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Comparison of Zeiss Cirrus and Optovue RTVue OCT Angiography Systems: A Quantitative and Qualitative Approach Examining the Three Capillary Networks in Diabetic Retinopathy

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Abstract

BACKGROUND AND OBJECTIVES: Construct a method for visualizing the middle capillary plexus (MCP) using Zeiss optical coherence tomography angiography (OCTA) and compare to established segmentation methods using the Optovue system.

PATIENTS AND METHODS: Twenty eyes with diabetic retinopathy were imaged. Visualization of the MCP, image artifacts, preservation of pathological changes, foveal avascular zone (FAZ) area, and vessel length density (VLD) were compared between devices.

RESULTS: The authors successfully segmented the superficial (SCP), MCP, and deep (DCP) capillary plexuses on both devices. More images artifacts were detected on Optovue. Microaneurysms and telangiectatic vessels were better visualized in the MCP on the Optovue. FAZ area showed a strong correlation between the two instruments ($r^2 = 0.666$; $P < .0001$). The SCP had lower VLD compared to the MCP and DCP on both devices.

CONCLUSION: The authors provide an objective and consistent method for manual segmentation using Zeiss OCTA to visualize the three retinal capillary plexuses.

INTRODUCTION

Since its inception, optical coherence tomography angiography (OCTA) has inspired a steady rise in the number of studies capitalizing on its ability to provide a depth-resolved, contrast-free imaging of the retinal vasculature. This technology has been shown to be particularly useful in evaluating the microvascular changes associated with diabetes.^{1,2} The commercially available Angiovue software on the Avanti RTVue XR device (Optovue, Fremont, CA) uses a split-spectrum amplitude-decorrelation algorithm (SSADA), which reduces the effect of bulk-motion to improve signal-to-noise ratio in the axial direction.³ The SSADA algorithm, which compares only amplitude information between consecutive OCT B-scans, also splits the OCT spectrum into 11 sub-bands, further improving the signal-to-noise ratio but decreasing axial resolution of the final image.⁴ Another commercially available OCTA instrument, the Zeiss Cirrus HD-OCT 5000 (Zeiss Meditec, Dublin, CA) with Angioplex, is based on optical microangiography (OMAG), which compares both amplitude and phase differences between consecutive B-scans.^{5,6}

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The software currently available in these two OCTA devices automatically segments the retinal capillaries into two slabs: the superficial capillary plexus (SCP) and the deep capillary plexus (DCP), and a majority of the diabetic retinopathy (DR) literature evaluated only these two plexuses.^{7–14} However, previous work has demonstrated the existence of a physiologically distinct middle capillary plexus (MCP).^{15–18} As a consequence, the MCP is visualized, in part, within both slabs. Previously, we have demonstrated a manual segmentation procedure on Angioview software to elucidate and qualitatively evaluate the distinct MCP.¹⁹

In this study, we aim to assess the feasibility of using customized segmentation strategies to reveal the MCP using the Zeiss Angioplex OCTA in a cohort of patients with varying levels of DR. We then compare the capillary plexuses derived from the two devices (Optovue and Zeiss) in terms of motion artifacts, preservation of pathological changes, and quantitative parameters (including full-thickness foveal avascular zone [FAZ] and vessel length density) at each capillary plexus layer.

PATIENTS AND METHODS

Participants

This prospective, observational study was approved by the institutional review board at North-western University, complied with the Health Insurance Portability and Accountability Act, and followed the tenets of the Declaration of Helsinki. The study period was between September 2016 and January 2017. Informed consent was obtained from all subjects. Patients were recruited during their routine ophthalmologic examinations in the Department of Ophthalmology at Feinberg School of Medicine of Northwestern University in Chicago, Illinois. Images were captured with the Avanti RTVue XR and the Cirrus instruments. Each patient underwent imaging with both instruments on the same day of recruitment in the same order, first on Optovue and then Zeiss.

Inclusion criteria included patients diagnosed with different stages of DR, ranging from minimal non-proliferative (NPDR) to high-risk, and treated quiescent proliferative (PDR). We included only patients with images with adequate signal strength (scores > 50 on the Optovue instrument, and > 6 on the Zeiss instrument), as well as limited motion or shadow artifacts on OCTA images. Of the 22 total eligible eyes (11 patients), one eye was excluded for poor image quality.

Exclusion criteria were eyes that had undergone previous surgical retinal repair and those with other retinal disease such as high myopia (greater than −7D) that may influence the outcome of the segmentation protocol. We also excluded patients with significant cataracts (above nuclear opalescence grade 3 or nuclear color grade 3). Electronic medical records were reviewed to obtain demographic and clinical information.

Image Acquisition and Segmentation

The Optovue instrument has an A-scan rate of 70,000 scans per second, a light source centered at 840 nm, and a full-width at half maximum (FWHM) bandwidth of 45 nm and uses the SSADA algorithm for obtaining angiographic information.³ At each location on the

retina, the RTVue system captures two consecutive B-scans (M-B frames) each containing 304 A-scans (304 B-scan locations, each separated by 9.9 μm). Motion-correction technology (MCT) software corrects for motion between instrument and tissue using input data from two consecutive OCT volumes acquired via orthogonal fast-scan axes.²⁰ Projection artifacts, which are artificial decorrelation signal projections cast from more superficial layers onto the layers below, are partially removed by the Angiovue software on the Optovue instrument. We acquired a macular volumetric scan centered on the fovea using the $3 \times 3 \text{ mm}^2$ scanning area with 304 pixel $\times$ 304 pixel resolution.

The Zeiss instrument has an A-scan rate of 68,000 scans per second and light source with a central wavelength of 840 nm and a FWHM of 90 nm. OCTA images are generated using the OMAG algorithm.⁵ In a $3 \times 3 \text{ mm}^2$ scanning pattern, OMAG is achieved by four repeated B-scans at each position in the slow Y-axis (245 total B-scan locations, each separated by 12.5 μm) with 245 A-scans per B-scan in the fast X-axis. Real time retinal-tracking is accomplished by a line scan ophthalmoscope (LSO) to reduce motion artifacts.^{21,22} En face $3 \times 3 \text{ mm}^2$ angiograms centered on the fovea were captured and exported with a 429 pixel $\times$ 429 pixel resolution.

The SCP, MCP, and DCP were segmented on the Optovue instrument following the exact parameters (Method 3) as previously described by Park et al.¹⁹ In summary, the SCP boundaries were established at 3 μm beneath the inner limiting membrane (ILM) and 25 μm above the inner plexiform layer (IPL), the MCP boundaries at the preset IPL and 30 μm beneath the preset IPL, and the DCP boundaries at 45 μm and 60 μm beneath the IPL (Figure 1).

Using Optovue segmentation as a guide, we manually adjusted the segmentation depth on the Zeiss. The SCP was segmented from the ILM to 55 μm above the IPL. The MCP was segmented using the preset deep plexus setting and adjusting the boundaries from 55 μm to 6 μm above the IPL. The DCP was segmented by adjusting the preset deep plexus segmentation from 6 μm above to 20 μm below the IPL (Figure 1). For the DCP and MCP slabs, we activated the manual option to remove projection artifacts.

Of note, there were inherent differences in the software segmentation boundaries between the two systems. The Optovue segmentation lines are contoured to the ILM, IPL and retinal pigment epithelium (RPE). On the other hand, the Zeiss software uses only the ILM and RPE for the segmentation contours (Figure 1, B-scans).¹¹ Consequently, the segmentations could not be precisely aligned between devices, but rather manually adjusted as described above to capture the angiograms that visually resembled the expected capillary morphology in each plexus.

Calculation of Vessel Length Density

Vessel length density (VLD) was calculated using DiameterJ, a freely available open source plugin for ImageJ (developed by Wayne Rasband, National Institutes of Health, Bethesda, MD; available at <http://rsb.info.nih.gov/ij/index.html>). Full retinal thickness OCTA images were used to manually delineate the area of the FAZ. A masked, independent grader (PLN) traced and measured the area of the FAZ for all images taken on the Optovue first, followed

by all images captured on the Zeiss. SCP, MCP and DCP images were binarized and run through DiameterJ to attain a fiber length. This length was then divided by the total scan area with the FAZ subtracted using the following formula, adopted from Samara et al:²³
$$\text{VLD} = \text{vessel fiber length} / (\text{total scan area} - \text{FAZ area})$$

Statistics

We performed statistical tests with GraphPad Prism version 7 (GraphPad Prism, La Jolla, CA). We used a two-way analysis of variance to compare paired data points of VLD in corresponding plexus layers between the two machines. We used a linear regression analysis to assess the relationship between FAZ area measurements on the two devices.

Reproducibility of the segmentation and VLD methods was assessed by an intraclass correlation analysis using results obtained by three independent graders on a subset of seven eyes. A *P* value of less than .05 was considered statistically significant.

RESULTS

In this study, we examined 21 eyes from 11 patients (six male, five female) with clinical diagnosis of DR that ranged from NPDR to PDR (Table). Eleven eyes of six patients were diagnosed with NPDR and 10 eyes of five patients were diagnosed with PDR. The average patient age was 50 years (SD $\pm$ 13.1 years). Patient demographics are reported in the Table.

Qualitative Assessment

Our method of segmentation from the ILM on the Zeiss was consistently successful in visualizing the three distinct capillary plexuses. Figure 2 shows a side-by-side comparison between Zeiss and Optovue images of the three capillary plexuses. The two systems produced qualitatively similar images with preservation of key characteristics, such as consistent areas of capillary dropout in the DCP and a well-demarcated FAZ most visible in the MCP, as previously established by Park et al.¹⁹

Image Artifacts

In several eyes, despite the use of projection removal software, projection artifacts that were present on the Optovue images were not appreciably detected in the Zeiss counterpart images. Nearly all these observed artifacts or projection interferences appeared in the DCP on the Optovue images but not the Zeiss images as denoted by the red arrows (Figure 3). These artifacts obscured the FAZ borders in the DCP. Interestingly, microaneurysms and telangiectatic vessels were less clear in the Zeiss at the MCP level (Figure 4). Evidence of dilated vessel loops were captured by the Optovue in the MCP (Figure 4, top row), but were less appreciable in the Zeiss images.

VLD Correlation and FAZ Characteristics

Correlation analysis revealed a strong correlation ($r^2 = 0.67$; $P < .0001$) between the FAZ area measurements obtained using the two instruments (Figure 5). Of note, the FAZ border in eyes imaged by the Zeiss revealed vessel discontinuity not reflected on corresponding eyes imaged on the Optovue (Figure 5). Importantly, the intraclass correlation coefficient (ICC) for FAZ quantification on the Zeiss was 0.9466, demonstrating strong reproducibility.

The SCP had significantly lower VLD compared to both the MCP and DCP, and this difference was reflected in both machines (Figures 6A and 6B). VLD showed no significant difference between the MCP and DCP in either machine, although the Zeiss showed a trend toward greater vessel density in the DCP ($P = .1$). The Zeiss instrument showed trend for lower VLD in the SCP ($P > .99$) and MCP ($P = .39$) layers, whereas it tended to capture a greater VLD in the DCP ($P = .93$), though none of these differences were statistically significant (Figures 6C and 6D). Overall, the differences in VLD at each plexus layer were not statistically significant between the two instruments.

DISCUSSION

This study provides a new method for visualizing the MCP using the Zeiss OCTA device and a comparison of two OCTA systems (Angioplex and Angiovue) in their ability to image retinal vasculature across three distinct capillary plexuses. Using customized and consistent segmentation protocols in eyes with DR, we were able to establish qualitatively and quantitatively similar SCP, MCP and DCP angiograms between the two devices.

Park et al. characterized the three capillary plexuses using the Optovue system by exploiting the presence of projection artifacts. Of note, this method left small gaps between the SCP and MCP, and the MCP and DCP, in order to set discrete slabs without overlap. In the present study, we used the Zeiss Angioplex software to identify and implement an effective segmentation scheme without gaps between the en face slabs. Using this algorithm, we found that images on the Zeiss system were qualitatively similar to the corresponding images on the Optovue, as shown on Figure 2. Consistent with Park et al.,¹⁹ the FAZ had the smallest and most well-demarcated border in the MCP on both devices in this study. Areas of capillary nonperfusion were similar between devices as highlighted by the red circles in the DCP (Figure 2).

Consistent with other studies, we found motion artifacts in Optovue images not seen in the corresponding Zeiss image (Figure 3, Red arrows). A previous study performed by Munk et al. compared the Optovue and Zeiss machines, in addition to two other instruments (Topcon swept-source and Spectralis OCT2).²⁴ Although not statistically significant, their study also found that motion artifacts were less prominent in the Zeiss system as compared to the Optovue. Similarly, a study by De Vitis et al. compared Optovue and Zeiss systems and found the mean number of motion artifacts significantly lower in Zeiss images.²⁵ This could be a result of patient fatigue due to longer image acquisition time with the Optovue,^{25,26} or differences in motion artifact correction algorithms.^{20,27}

Differences in the ability to image deeper vasculature was evidenced by microaneurysms and telangiectatic vessels appearing in the MCP on the Optovue that were less prominent on the Zeiss (Figure 4). Similarly, Munk et al. found that FAZ borders were most distinguishable in the Optovue compared to the Zeiss system.²⁴ This may be explained by differences in the integrated projection artifact removal software or differences between OMAG and SSADA image acquisition and / or post-processing.

Though the MCP and DCP did not significantly differ from one another, both the MCP and DCP consistently demonstrated greater VLDs than the SCP in both machines, consistent with previous findings in diabetic eyes.²³ Previous studies have shown excellent repeatability and reproducibility of measurements within each OCTA device.^{28–30} Our quantitative analyses showed two OCTA systems (Optovue and Zeiss) had similar performance regarding assessment of the VLD (Figure 6). Therefore, our study adds to these previous studies by showing reproducible measurements of VLD between the Optovue and Zeiss devices.

One major limitation of this study is that all patients had a diagnosis of DR, which may limit the wide applicability of our findings. Additionally, several images were excluded from the comparison due to algorithm failure in the DiameterJ plugin. A total of 11 (of 63 total) Optovue images and seven (of 63 total) Zeiss images were excluded due to a lack of “discrete interconnecting fiber networks in the images.” Future studies using different software techniques are warranted.

In conclusion, using customized segmentation on the Zeiss with Angioplex OCTA system we have qualitatively recapitulated the MCP as a separate capillary network. The customized segmentation strategy allowed us to reproduce the three macular capillary plexus layers, with strong correlation for quantitative capillary parameters compared to the Optovue instrument. In another study using this customized segmentation, we have shown that vascular pathology on OCTA can be linked to structural changes on en face OCT within each of the three capillary plexuses using the Zeiss OCTA.³¹ However, given the relative paucity of studies that evaluate the MCP as a distinct and potentially important layer during retinal pathologic changes, this study provides a standardized method for future evaluation of this plexus in the clinical setting.

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Figure 1.

Segmentation of the three capillary plexuses on Optovue and Zeiss instruments. The Optovue segmentation boundaries were carried out as follows: superficial capillary plexus (SCP) boundaries were established at 3 μm beneath the inner limiting membrane (ILM) and 25 μm above the inner plexiform layer (IPL), the middle capillary plexus (MCP) boundaries at the preset IPL and 30 μm beneath the preset IPL, and the deep capillary plexus (DCP) boundaries at 45 μm and 60 μm beneath the IPL. On the Zeiss images, the SCP recapitulates the inclusion of the nerve fiber layer, ganglion cell layer, and IPL with boundaries set at 0 μm offset from the ILM to 55 μm above the IPL. The MCP consists of a 49 μm thick slab with boundaries set at 55 μm to 6 μm above the IPL. The DCP consists of a 26 μm thick slab to capture the outer plexiform layer, with boundaries set at 6 μm above to 20 μm below the IPL.

Figure 2. Recapitulation of optical coherence tomography angiography plexus layers. Representative images are shown depicting the qualitative reproduction of the superficial, middle, and deep capillary plexus layers on the Zeiss instrument. Red circles indicate areas of capillary dropout that are visualized using both devices.

Figure 3.

Motion artifacts in the deep capillary plexus. Representative examples of obvious motion artifacts in the deep plexus layers in the Optovue instrument that are not present in the Zeiss images. Red arrows indicate motion artifact discontinuities in the en face angiogram.

Figure 4.

Vascular pathological changes in the middle capillary plexus (MCP) are not equally visualized on the two instruments. Top row: Microaneurysms/telangiectatic vessels (red circles) are depicted in the MCP layers on the Optovue instrument. Bottom row: Corresponding locations of these findings are circled on photographs taken on the Zeiss instrument.

Figure 5.

Foveal avascular zone (FAZ) on full retinal thickness angiogram. Representative images of full-thickness angiograms, red arrows pointing to vessel discontinuity along the FAZ border (left). Difference in measured FAZ area between the two instruments for each eye, $n = 21$ (upper right). Correlation of FAZ areas between the two instruments, line shows a best-fit linear regression with each point representing a single eye plotted against the measured FAZ on each machine, $n = 21$ (lower right).

Figure 6.

Intra- and inter-instrument comparison of each vessel layer – superficial (SCP), middle (MCP), and deep (DCP) capillary plexuses. (A) Scatter-plot depicts the individual vessel length density (VLDs) for each eye. Error bars are shown as mean $\pm$ standard deviation. (B) Intra-instrument VLD differences between plexus layers. (C) VLD are plotted as paired points representing each plexus layer within each eye across the two instruments. (D) Inter-instrument VLD differences between the Zeiss and Optovue at each plexus layer.

TABLE 1**Demographic Characteristics of Study Participants With Diabetic Retinopathy**

Patients (Eyes)	11 / 21
Male / Female	6 / 5
Patients With NPDR (Eyes)	6 (11)
Patients With PDR (Eyes)	5 (10)
Age $\pm$ SD (Range)	50 $\pm$ 13.1 (39 – 71)
Duration of DM in Years $\pm$ SD (Range)	16.5 $\pm$ 9.7 (6 – 36)
HbA1c $\pm$ SD (Range)	9.1 $\pm$ 2.7 (6.4 – 13.3)
Eyes With Intraretinal Cysts (%)	8 (38.1)

DM = diabetes mellitus, HbA1c = glycated hemoglobin, percent of total hemoglobin, NPDR = nonproliferative diabetic retinopathy, PDR = proliferative diabetic retinopathy, SD = standard deviation