 2D), DRL (Figure 2E) and FAZ circularity (Figure 2F) of a single image. Averaged image analysis of the SRL nasal VLD in both control and RVO eyes was significantly less (Control Single: 21.9 ± 1.4 mm^{-1} versus Control Averaged: 19.7 ± 1.2 mm^{-1}, p<0.01; RVO Single: 21.1 ± 2.7 mm^{-1} versus RVO Averaged: 18.3 ± 2.0 mm^{-1}, p=0.02) and was similarly significantly less in the SRL Inner Ring VLD of the control eyes (Control Single: 21.2 ± 1.7 mm^{-1} versus Control Averaged: 18.0 ± 1.1 mm^{-1}, p=0.02) but not in RVO eyes (RVO Single: 18.7 ± 2.6 mm^{-1} versus RVO Averaged: 16.7 ± 2.6 mm^{-1}, p=0.09). Total VLD of the SRL in single versus averaged eyes was significantly less in the control eyes (Control Single: 20.0 ± 1.7 mm^{-1} versus Control Averaged: 18.8 ± 1.1 mm^{-1}, p=0.01) and was marginally different in the RVO eyes (RVO Single: 17.8 ± 2.4 mm^{-1} versus RVO Averaged: 15.5 ± 2.5 mm^{-1}, p=0.05). In the DRL, the Inner Ring VLD was significantly less in the control eyes (Control Single: 21.2 ± 1.3 mm^{-1} versus Control Averaged: 20.2 ± 1.2 mm^{-1}, p=0.04) but not in the RVO eyes. Total VLD in the DRL was significantly less in both the control (Control Single: 20.0 ± 1.2 mm^{-1} versus Control Averaged: 18.1 ± 1.0 mm^{-1},

p<0.01) and in the RVO eyes (RVO single: 18.5 ±1.6 mm^{-1} versus RVO Averaged: 16.2 ±1.4 mm^{-1}, p<0.01).

Averaged image analysis of PD for both the SRL and DRL in control eyes was significantly less compared to single images for all parameters (Table 1) except SRL inferior PD (Control Single: 38 ± 5% versus Control Averaged: 34 ± 4%, p=0.09). In the RVO eyes, averaged image analysis of PD for both SRL and DRL was also less compared to single images but was only statistically significant for the SRL Total PD (RVO Single: 35 ± 3% versus RVO Averaged: 31 ± 3%, p=0.01) and DRL Total PD (RVO Single: 35 ± 1% versus RVO Averaged: 31 ± 3%, p<0.01).

Table 2 shows the univariate linear regression analysis comparing the quantitative metrics for both averaged and single images with BCVA. In the averaged images, factors including FAZ Size, SRL Superior VLD, SRL Inferior VLD, SRL Nasal VLD, SRL Temporal VLD, SRL Inner Ring VLD, SRL Total VLD, DRL Nasal VLD, DRL Inner Ring VLD, DRL Total VLD, SRL Superior PD, SRL Temporal PD, SRL Inner Ring PD, SRL Total PD, DRL Nasal PD, DRL Inner Ring PD, DRL Total PD had a significant associated with LogMAR BCVA. In comparison for the single images, factors including FAZ Size, FAZ Circularity, SRL Superior VLD, SRL Inferior VLD, SRL Nasal VLD, SRL Temporal VLD, SRL Inner Ring VLD, SRL Total VLD, DRL Nasal VLD, DRL Inner Ring VLD, DRL Total VLD, SRL Superior PD, SRL Inner Ring PD, SRL Total PD, DRL Nasal PD, DRL Inner Ring PD, and DRL Total PD had a significant association with LogMAR BCVA. FAZ circularity was the only factor that was significantly associated with BCVA in the univariate analysis of the single images but not significant in the averaged images. SRL Temporal PD was marginally significant in the univariate analysis of the averaged images but not in the single image. All significantly-associated VLD and PD factors demonstrated that increased VLD and PD was associated with better BCVA whereas increased FAZ Size and decreased FAZ circularity were both associated with worse BCVA.

When all OCTA parameters significantly associated with BCVA on univariate analysis were included in the multivariate linear regression, averaging overall resulted in an increased R^2 value from 0.93 to 0.95, for single and averaged groups, respectively.

Discussion

In this study, we evaluated the impact of multiple en face image averaging on quantitative parameters in eyes with unilateral RVO. Utilizing a previously automated algorithm described by Uji and colleagues,[17] we showed that qualitative improvements include fewer discontinuous vessels, fewer artifacts including artefactual flow signals in nonvascular areas such as the FAZ, better visualization of collaterals especially in the DRL, and smoother and more uniform capillaries. Interestingly, univariate and multivariate analyses of these quantitative metrics shows that an averaged image was not significantly better at predicting BCVA compared to a single image. Previously, Uji et al. have suggested that the noise and vessel discontinuities in a non-averaged image may have significant impact on quantitative parameters.[17] However, though there were significant value differences within a few of these

parameters, they did not affect the ability to predict BCVA as the R^2 was very strong and not statistically different between the single versus averaged images.

Interestingly, in multivariate linear regression analysis associating OCTA parameters with BCVA, there was only a slight improvement in R^2 value for averaged versus single image groups. Both demonstrated a high correlation coefficient of 0.93 and 0.95 in the single and averaged groups, respectively. This small increase in the overall R^2 with averaging was not significant and likely negligible given the multiple number of parameters included for the multivariate analyses. The only factor that was significantly correlated with BCVA in the single but not in the averaged eyes was FAZ circularity (Table 2). Previous quantitative OCTA studies have shown that FAZ size was associated with BCVA in both diabetic retinopathy and RVO[3–6], but did not specifically analyze the FAZ circularity. Kwon and colleagues demonstrated that FAZ circularity was associated with central visual field defects in glaucoma patients although these FAZ measurements were drawn manually and not automatically derived from an algorithm as we performed in our study.[22] These authors surmised that impaired ocular hemodynamics may play an important role in glaucomatous optic nerve damage,[22] and as seen in our current study, may also correlate to BCVA in retinal vascular disease. Although FAZ circularity was not significantly associated with BCVA in the averaged RVO eyes, these findings including the strong R^2 demonstrate that quantitative metrics obtained from a high quality single image may be equally as useful as an averaged image.

Consistent with prior reports analyzing the quantitative parameters of VLD and PD in normal eyes,[15] we found that these metrics in the SRL and DRL of the RVO averaged images demonstrated lower values when compared to single image analysis (Table 1 and Figure 2). Previous studies have shown the clinical relevance of vessel density measurements in predicting clinical disease in RVO.[3, 7–13] In disease processes such as RVO, it is important to accurately measure this quantitative metric as it would be an ideal way to monitor the ischemic index over time. Accurately measuring the averaged VLD or PD or difference with treatment and time could provide clinicians a secondary measure to monitor for improvement, stability or worsening of macular ischemia, which is directly correlated with, and may perhaps precede and be predictive of BCVA.

The clinical significance of a decreased VLD and PD after averaging remains unclear. Typically, noise reduction would decrease VLD and PD while more continuous vessels in a localized area would increase VLD. Uji et al. suggested that the effect of averaging likely reduces more noise rather than affecting the amount of vessel continuity.[17] Spaide and colleagues have pointed out several other weaknesses of OCTA including projection artifacts, eye motion artifacts including discontinuous vessels and potential decorrelation to cause false negative or positive appearance of flow, and variability of blood flow given its pulsatile nature that can affect measurement of flow in a single area of interest.[16] As demonstrated in our study, averaging with registration can assist with movement artifacts, decreasing false negative and positive appearances of flow, and improve continuity of vascular structures. The averaging effect also likely removes irregular tiny vessel segments/spines therefore decreasing quantitative vessel measurements. However, this can also possibly introduce new artifacts such as averaging multiple en face OCTA images from

different time points, which may inadvertently lower the quantitative flow parameters. As Spaide and colleagues pointed out, blood flow is pulsatile in nature and imaging the same area including the macula may show variability in the amount of flow detected in that region.[16] Our 5 images were acquired sequentially but still required several minutes between each acquisition. Averaging of 5 different time points within in each cardiac cycle may subtly affect the quantitative measurements. This may partially explain the decrease in VLD in the averaged compared to the single image but unlikely the sole cause and further exploration and improvements such as imaging according to the cardiac cycle or volume rendering may further enhance OCTA quantitative analysis.[16]

Previous averaging studies of normal eyes demonstrated that for the SRL, significant differences in VLD occurred continuously as more images were averaged between 2 to 9 frames. The largest difference occurred in the first level of averaging (2 frames), with a diminished magnitude of benefit after 5 frames of averaging. For the DRL, the ideal number of averaged images was more than 3 frames and no significant differences were found after averaging more than 6 frames.[17] Given these findings, we decided on averaging 5 images for each included eye. In clinical practice, acquiring 5 high quality images and having the patient maintain central fixation, especially in diseased eyes, remains difficult. This is one of the major limitations to spectral-domain OCTA,[10, 16] especially compared to swept-source OCTA due to the speed of image acquisition. In addition, all of our patients' eyes did not have baseline CME at the time of image acquisition either due to previous anti-VEGF treatment or no initial CME. This was important to not only acquire high quality images and prevent artefactual blockage of the capillary plexuses especially within the DRL, but also allowed for patient fixation. Although BCVA was significantly worse in the RVO eyes compared to normal eyes, we were still able to acquire good images and registered image averaging could still be successfully accomplished.

This study provides important information about the ability to analyze quantitative metrics in averaged versus single OCTA images in RVO eyes and is, to the best of our knowledge, the first study to evaluate this form of OCTA image processing. However, we acknowledge several limitations of this report. The primary limitations of this study are its cross-sectional design, limited sample size, and the limitations of spectral-domain OCTA, which may not be able to detect slow flow below the threshold of its acquisition speed. The small sample size could affect the ability to detect small significant differences in both the SRL and DRL metrics, and may be underpowered to demonstrate a true multivariate analysis to correlate a single versus averaged image to BCVA in RVO. Furthermore, automated segmentation boundaries, especially in diseased eyes could lead to segmentation errors and affect the quantitative metrics analysis especially in the single images. We have tried to minimize the amount of segmentation errors by excluding eyes with CME. We believe that averaging would help to diminish some of the effects of segmentation errors on the quantitative metrics, and automated registering based on the SRL may assist in reducing the amount of segmentation error as the internal limiting membrane is typically used and easily identified as the anterior boundary in the commercial algorithms.[17]

Despite these limitations, our study has successfully showed the qualitative and quantitative improvements with registered image averaging in RVO. Quantitative parameters such as

FAZ size and VLD are significantly associated with BCVA in RVO. However, though averaged quantitative parameters such as VLD and PD may be more accurate due to less artifacts and vessel discontinuities, averaging does not necessarily improve the ability to define this association compared to a single OCTA scan. Larger studies in the future are needed to explore this correlation and truly distinguish the difference in quantitative analysis of single versus multiple en face imaging averaging.

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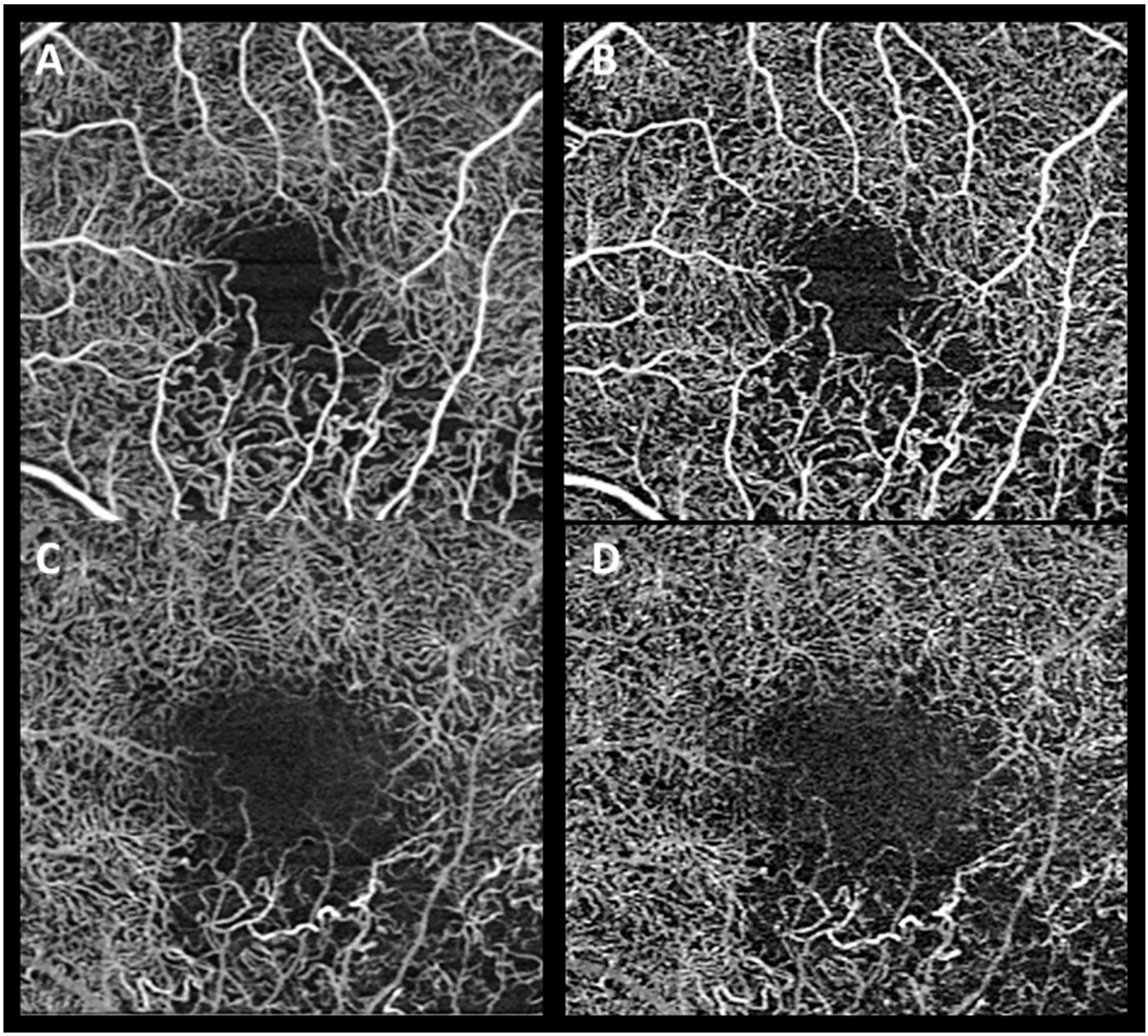

Figure 1.

Qualitative differences in averaged versus single spectral domain optical coherence tomography angiography images of the superficial and deep retinal layers.

Panel (**A**) is an averaged superficial retinal layer (SRL) versus a single SRL (**B**) image of an eye with a branch retinal vein occlusion inferotemporally. Similarly, panel (**C**) is the averaged deep retinal layer (DRL) versus single DRL (**D**). In the averaged images, there are less movement artifacts and noise and improved continuity of vascular structures.

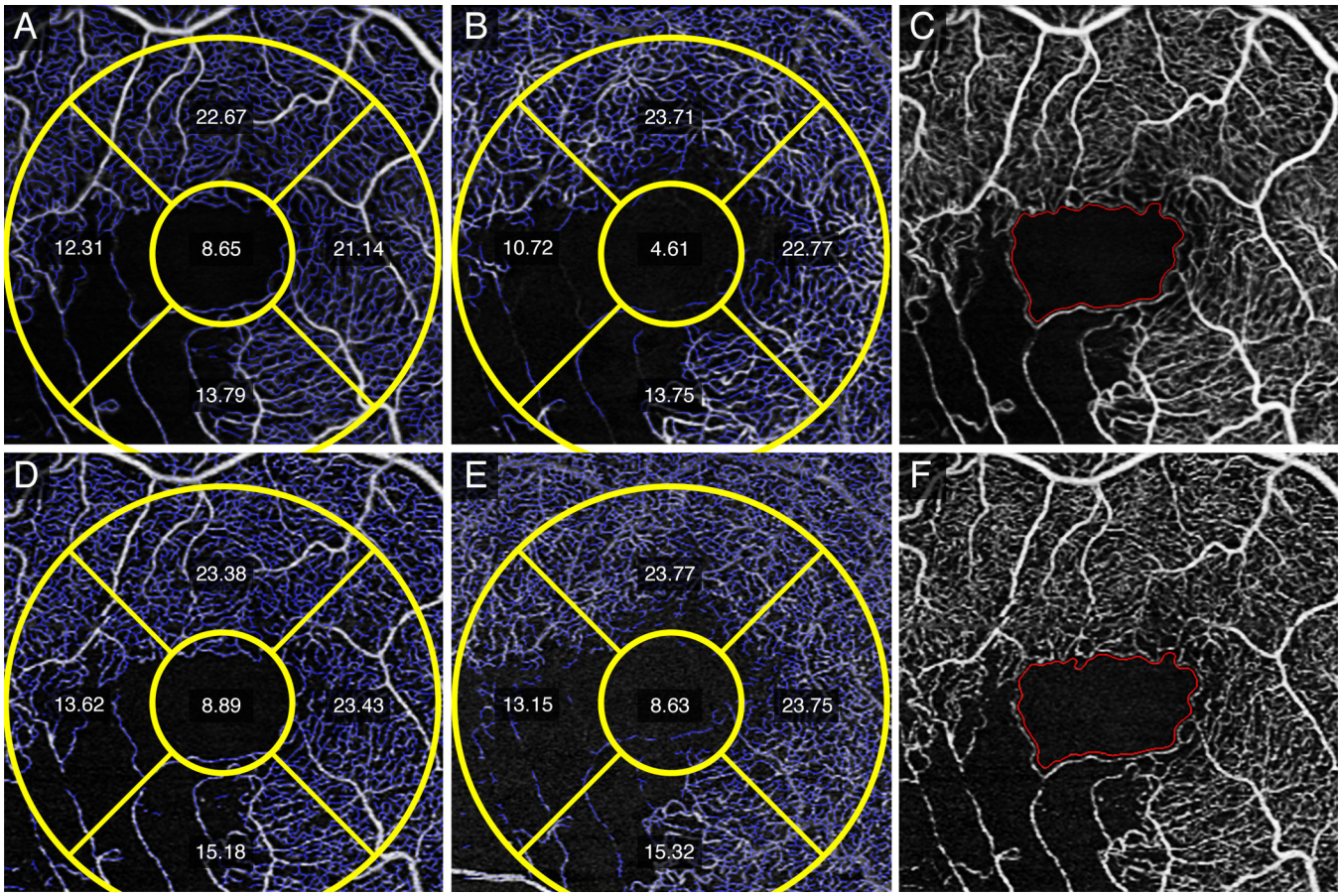

Figure 2.

Quantitative vessel length density, foveal avascular zone (FAZ) size, and FAZ circularity of a right eye (OD) with an inferotemporal branch retinal vein occlusion.

Panels include the averaged superficial retinal layer (SRL) (**A**), deep retinal layer (DRL) (**B**), and the entire retina (**C**) images with quantitative vessel length density (VLD) measurements in the parafoveal Early Treatment Diabetic Retinopathy Study (ETDRS) subfields, size of the foveal avascular zone (FAZ) and FAZ circularity. Single SRL (**D**), DRL (**E**), and the entire retina (**F**) images show increased VLD measurements and FAZ size likely due to increased noise and artifacts and less vessel continuity.

OCTA Quantitative Variables	Control (std) Single Images	Control (std) Averaged Images	P-Value	RVO (std) Single Images	RVO (std) Averaged Images	P-Value
FAZ Size	0.25 (0.11)	0.28 (0.09)	0.59	0.54 (0.61)	0.52 (0.43)	0.95
FAZ Circularity	0.67 (0.08)	0.66 (0.10)	0.79	0.47 (0.17)	0.50 (0.18)	0.65
SRL Superior VLD	21.5 (1.2)	19.8 (1.0)	**<0.01**	19.2 (4.3)	17.6 (4.8)	0.42
SRL Inferior VLD	20.3 (3.2)	18.6 (2.5)	0.22	16.5 (5.4)	14.3 (5.0)	0.36
SRL Nasal VLD	21.9 (1.4)	19.7 (1.2)	**<0.01**	21.1 (2.7)	18.3 (2.0)	**0.02**
SRL Temporal VLD	20.9 (1.5)	19.4 (1.2)	**0.03**	18.2 (4.0)	16.4 (3.8)	0.31
SRL Inner Ring VLD	21.2 (1.7)	18.0 (1.1)	**0.02**	18.7 (2.6)	16.7 (2.6)	0.09
SRL Total VLD	20.0 (1.7)	18.8 (1.1)	**0.01**	17.8 (2.4)	15.5 (2.5)	**0.05**
DRL Superior VLD	22.0 (1.3)	21.2 (1.1)	0.44	19.7 (5.6)	18.3 (5.7)	0.61
DRL Inferior VLD	21.6 (1.8)	20.5 (1.7)	0.38	17.4 (5.1)	15.9 (5.8)	0.55
DRL Nasal VLD	21.2 (1.6)	19.9 (1.6)	0.05	21.3 (2.9)	19.3 (3.1)	0.17
DRL Temporal VLD	20.1 (1.2)	19.1 (0.83)	0.09	18.4 (3.0)	16.8 (3.2)	0.25
DRL Inner Ring VLD	21.2 (1.3)	20.2 (1.2)	**0.04**	19.2 (2.0)	17.6 (1.9)	0.08
DRL Total VLD	20.0 (1.2)	18.1 (1.0)	**<0.01**	18.5 (1.6)	16.2 (1.4)	**<0.01**
SRL Superior PD	40 (2)	37 (1)	**<0.01**	37 (10)	34 (10)	0.60
SRL Inferior PD	38 (5)	34 (4)	0.09	34 (10)	31 (10)	0.57
SRL Nasal PD	40 (1)	36 (2)	**<0.01**	41 (7)	37 (7)	0.24
SRL Temporal PD	39 (2)	37 (2)	**0.01**	36 (5)	33 (6)	0.32
SRL Inner Ring PD	39 (2)	36 (2)	**<0.01**	37 (4)	34 (4)	0.11
SRL Total PD	37 (2)	34 (2)	**<0.01**	35 (3)	31 (3)	**0.01**
DRL Superior PD	39 (2)	42 (2)	**0.01**	37 (10)	34 (10)	0.60
DRL Inferior PD	37 (2)	40 (3)	**0.02**	34 (10)	31 (10)	0.57
DRL Nasal PD	38 (3)	41 (2)	**0.02**	41 (7)	37 (7)	0.25
DRL Temporal PD	36 (1)	39 (2)	**<0.01**	36 (5)	33 (6)	0.32
DRL Inner Ring PD	38 (2)	40 (2)	**<0.01**	37 (4)	34 (4)	0.11
DRL Total PD	34 (1)	38 (2)	**<0.01**	35 (3)	31 (3)	**<0.01**

DRL = Deep Retinal Layer; FAZ = Foveal Avascular Zone; PD= Perfusion Density: defined as the total area covered by perfused vasculature per unit area (%); SRL = Superficial Retinal Layer; RVO = retinal vein occlusion; std = Standard Deviation; VLD = Vessel Length Density: defined as the total length of perfused vasculature per unit area (mm/mm^2)

T-test: Comparing means of quantitative variables for single versus averaged images in both Control and RVO eyes

bold = significance set at $p < 0.05$

Variable	Association with BCVA (Univariate linear regression) (Averaged images)		Association with BCVA (Univariate linear regression) (Single images)	
	Coefficient	P-value	Coefficient	P-value
FAZ Size	0.26	**0.019**	0.36	**<0.01**
FAZ Circularity	−0.73	0.063	−0.96	**0.0020**
SRL Superior VLD	−0.042	**0.027**	−0.051	**0.0090**
SRL Inferior VLD	−0.024	**0.042**	−0.015	**0.033**
SRL Nasal VLD	−0.11	**<0.01**	−0.080	**0.0020**
SRL Temporal VLD	−0.050	**0.021**	−0.047	**0.026**
SRL Inner Ring VLD	−0.079	**<0.01**	−0.072	**<0.01**
SRL Total VLD	−0.086	**<0.01**	−0.075	**<0.01**
DRL Superior VLD	−0.014	0.48	−0.015	0.497
DRL Inferior VLD	−0.023	0.072	−0.022	0.081
DRL Nasal VLD	−0.072	**<0.01**	−0.057	**0.017**
DRL Temporal VLD	−0.018	0.46	−0.029	0.295
DRL Inner Ring VLD	−0.083	**0.009**	−0.075	**0.010**
DRL Total VLD	−0.098	**0.015**	−0.089	**0.006**
SRL Superior PD	−2.91	**0.024**	−2.3	**0.016**
SRL Inferior PD	−0.94	0.089	−1.3	0.12
SRL Nasal PD	−4.2	0.15	−4.6	0.088
SRL Temporal PD	−2.5	**0.049**	−2.2	0.085
SRL Inner Ring PD	−5.3	**<0.01**	−5.8	**<0.01**
SRL Total PD	−5.5	**<0.01**	−6.0	**<0.01**
DRL Superior PD	−0.83	0.48	−0.66	0.48
DRL Inferior PD	−1.2	0.14	−1.2	0.14
DRL Nasal PD	−3.1	**0.005**	−3.3	**<0.01**
DRL Temporal PD	−1.7	0.38	−1.1	0.55
DRL Inner Ring PD	−4.8	**<0.01**	−5.5	**<0.01**
DRL Total PD	−6.1	**<0.01**	−6.7	**<0.01**

DRL = Deep Retinal Layer; FAZ = Foveal Avascular Zone; PD = Perfusion Density; SRL = Superficial Retinal Layer; VLD = Vessel Length Density

Results of Univariate linear regressions for the ability of listed variables to predict BCVA (logMAR) in retinal vein occlusion patients.

(+) coefficient = worse logMAR BCVA versus (−) coefficient = better logMAR BCVA.

bold = significance set at $p<0.05$